CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022580Orig1s020

Trade Name:	QSYMIA
Generic or Proper Name:	phentermine and topiramate extended-release
Sponsor:	Vivus, Inc.
Approval Date:	March 8, 2022
Indication:	Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release, an antiepileptic drug, indicated as 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: • 30 kg/m2 or greater (obese) 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

CENTER FOR DRUG EVALUATION AND RESEARCH

022580Orig1s020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 022580/S-020

SUPPLEMENT APPROVAL

Vivus, Inc.
Attention: Santosh T. Varghese, MD
Chief Medical Officer
900 East Hamilton Ave
Suite 550
Campbell, CA 95008

Dear Dr. Varghese:

Please refer to your supplemental new drug application (sNDA) dated and received July 30, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qsymia (phentermine and topiramate extended-release) capsules.

This Prior Approval sNDA provides for proposed modifications to the approved Qsymia risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Qsymia was originally approved on July 17, 2012, and the most recent REMS modification was approved on March 31, 2021. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS are to convert the REMS document to the new standardized format and provide the Applicant's name change throughout the REMS Document and REMS materials. This modification also removes ETASU A, prescriber training, as an element of the REMS, updates the goals to reflect the removal of ETASU A, and removes the REMS materials associated with prescriber training.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS and that an element of the REMS is no longer necessary to ensure the benefits of the drug outweigh the risk:

Elements to Assure Safe Use: We have determined that ETASU A, prescriber training, is no longer necessary in this REMS to ensure that the benefits of the drug outweigh the risks. Removal of this ETASU is supported by data showing adequate knowledge of the risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy, the importance of pregnancy prevention for patients of reproductive potential receiving Qsymia, and the need to discontinue Qsymia immediately if pregnancy occurs among cohorts of prescribers who are trained and those who are not yet trained. In addition, removing ETASU A would decrease the burden of the pharmacy to report prescriber data to the REMS program.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Finally, removing ETASU A also removes the REMS materials associated with prescriber training.

Your proposed modified REMS, initially submitted on July 30, 2021, amended and appended to this letter, is approved. The modified REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on July 17, 2012.

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

Program Implementation and Operations (per reporting period and cumulatively)

1. Pharmacy Enrollment Statistics
   a. Number and type (mail order, chain, independent) of pharmacies certified
   b. Number of chain dispensing locations certified

2. REMS Compliance
   a. Number and type of pharmacy decertified and the reason for decertification
   b. Summary of annual compliance reports provided to VIVUS by corporate chains, mail order pharmacies, and contracted distributors
   c. Copy of the audit plan for each stakeholder including the criteria for non-compliance (noncompliance plan)
   d. Number of audits expected and performed
   e. Summary report of deviations found, associated corrective and preventative actions and status of corrective actions

3. Report on the periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21CFR 208.24 and Risk of Birth Defects with Qsymia patient brochure
   a. Pharmacist Materials Distribution Survey (beginning with the 11-year (12th) REMS assessment)
      i. Assessment of pharmacists' compliance with the Qsymia REMS dispensing requirements, specifically the provision of a Medication Guide and Risk of Birth Defects with Qsymia patient brochure with each dispensing of Qsymia

4. Patient Demographics and Prescription Data

a. Patient Demographics
   i. Unique number of patients received Qsymia stratified by gender
   ii. Unique number of patients of reproductive potential receiving Qsymia stratified by age groups (12-17, 18-29, 30-39, 40-49, and >50)
   iii. Average duration of Qsymia treatment among patients of reproductive potential

b. Prescription Data
   i. Provide a table that includes the following for the overall population and another table for patients of reproductive potential :
      a. Total number of unique patients
      b. Number and percentage of total prescriptions dispensed
      c. Number and percentage of total prescriptions dispensed for new and refill
      d. Number and percentage of total prescriptions dispensed by dosage strength

Knowledge (per reporting period and cumulatively)

5. Patients of reproductive potential (beginning with the 11-year (12th) REMS assessment)
   a. Assessment of patients of reproductive potential understanding of:
      i. Increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
      ii. Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia therapy
      iii. Need to promptly discontinue Qsymia therapy in the event of a pregnancy
   b. Assessment of the receipt, reading, and understanding by patients of reproductive potential of the Qsymia Medication Guide and Risk of Birth Defects with Qsymia patient brochure
   c. Assessment of patients of reproductive potential receipt of counseling about pregnancy prevention and effective contraceptive use including:
      i. Counseling provider (i.e., prescriber, office nurse, pharmacist)
      ii. Duration of time spent counseling
      iii. Frequency of patient counseling (each visit while receiving Qsymia; first time prescribed Qsymia

6. Pharmacists (beginning with the 11-year (12^{th}) REMS assessment)

a. Assessment of pharmacists' understanding of:
   i. Increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
   ii. Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia therapy
   iii. Need to promptly discontinue Qsymia therapy in the event of a pregnancy

b. Assessment of pharmacists' awareness and understanding of the need to provide a Medication Guide and Risk of Birth Defects with Qsymia patient brochure with every Qsymia prescription dispensed

Health Outcomes and/or Surrogates of Health Outcomes

7. Safety Surveillance
   a. Summary of pregnancy cases associated with Qsymia, including the source of the report, pregnancy outcome, and cases of congenital malformations for each exposed pregnancy
   b. Overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

8. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022580 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022580 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 022580/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022580/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022580/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022580/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA022580

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Martin White, Regulatory Project Manager, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D., M.P.H.
Deputy Director for Safety (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:
- Medication Guide (included in REMS enclosure)
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONIKA A HOUSTOUN
03/08/2022 11:48:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022580Orig1s020

REMS DOCUMENTS

Risk Evaluation and Mitigation Strategy (REMS) Document

Qsymia (phentermine and topiramate extended-release) Capsules

REMS Program

I. Administrative Information

Application Number: NDA 22580
Application Holder: VIVUS LLC
Initial REMS Approval: 07/2012
Most Recent REMS Update: 03/2022

II. REMS Goal

To inform certified pharmacies and patients of reproductive potential about:

1. The increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
2. The importance of pregnancy prevention for patients of reproductive potential receiving Qsymia
3. The need to discontinue Qsymia immediately if pregnancy occurs

III. REMS Requirements

VIVUS LLC must ensure that pharmacies and wholesalers-distributors comply with the following requirements:

1. Pharmacies that dispense Qsymia must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative successfully complete the Pharmacy Training Program and submit it to the REMS Program. 3. Have the authorized representative enroll in the REMS Program on behalf of the pharmacy by completing and submitting the Pharmacy Enrollment Form to the REMS Program. 4. Train all relevant staff involved in dispensing on the risks associated with Qsymia and requirement to provide the Medication Guide and Risk of Birth Defects with Qsymia using the Pharmacy Training Program. 5. Establish processes and procedures to provide the Medication Guide and the Risk of Birth Defects with Qsymia to each patient each time Qsymia is dispensed.

Before dispensing	6. Provide the patient with the Medication Guide and the Risk of Birth Defects with Qsymia through the processes and procedures established as a requirement of the REMS Program.
At all times	7. Not distribute, transfer, loan, or sell Qsymia. 8. Maintain records of standard operating procedures, training, and providing the Medication Guide and the Risk of Birth Defects with Qsymia. 9. Maintain and submit annual compliance reports to the REMS Program. 10. Comply with audits carried out by VIVUS LLC to ensure that all processes and procedures are in place and are being followed.

2. Wholesalers-distributors that distribute Qsymia must:

To be able to distribute	1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies.
At all times	2. Distribute only to certified pharmacies. 3. Maintain and submit annual compliance reports of adherence to distribution requirements of the REMS Program.

VIVUS LLC must provide training to pharmacies who dispense Qsymia.

The training includes the following educational material: Pharmacy Training Program. The training must be available online and hard copy by mail or fax.

To support REMS Program operations, VIVUS LLC must:

1. Establish and maintain a REMS website, www.qsymiarems.com. The REMS website must include the capability to complete pharmacy certification online, to locate certified pharmacies, and the option to print the Prescribing Information, Medication Guide, and REMS materials. The product website for consumers and healthcare providers must include prominent REMS-specific links to the REMS website. The REMS website must not link back to the promotional product website.
2. Make the REMS website fully operational and all REMS materials available through the website within 90 calendar days of REMS modification.
3. Establish and maintain a REMS support center for REMS participants at 1-888-998-4887 and a Pharmacy support center for pharmacists at 1-855-302-6698.
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the Qsymia REMS Program.
5. Ensure pharmacies are able to become certified online and by phone.
6. Provide the Pharmacy Training Program and the Prescribing Information to pharmacies who (1) attempt to dispense Qsymia and are not yet certified or (2) inquire about how to become certified.
7. Notify pharmacies within 2 business days after they become certified in the REMS Program.

8. Provide authorized wholesalers-distributors access to the database of certified pharmacies.

To ensure REMS participants' compliance with the REMS Program, VIVUS LLC must:

9. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Qsymia distribution and dispensing; certification of pharmacies, and audits of REMS participants. These records must be readily available for FDA inspections.
10. Establish a plan for addressing noncompliance with REMS Program requirements.
11. Monitor pharmacies and wholesalers-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
12. Audit certified pharmacies no later than 180 calendar days after they become certified and a representative sample of certified pharmacies every two years, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the Qsymia REMS Program based on monitoring and evaluation of the Qsymia REMS Program.

IV. REMS Assessment Timetable

VIVUS LLC must submit REMS Assessments at 6 months and 12 months from the date of initial approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. VIVUS LLC must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Qsymia REMS**:**

Enrollment Forms

Pharmacy

1. Independent Pharmacy Enrollment Form
2. Corporate Entity of Retail Chain Pharmacy Enrollment Form
3. Mail Order Pharmacy Enrollment Form

Training and Educational Materials

Pharmacy:

4. Pharmacy Training Program

Patient:

5. Medication Guide
6. Risk of Birth Defects with Qsymia

Other Materials

7. REMS Program Website

RE-03-001-05

Qsymia® Risk Evaluation and Mitigation Strategy (REMS)

Pharmacy Enrollment Form - Corporate Entity of Retail Chain Pharmacy

Because of the teratogenic risk associated with Qsymia therapy, Qsymia is available through a limited program under the REMS. Under the Qsymia REMS, only certified pharmacies may distribute Qsymia. I understand that my certified retail pharmacy dispensing locations must comply with the program requirements for certified pharmacies and the terms contained in this form. As the Authorized Corporate Pharmacy Representative, I acknowledge that:

1. I have reviewed and successfully completed the Qsymia Pharmacy Training Program and the knowledge assessment questions.
2. I understand the risks associated with Qsymia.
3. I understand and agree to comply with the requirements of the Qsymia REMS program for pharmacies.
    a. The pharmacy management system will be in place to systematically direct that all certified retail pharmacy dispensing locations provide a Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure to each patient each time Qsymia is dispensed.
    b. All certified retail pharmacy dispensing locations will not distribute, transfer, loan, or sell Qsymia to another pharmacy or distributor.
    c. All certified retail pharmacy dispensing locations will complete training of pharmacists and staff involved with the dispensing of Qsymia and will comply with the REMS requirement to provide a Medication Guide and the *Risk of Birth Defects with Qsymia* each time Qsymia is dispensed.
    d. I will maintain all records of certified retail pharmacy dispensing location training and acknowledgement forms.
    e. All certified retail pharmacy dispensing locations are subject to, and must comply with, surveys to assess compliance with the REMS requirements in order to maintain pharmacy certification.
    f. Each corporate entity of a certified retail chain pharmacy is subject to, and must comply with, audit requirements to ensure that the REMS requirements are being followed to maintain their pharmacy certification under the Qsymia REMS.
4. I will oversee compliance with the Qsymia REMS program requirements and will provide annual compliance reports back to VIVUS to assess effectiveness and comply with all audit requirements.

Authorized Corporate Pharmacy Representative to complete (all fields required):

First Name_____ **Last Name** _____

Phone Number_____ **Fax**_____

Email_____

Corporate Pharmacy Name _____

Address_____ **City**_____

State_____ **Zip Code** _____

Signature_____ **Date**_____
Authorized Corporate Pharmacy Representative

Please fax completed form to the Qsymia REMS Pharmacy Support Center (855-302-6699).

Once this form is successfully processed, you will receive a corporate pharmacy enrollment confirmation via fax and/or email from the Qsymia REMS Pharmacy Support Center. Your corporate entity will be considered certified and your retail chain dispensing locations will be eligible to complete their certification procedures.

The Qsymia Pharmacy Training Program for your pharmacy dispensing locations will be made available through the Qsymia REMS Pharmacy Support Center. Once the training program and knowledge assessment are completed at a pharmacy dispensing location within your organization, it is your responsibility to capture the pharmacy dispensing location information noted below and provide it to the Qsymia REMS Pharmacy Support Center. Once the Qsymia REMS Pharmacy Support Center receives, processes, and confirms the required pharmacy dispensing location information from you, this pharmacy dispensing location will be considered certified and permitted to order, receive, and dispense Qsymia.

The following required pharmacy dispensing location fields must be provided to the Authorized Corporate Pharmacy Representative for each trained pharmacy dispensing location: Responsible Pharmacist first and last name, dispensing pharmacy address with zip code, phone and fax numbers, pharmacy DEA, NCPDP ID and NPI numbers; and pharmacy store # (optional).

If you have any questions or require additional information, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698.

Qsymia® Risk Evaluation and Mitigation Strategy (REMS)

Pharmacy Enrollment Form - Independent Pharmacy

Because of the teratogenic risk associated with Qsymia therapy, Qsymia is available through a limited program under the REMS. Under the Qsymia REMS, only certified pharmacies may distribute Qsymia. I understand that my independent pharmacy dispensing location must comply with the program requirements for certified pharmacies and the terms of the agreement contained in this form. As the designated Authorized Pharmacy Representative, I acknowledge that:

1. I have reviewed and successfully completed the Qsymia Pharmacy Training Program and the knowledge assessment questions.
2. I understand the risks associated with Qsymia.
3. I understand and agree to comply with the requirements of the Qsymia REMS program for pharmacies.
    a. My certified pharmacy will establish processes and procedures to systematically direct that certified independent pharmacy dispensing locations provide a Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure to each patient each time Qsymia is dispensed.
    b. My certified pharmacy will not distribute, transfer, loan, or sell Qsymia to another pharmacy or distributor.
    c. Pharmacy training of pharmacists involved with the dispensing of Qsymia has been completed and documented including the need to provide a Medication Guide and the *Risk of Birth Defects with Qsymia* each time Qsymia is dispensed in order to comply with the REMS requirements.
    d. My certified pharmacy is subject to, and must comply with, survey requirements to ensure that the REMS requirements are being following to maintain pharmacy certification under the Qsymia REMS. Failure to comply may result in decertification.
4. I will oversee compliance with the Qsymia REMS program requirements.

Authorized Pharmacy Representative to complete (all fields required):

First Name _____ **Last Name** _____ _____

Phone Number _____ **Fax** _____

Email _____

Address _____ **City** _____

State _____ **Zip Code** _____

Pharmacy Name _____

Pharmacy DEA# _____ **Pharmacy NCPDP ID** _____

Pharmacy NPI _____ **Pharmacy Store # (optional)** _____

Signature _____ **Date** _____
Authorized Pharmacy Representative

Please fax completed form to the Qsymia REMS Pharmacy Support Center (1-855-302-6699).

Once this form is successfully processed, your pharmacy will receive a confirmation from VIVUS and you will be considered certified and permitted to order, receive, and dispense Qsymia.

If you have any questions or require additional information, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698.

Qsymia® Risk Evaluation and Mitigation Strategy (REMS)

Pharmacy Enrollment Form - Mail Order Pharmacy

Because of the teratogenic risk associated with Qsymia therapy, Qsymia is available through a limited program under the REMS. Under the Qsymia REMS, only certified pharmacies may distribute Qsymia. I understand that my certified mail order pharmacy must comply with the program requirements for certified pharmacies and the terms contained in this form. As the Authorized Pharmacy Representative, I acknowledge that:

1. I have reviewed and successfully completed the Qsymia Pharmacy Training Program and the knowledge assessment questions.
2. I understand the risks associated with Qsymia.
3. I understand and agree to comply with the requirements of the Qsymia REMS program for pharmacies.
    a. The pharmacy management system is in place to systematically direct that a Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure be provided to each patient each time Qsymia is dispensed.
    b. The pharmacy will not distribute, transfer, loan or sell Qsymia to another pharmacy or distributor.
    c. The pharmacists and staff involved with the dispensing of Qsymia will be trained before dispensing Qsymia about the risks associated with Qsymia and the REMS requirement to provide a Medication Guide and the *Risk of Birth Defects with Qsymia* each time Qsymia is dispensed.
    d. The pharmacy and pharmacy personnel will cooperate with pharmacy audit requirements in order to maintain pharmacy certification.
4. I will oversee compliance with the Qsymia REMS program requirements and will provide annual compliance reports back to VIVUS to assess effectiveness and comply with all audit requirements.

Reference ID: 4949210

Authorized Pharmacy Representative to complete (all fields required):

First Name _____ **Last Name** _____

Phone Number _____ **Fax** _____

Email _____

Mail Order Pharmacy Name _____

Address _____ **City** _____

State _____ **Zip Code** _____

Signature _____ **Date** _____
Authorized Pharmacy Representative

Please fax this completed form to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699.

If you have any questions or require additional information, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698.

Qsymia® (phentermine and topiramate extended-release) capsules CIV Pharmacy Training Program

Overview

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for Qsymia to ensure the benefits of Qsymia outweigh the increased risk of teratogenicity.

Purpose

The purpose of the REMS is to inform certified pharmacies and patients of reproductive potential (PRP) about the:

- Increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
- Importance of pregnancy prevention for PRP
- Need to discontinue Qsymia immediately if pregnancy occurs

Qsymia® (phentermine and topiramate extended-release) capsules CIV

Reference ID: 4949210

The Qsymia Pharmacy Training Program

Complete the Qsymia Pharmacy Certification in 2 easy steps:

1. Read through the entirety of this Pharmacy Training Program and confirm you understand the program's content by completing the knowledge assessment questions.

- For mail order pharmacies, your knowledge assessment may be completed by the Authorized Pharmacy Representative and faxed to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699
- For chain pharmacies, your knowledge assessment responses may be managed by your Authorized Pharmacy Representative. Please contact your corporate Authorized Pharmacy Representative for instructions on completing your knowledge assessment
- For independent pharmacies, your knowledge assessment may be completed and faxed to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699

2. Complete Pharmacy Enrollment Form and fax to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699.

- For mail order pharmacies, a Pharmacy Enrollment Form must be completed by the Authorized Representative for the mail order pharmacy organization.
- For chain pharmacies, a Pharmacy Enrollment Form must be completed by the Authorized Representative for the corporate chain organization.
- For chain pharmacy dispensing locations, a Pharmacy Enrollment Form must be completed by the Responsible Pharmacist, and can be obtained from the Authorized Representative for the corporate chain organization.
- For independent pharmacies, a Pharmacy Enrollment Form is required for the Authorized Pharmacy Representative for the dispensing pharmacy location.

The Qsymia Pharmacy Training Program

Step 1: Complete Pharmacy Training Program, Including Knowledge Assessment

These training materials are being provided to assist pharmacists with understanding the risks of Qsymia and the pharmacy requirements under the REMS. Before you are eligible to dispense Qsymia, it is important to be aware of the increased risk of teratogenicity associated with Qsymia therapy.

The information presented in this Training Program does not include a complete list of all risks and safety information on Qsymia. Before dispensing Qsymia, please read the accompanying Qsymia Prescribing Information and the *Risk of Birth Defects with Qsymia* patient brochure.

Further information is also available on the Website, **www.QsymiaREMS.com** or by calling the Qsymia REMS Pharmacy Support Center at 1-855-302-6698.

Indication and Patient Selection

Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of use:

- The effect of Qsymia on cardiovascular morbidity and mortality has not been established
- 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

Increased Risk of Teratogenicity

- Qsymia is contraindicated in pregnant patients because the use of Qsymia can cause fetal harm. Available data indicate an increase in oral clefts (cleft lip with or without cleft palate) in infants exposed to topiramate, one of the components of Qsymia, during the first trimester of pregnancy.

Increased Risk of Teratogenicity

Studies evaluating the risk of major congenital malformations and/or oral clefts with exposure to topiramate, a component of Qsymia, during pregnancy include the following:

- The North American Anti-Epileptic Drug (NAAED) Pregnancy Registry (2010) analysis
- A retrospective evaluation of a Wolters Kluwer claims database (January 2003-December 2010 from the United States)
- A retrospective observational study using 4 U.S. electronic healthcare database (FORTRESS)
- A case-control study using data from the Slone Epidemiology Center Birth Defects Study (BDS, 1997-2009) and the Centers for Disease Control's (CDC's) National Birth Defects Prevention Study (NBDPS, 1996-2007).

The NAAED Pregnancy Registry suggested an estimated increase in risk for oral clefts of 9.60 (95% CI 3.60 – 25.70).

An increase in oral clefts was observed with all dose strengths of topiramate.

Summary of Data on Teratogenicity Risk

SUMMARY OF STUDIES EVALUATING THE ASSOCIATION OF TOPIRAMATE IN UTERO EXPOSURE AND ORAL CLEFTS

EPIDEMIOLOGY STUDY	ORAL CLEFTS		MAJOR CONGENITAL MALFORMATIONS	
	PREVALENCE/ ODDS RATIO	95% CI	ESTIMATED INCREASE IN RISK	95% CI
WOLTERS KLUWER[a]	1.47	0.36-6.06	1.12	0.81-1.55
FORTRESS[a]	2.22	0.78-6.36	1.21	0.99-1.47
SLONE/CDC	5.36	1.49-20.07	1.01	0.37-3.22

[a]Sponsored by the maker of Qsymia® (phentermine and topiramate extended-release) capsules CIV.

CI=confidence interval.

These data show that exposure to topiramate, a component of Qsymia, in pregnancy is associated with a 2- to 5-fold increase in risk of oral clefts.

Other data sources confirm the increased risk of oral clefts with topiramate exposure during pregnancy (ie, animal studies and Adverse Event Reporting System data).

Qsymia® (phentermine and topiramate extended-release) capsules CIV

Reference ID: 4949210

Counseling Provided by HCPs for Patients of Reproductive Potential*

Qsymia can cause fetal harm.

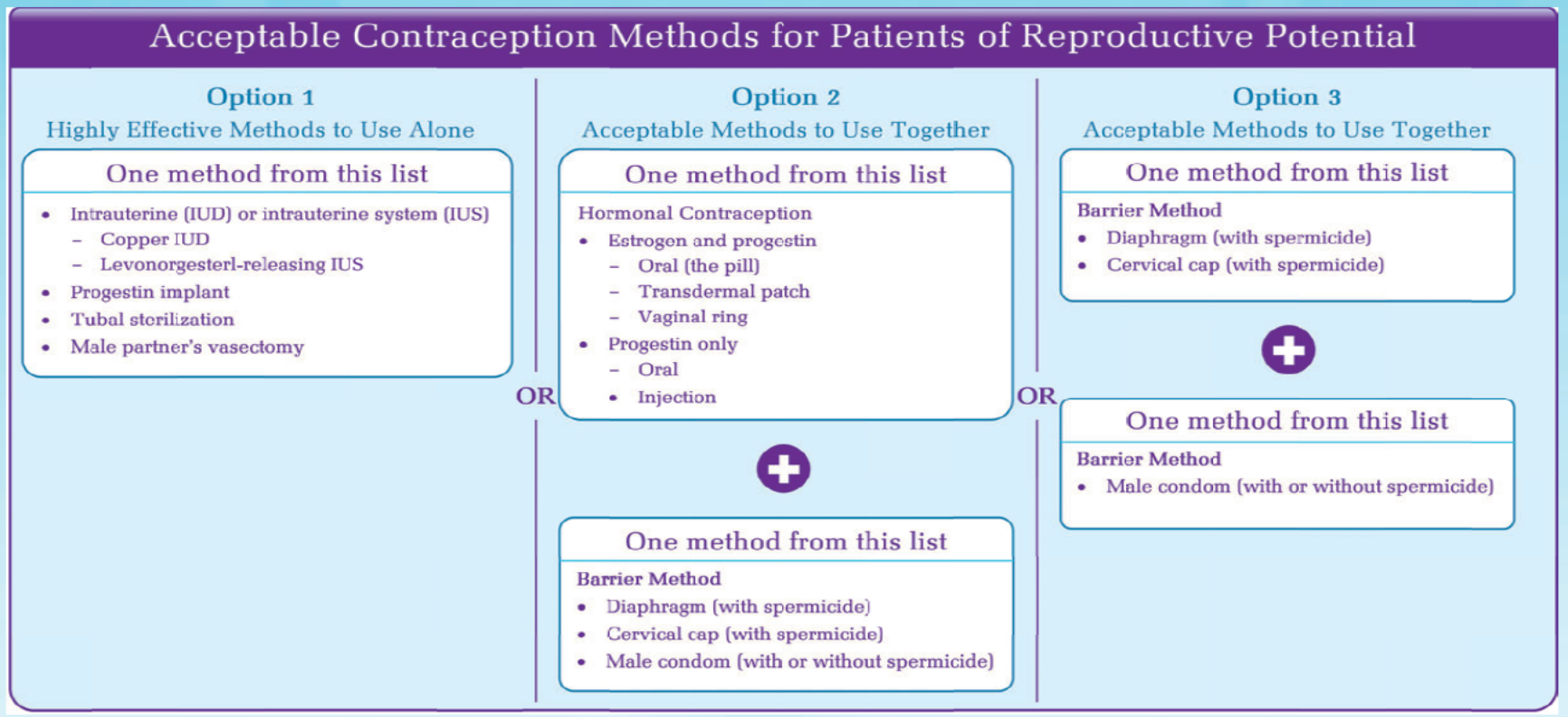
Advise patients of reproductive potential that labeling recommends:

- Pregnancy testing prior to beginning Qsymia and monthly during therapy. Specific documentation of the result is not required at the pharmacy level
- Use of effective contraception consistently during Qsymia therapy because Qsymia can cause certain kinds of birth defects (oral clefts). Even patients who believe they cannot become pregnant should use effective contraception while taking Qsymia due to the potential for increased fertility associated with weight loss
- If a patient becomes pregnant while taking Qsymia, Qsymia should be discontinued immediately and the patient advised to notify their healthcare provider

*Patients of reproductive potential are patients who have NOT had a hysterectomy, bilateral oophorectomy, or medically documented spontaneous ovarian failure, and have not gone through menopause. Menopause should be clinically confirmed by an individual's healthcare provider.

Advise nursing mothers not to use Qsymia. Qsymia may be present in human milk because topiramate and amphetamines (phentermine has pharmacologic activity and a chemical structure similar to amphetamines) are excreted in human milk.

Acceptable Contraceptive Methods for Patients of Reproductive Potential (con't)



Patient education and other support tools are available at
www.QsymiaREMS.com

Qsymia® (phentermine and topiramate extended-release) capsules [C]

Reference ID: 4949210

Qsymia Is Only Dispensed Through Certified Pharmacies

Under the REMS, Qsymia is only available through certified pharmacies. To become a certified pharmacy, an authorized or responsible pharmacy representative must agree to:

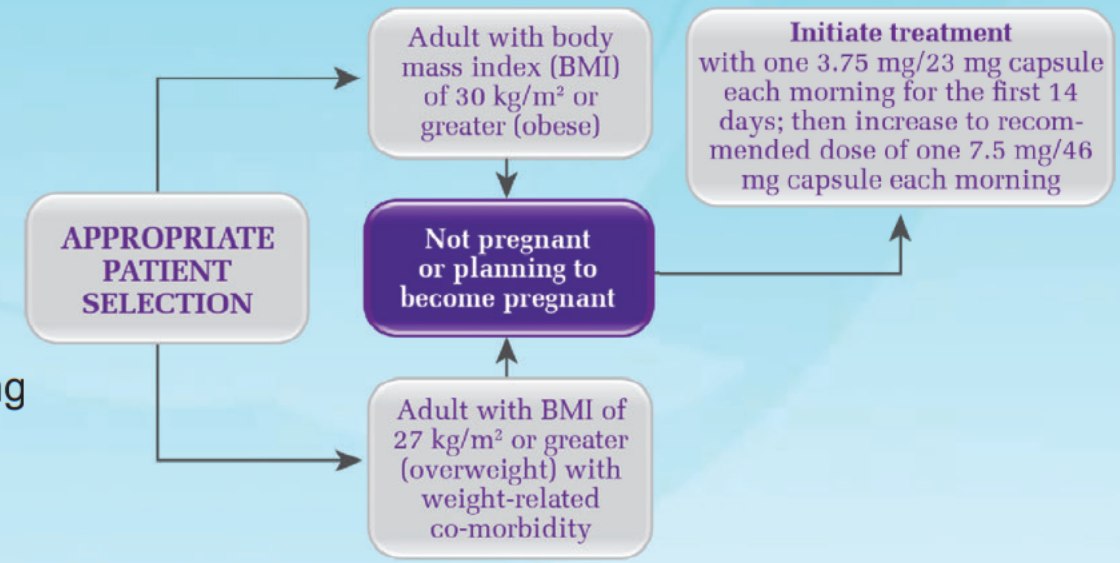
1. Refrain from reselling or transferring Qsymia to another pharmacy or distributor
2. Train pharmacists and staff involved with the dispensing of Qsymia about the risks associated with Qsymia and the REMS requirement to provide a Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure each time Qsymia is dispensed
3. To be subject to and comply with audits (as applicable) to evaluate understanding of the risks associated with the use of Qsymia, and compliance with the requirements of the REMS

The list of certified pharmacies will be updated within 1-2 business days after a new pharmacy is certified and eligible to dispense. Prescribers and patients will be able to use a "Certified Pharmacy Locator" tool to identify certified pharmacies in their area and can be found at www.QsymiaREMS.com.

Please note that Qsymia is not available outside this network of certified pharmacies.

Prescriber Dosing and Management Algorithm

- Prescriber needs to initiate treatment by providing ***two*** prescriptions
  - one for 3.75 mg/23 mg 1 po qAM #14 (no refills) and
  - a second for 7.5 mg/46 mg 1 po qAM #30 (with refills potentially)

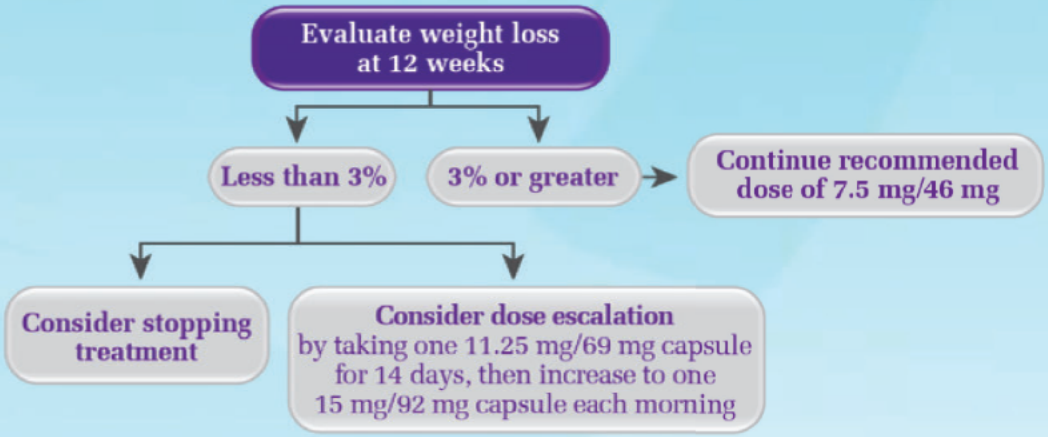


Only one Qsymia capsule to be taken daily, using sequence for dose escalations noted above.

Please see Qsymia Prescribing Information.

Prescriber Dosing and Management Algorithm (con't)

- Prescriber needs to escalate dose by providing ***two*** prescriptions
  - one for 11.25 mg/69 mg 1 po qAM #14 (no refills) and
  - a second for 15 mg/92 mg 1 po qAM #30 (with refills potentially)



Only one Qsymia capsule to be taken daily, using sequence for dose escalations noted above.

Please see Qsymia Prescribing Information.

Patient Counseling

1. The Medication Guide and patient brochure contain important information that patients should read and become familiar with.

2. Qsymia should be taken in the morning, with or without food.

3. Avoid taking Qsymia in the evening due to the possibility of insomnia.

4. Advise patients to start treatment with Qsymia as follows:
   - Take one Qsymia 3.75 mg/23 mg capsule once each morning for the first 14 days
   - After the first 14 days, take one Qsymia 7.5 mg/46 mg capsule once each morning
   - Do not take Qsymia 3.75 mg/23 mg and Qsymia 7.5/46 mg capsules together

5. If an increase in Qsymia dose is prescribed, advise patients to increase the dose of Qsymia as follows:
   - Take one Qsymia 11.25 mg/69 mg capsule once each morning for 14 days
   - After the 14 days, take one Qsymia 15 mg/92 mg capsule once each morning
   - Do not take Qsymia 11.25 mg/69 mg and Qsymia 15 mg/92 mg capsules together

6. Advise patients NOT to stop Qsymia without talking with their HCP as serious side effects such as seizures may occur.

Important Safety Information

Qsymia® is contraindicated in pregnancy; in patients with glaucoma; in hyperthyroidism; in patients receiving treatment or within 14 days following treatment with monoamine oxidase inhibitors (MAOIs); or in patients with hypersensitivity or idiosyncrasy to sympathomimetic amines, topiramate, or any of the inactive ingredients in Qsymia.

Qsymia can cause fetal harm. Patients of reproductive potential should have a pregnancy test before treatment and monthly thereafter and use effective contraception consistently during Qsymia therapy. If a patient becomes pregnant while taking Qsymia, treatment should be discontinued immediately, and the patient should be informed of the potential hazard to the fetus.

Qsymia can cause an increase in resting heart rate. Regular measurement of resting heart rate is recommended for all patients taking Qsymia, especially patients with cardiac or cerebrovascular disease or when initiating or increasing the dose of Qsymia. Qsymia has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and therefore use is not recommended.

Topiramate, a component of Qsymia, increases the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Qsymia in patients who experience suicidal thoughts or behaviors. Qsymia is not recommended in patients with a history of suicidal attempts or active suicidal ideation.

Acute angle closure glaucoma has been reported in patients treated with topiramate, a component of Qsymia. Symptoms include acute onset of decreased visual acuity and/or eye pain. Symptoms typically occur within 1 month of initiating treatment with topiramate but may occur at any time during therapy. The primary treatment to reverse symptoms is immediate discontinuation of Qsymia.

Reference ID: 4949210

Important Safety Information (con't)

Qsymia can cause mood disorders, including depression and anxiety, as well as insomnia. Qsymia can cause cognitive dysfunction (e.g., impairment of concentration/attention, difficulty with memory, and speech or language problems, particularly word-finding difficulties). Since Qsymia has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles.

Hyperchloremic, non-anion gap, metabolic acidosis has been reported in patients treated with Qsymia. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Qsymia.

Qsymia can cause an increase in serum creatinine. If persistent elevations in creatinine occur while taking Qsymia, reduce the dose or discontinue Qsymia.

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). Qsymia has not been studied in combination with insulin. A reduction in the dose of antidiabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia.

The most commonly observed side effects in controlled clinical studies, 5% or greater and at least 1.5 times placebo, include paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

To report negative side effects, contact VIVUS LLC., at 1-888-998-4887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Additional Information and Tools

Additional information and tools can be found at **www.QsymiaREMS.com**.

- Risk of Birth Defects with Qsymia patient brochure
- Qsymia Prescribing Information
- Qsymia Medication Guide

For more information on Qsymia or the Qsymia REMS Program contact VIVUS Medical Information at 1-888-998-4887 or visit www.QsymiaREMS.com.

For more information on Pharmacy Certification, contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698.

Qsymia® (phentermine and topiramate extended-release) capsules CIII

Reference ID: 4949210

Completing the Program

Step 2: Confirm Understanding Through Knowledge Assessment

Confirm that you've read through and understand the Qsymia Pharmacy Training Program by completing the knowledge assessment questions.

Knowledge assessment questions: (choose True or False)	True	False
1. The major risk for patients of reproductive potential (PRP) is that of teratogenicity (birth defects), specifically the risk of cleft lip with or without cleft palate.	☐	☐
2. If a patient thinks they are pregnant, they should continue taking Qsymia until the pregnancy is confirmed.	☐	☐
3. The Qsymia REMS specifically prohibits certified pharmacies from reselling or redistributing Qsymia to another pharmacy or distributor.	☐	☐
4. The Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* should be dispensed only with new prescriptions.	☐	☐
5. Qsymia is not available outside the network of certified pharmacies.	☐	☐

Pharmacy Knowledge Assessment

1 of 5

True or False:
The major risk for patients of reproductive potential (PRP) is that of teratogenicity (birth defects), specifically the risk of cleft lip with or without cleft palate.

Qsymia® (phentermine and topiramate extended-release) capsules CIII

Reference ID: 4949210

Pharmacy Knowledge Assessment (con't)

1 of 5

True or False:
The major risk for patients of reproductive potential (PRP) is that of teratogenicity (birth defects), specifically the risk of cleft lip with or without cleft palate.

The correct answer is TRUE.

Topiramate, a component of Qsymia® (phentermine and topiramate extended-release) capsules CIV, has been associated with an increased risk of cleft lip with or without cleft palate in infants exposed to topiramate during the first trimester of pregnancy.

Qsymia® (phentermine and topiramate extended-release) capsules CIV

Reference ID: 4949210

Pharmacy Knowledge Assessment (con't)

2 of 5

True or False:
If a patient thinks they are pregnant, they should continue taking Qsymia until the pregnancy is confirmed.

Qsymia® (phentermine and topiramate extended-release) capsules CIII

Reference ID: 4949210

Pharmacy Knowledge Assessment (con't)

2 of 5

True or False:
If a patient thinks they are pregnant, they should continue taking Qsymia until the pregnancy is confirmed.

The correct answer is FALSE.

If a patient believes they might be pregnant, they should stop taking Qsymia immediately and contact their healthcare provider.

Pharmacy Knowledge Assessment (con't)

3 of 5

True or False:
The Qsymia REMS specifically prohibits certified pharmacies from reselling or redistributing Qsymia to another pharmacy or distributor.

Qsymia® (phentermine and topiramate extended-release) capsules CIII

Reference ID: 4949210

Pharmacy Knowledge Assessment (con't)

3 of 5

True or False:
The Qsymia REMS specifically prohibits certified pharmacies from reselling or redistributing Qsymia to another pharmacy or distributor.

The correct answer is TRUE.

To be eligible for initial certification, and to maintain ongoing certification, pharmacies must agree and abide by the requirement that they not resell or redistribute Qsymia to any other pharmacy, distributor, physician's office, or any other location. Qsymia is only available through the network of certified pharmacies.

Pharmacy Knowledge Assessment (con't)

4 of 5

True or False:
The Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* should be dispensed only with new prescriptions.

Qsymia® (phentermine and topiramate extended-release) capsules CIII

Reference ID: 4949210

Pharmacy Knowledge Assessment (con't)

4 of 5

True or False:
The Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* should be dispensed only with new prescriptions.

The correct answer is FALSE.

A Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* must be provided to the patient each time Qsymia is dispensed, whether the prescription being filled is a new prescription or a refill. This is a condition of certification, and systems must be in place to remind the pharmacist of this requirement each time they dispense a prescription for Qsymia.

Pharmacy Knowledge Assessment (con't)

5 of 5

True or False:
Qsymia is not available outside the network of certified pharmacies.

Qsymia® (phentermine and topiramate extended-release) capsules CIV

Reference ID: 4949210

Pharmacy Knowledge Assessment (con't)

5 of 5

True or False:
Qsymia is not available outside the network of certified pharmacies.

The correct answer is TRUE.

Qsymia is only available through the network of certified pharmacies.

Qsymia® (phentermine and topiramate extended-release) capsules CIII

Reference ID: 4949210

Qsymia® (phentermine and topiramate extended-release) capsules CIV Pharmacy Training Program

Overview

The Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for Qsymia to ensure the benefits of Qsymia outweigh the increased risk of teratogenicity.

Purpose

The purpose of the REMS is to inform certified pharmacies and patients of reproductive potential (PRP) about the:

- Increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
- Importance of pregnancy prevention for PRP
- Need to discontinue Qsymia immediately if pregnancy occurs

Complete the Qsymia Pharmacy Certification in 2 easy steps:

1. Read through the entirety of this Pharmacy Training Program and confirm you understand the program's content by completing the knowledge assessment questions.

- For mail order pharmacies, your knowledge assessment responses may be completed by the Authorized Pharmacy Representative and faxed to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699.
- For chain pharmacies, your knowledge assessment responses may be managed by your Authorized Pharmacy Representative. Please contact your corporate Authorized Pharmacy Representative for instructions on completing your knowledge assessment
- For independent pharmacies, your knowledge assessment may be completed and faxed to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699.
  - Complete Pharmacy Enrollment Form and fax to VIVUS at 1-855-302-6699

- For mail order pharmacies, a Pharmacy Enrollment Form must be completed by the Authorized Representative for the mail order pharmacy organization.
- For chain pharmacies, a Pharmacy Enrollment Form must be completed by the Authorized Representative for the corporate chain organization.
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Step 1: Complete Pharmacy Training Program Including Knowledge Assessment

These training materials are being provided to assist pharmacists with understanding the risks of Qsymia and the pharmacy requirements under the REMS. Before you are eligible to dispense Qsymia, it is important to be aware o the increased risk of teratogenicity associated with Qsymia therapy.

The information presented in this Training Program does not include a complete list of all risks and safety information on Qsymia. Before dispensing Qsymia, please read the accompanying Qsymia Prescribing Information, Qsymia Medication Guide, and the *Risk of Birth Defects with Qsymia* patient brochure.

Further information is also available on the Website, www.QsymiaREMS.com or by calling the Qsymia REMS Pharmacy Support Center at 1-855-302-6698.

Indication and Patient Selection

Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese), or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of use:

- The effect of Qsymia on cardiovascular morbidity and mortality has not been established
- 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

Increased Risk of Teratogenicity

- Qsymia is contraindicated in pregnant patients because the use of Qsymia can cause fetal harm. Available data indicate an increase in oral clefts (cleft lip with or without cleft palate) in infants exposed to topiramate, one of the components of Qsymia, during the first trimester of pregnancy.

Studies evaluating the risk of major congenital malformations and/or oral clefts with exposure to topiramate, a component of Qsymia, during pregnancy include the following:

- The North American Anti-Epileptic Drug (NAAED) Pregnancy Registry (2010) analysis
- A retrospective evaluation of a Wolters Kluwer claims database (January 2003-December 2010 from the United States)
- A retrospective observational study using 4 U.S. electronic healthcare databases (FORTRESS)
- A case-control study using data from the Slone Epidemiology Center Birth Defects Study (BDS, 1997-2009) and the Centers for Disease Control's (CDC's) National Birth Defects Prevention Study (NBDPS, 1996-2007)

The NAAED Pregnancy Registry suggested an estimated increase in risk for oral clefts of 9.60 (95% CI 3.60 – 25.70).

An increase in oral clefts was observed with all dose strengths of topiramate.

SUMMARY OF STUDIES EVALUATING THE ASSOCIATION OF TOPIRAMATE IN UTERO EXPOSURE AND ORAL CLEFTS

EPIDEMIOLOGY STUDY	ORAL CLEFTS		MAJOR CONGENITAL MALFORMATIONS	
	PREVALENCE/ ODDS RATIO	95% CI	ESTIMATED INCREASE IN RISK	95% CI
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[a]Sponsored by the maker of Qsymia® (phentermine and topiramate extended-release) capsules CIV.

CI=confidence interval.

These data show that exposure to topiramate, a component of Qsymia, in pregnancy is associated with a 2- to 5-fold increase in risk of oral clefts.

Other data sources confirm the increased risk of oral clefts with topiramate exposure during pregnancy (i.e., animal studies and Adverse Event Reporting System data for tompiramate).

Patient Counseling

Counseling Provided by HCPs for Patients of Reproductive Potential*

Qsymia can cause fetal harm.

Advise patients of reproductive potential that labeling recommends:

- Pregnancy testing prior to beginning Qsymia and monthly during therapy. Specific documentation of the result is not required at the pharmacy level.
- Use of effective contraception consistently during Qsymia therapy because Qsymia can cause certain kinds of birth defects (oral clefts). Even patients who believe they cannot become pregnant should use effective contraception while taking Qsymia due to the potential for increased fertility associated with weight loss.
- If a patient becomes pregnant while taking Qsymia, Qsymia should be discontinued immediately and the patient advised to notify their healthcare provider.

Acceptable Contraception Methods for Patients of Reproductive Potential

Option 1 – Highly Effective Methods to Use Alone

One method from this list

- Intrauterine (IUD) or intrauterine system (IUS)
  - Copper IUD
  - Levonorgesterl-releasing IUS
- Progestin implant
- Tubal sterilization
- Male partner's vasectomy

OR

Option 2 – Acceptable Methods to Use Together

One method from this list	+	One method from this list
Hormonal Contraception • Estrogen and progestin – Oral (the pill) – Transdermal patch – Vaginal ring • Progestin only – Oral – Injection		Barrier Method • Diaphragm (with spermicide) • Cervical cap (with spermicide) • Male condom (with or without spermicide)

OR

Option 3 – Acceptable Methods to Use Together

One method from this list	+	One method from this list
Barrier Method • Diaphragm (with spermicide) • Cervical cap (with spermicide)		Barrier Method • Male condom (with or without spermicide)

*Patients of reproductive potential are patients who have NOT had a hysterectomy, bilateral oophorectomy, or medically documented spontaneous ovarian failure, and have not gone through menopause. Menopause should be clinically confirmed by an individual's healthcare provider.

Advise nursing mothers not to use Qsymia. Qsymia may be present in human milk because topiramate and amphetamines (phentermine has pharmacologic activity and a chemical structure similar to amphetamines) are excreted in human milk.

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1) Refrain from reselling or transferring Qsymia to another pharmacy or distributor.
2) Train pharmacists and staff involved with the dispensing of Qsymia about the risks associated with Qsymia and the REMS requirement to provide a Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure each time Qsymia is dispensed.
3) To be subject to and comply with audits (as applicable) to evaluate understanding of the risks associated with the use of Qsymia, and compliance with the requirements of the REMS.

The list of certified pharmacies will be updated within 1-2 business days after a new pharmacy is certified and eligible to dispense. Prescribers and patients will be able to use a "Certified Pharmacy Locator" tool to identify certified pharmacies in their area and can be found at www.QsymiaREMS.com.

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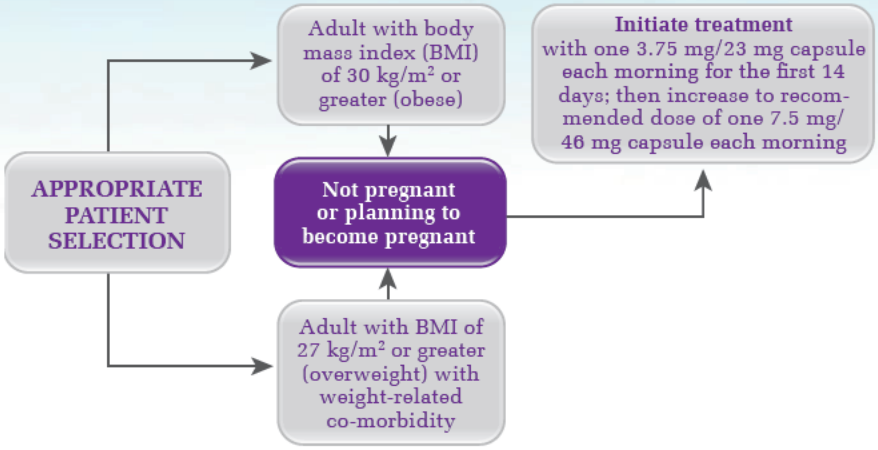
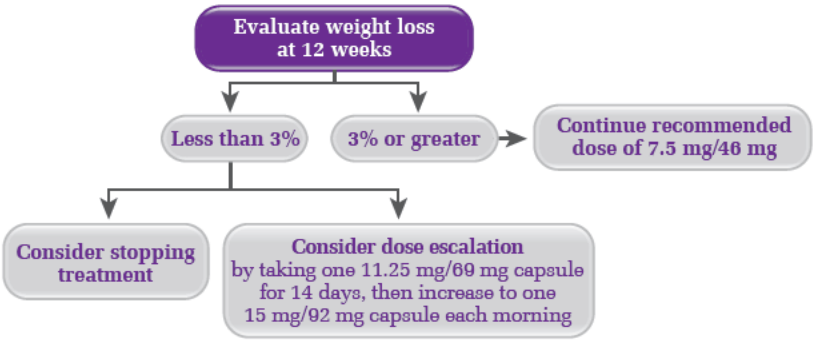
Prescriber Dosing and Management Algorithm

- Prescriber needs to initiate treatment by providing ***two*** prescriptions
  - one for 3.75 mg/23 mg 1 po qAM #14 (no refills) and
  - a second for 7.5 mg/46 mg 1 po qAM #30 (with refills potentially)
- Prescriber needs to escalate dose by providing ***two*** prescriptions
  - one for 11.25 mg/69 mg 1 po qAM #14 (no refills) and
  - a second for 15 mg/92 mg 1 po qAM #30 (with refills potentially)

Only one Qsymia capsule to be taken daily using sequence for dose escalations noted above.

Please see Qsymia Prescribing Information.





www.QsymiaREMS.com

Reference ID: 4949210

Patient Counseling

1. The Medication Guide and patient brochure contain important information that patients should read become familiar with.
2. Qsymia should be taken in the morning, with or without food.
3. Avoid taking Qsymia in the evening due to the possibility of insomnia.
4. Advise patients to start treatment with Qsymia as follows:
   - Take one Qsymia 3.75 mg/23 mg capsule once each morning for the first 14 days
   - After the first 14 days, take one Qsymia 7.5 mg/46 mg capsule once each morning
   - Do not take Qsymia 3.75 mg/23 mg and Qsymia 7.5/46 mg capsules together
5. If an increase in Qsymia dose is prescribed, advise patients to increase the dose of Qsymia as follows:
   - Take one Qsymia 11.25 mg/69 mg capsule once each morning for 14 days
   - After the 14 days, take one Qsymia 15 mg/92 mg capsule once each morning
   - Do not take Qsymia 11.25 mg/69 mg and Qsymia 15 mg/92 mg capsules together
6. Advise patients NOT to stop Qsymia without talking with their HCP as serious side effects such as seizures may occur.

Important Safety Information

Qsymia® is contraindicated in pregnancy; in patients with glaucoma; in hyperthyroidism; in patients receiving treatment or within 14 days following treatment with monoamine oxidase inhibitors (MAOIs); or in patients with hypersensitivity or idiosyncrasy to sympathomimetic amines, topiramate, or any of the inactive ingredients in Qsymia.

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Qsymia can cause an increase in resting heart rate. Regular measurement of resting heart rate is recommended for all patients taking Qsymia, especially patients with cardiac or cerebrovascular disease or when initiating or increasing the dose of Qsymia. Qsymia has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and therefore use is not recommended.

Topiramate, a component of Qsymia, increases the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Qsymia in patients who experience suicidal thoughts or behaviors. Qsymia is not recommended in patients with a history of suicidal attempts or active suicidal ideation.

Acute angle closure glaucoma has been reported in patients treated with topiramate, a component of Qsymia. Symptoms include acute onset of decreased visual acuity and/or eye pain. Symptoms typically occur within 1 month of initiating treatment with topiramate but may occur at any time during therapy. The primary treatment to reverse symptoms is immediate discontinuation of Qsymia.

Qsymia can cause mood disorders, including depression and anxiety, as well as insomnia. Qsymia can cause cognitive dysfunction (e.g., impairment of concentration/attention, difficulty with memory, and speech or language problems, particularly word-finding difficulties). Since Qsymia has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles.

Hyperchloremic, non-anion gap, metabolic acidosis has been reported in patients treated with Qsymia. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing Qsymia.

Qsymia can cause an increase in serum creatinine. If persistent elevations in creatinine occur while taking Qsymia, reduce the dose or discontinue Qsymia.

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin and/or insulin secretagogues (e.g., sulfonylureas). Qsymia has not been studied in combination with insulin. A reduction in the dose of antidiabetic medications which are non-glucose-dependent should be considered to mitigate the risk of hypoglycemia.

The most commonly observed side effects in controlled clinical studies, 5% or greater and at least 1.5 times placebo, include paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

To report negative side effects, contact VIVUS LLC at 1-888-998-4887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Additional Information and Tools

Additional information and tools can be found at www.QsymiaREMS.com

- ***Risk of Birth Defects with Qsymia*** **patient brochure**
- **Qsymia Prescribing Information**
- **Qsymia Medication Guide**

For more information on Qsymia or the Qsymia REMS Program, contact VIVUS at 1-888-998-4887 or visit www.QsymiaREMS.com.

For more information on Pharmacy Certification, contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Completing the Program

Confirm that you've read through and understand the Qsymia Pharmacy Training Program by completing the knowledge assessment questions.

Knowledge assessment questions (choose True or False):

		True	False
1	The major risk for patients of reproductive potential (PRP) is that of teratogenicity (birth defects), specifically the risk of cleft lip with or without cleft palate.	☐	☐
2	If a patient thinks they are pregnant, they should continue taking Qsymia until the pregnancy is confirmed.	☐	☐
3	The Qsymia REMS specifically prohibits certified pharmacies from reselling or redistributing Qsymia to another pharmacy or distributor.	☐	☐
4	The Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* should be dispensed only with new prescriptions.	☐	☐
5	Qsymia is not available outside the network of certified pharmacies.	☐	☐

1 of 5

True or False: The major risk for patients of reproductive potential (PRP) is that of teratogenicity (birth defects), specifically the risk of cleft lip with or without cleft palate.

The correct answer is TRUE.

Topiramate, a component of Qsymia® (phentermine and topiramate extended-release) capsules CIV, has been associated with an increased risk of cleft lip with or without cleft palate in infants exposed to topiramate during the first trimester of pregnancy.

2 of 5

True or False: If a patient thinks they are pregnant, they should continue taking Qsymia until the pregnancy is confirmed.

The correct answer is FALSE.

If a patient believes they might be pregnant, they should stop taking Qsymia immediately and contact their healthcare provider.

3 of 5

True or False: The Qsymia REMS specifically prohibits certified pharmacies from reselling or redistributing Qsymia to another pharmacy or distributor.

The correct answer is TRUE.

To be eligible for initial certification, and to maintain ongoing certification, pharmacies must agree and abide by the requirement that they not resell or redistribute Qsymia to any other pharmacy, distributor, physician's office, or any other location. Qsymia is only available through the network of certified pharmacies.

4 of 5

True or False: The Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* should be dispensed only with new prescriptions.

The correct answer is FALSE.

A Medication Guide and patient brochure *Risk of Birth Defects with Qsymia* must be provided to the patient each time Qsymia is dispensed, whether the prescription being filled is a new prescription or a refill. This is a condition of certification, and systems must be in place to remind the pharmacist of this requirement each time they dispense a prescription for Qsymia.

5 of 5

True or False: Qsymia is not available outside the network of certified pharmacies.

The correct answer is TRUE.

Qsymia is only available through the network of certified pharmacies.

MEDICATION GUIDE

QSYMIA® (Kyoo sim ee' uh)

(phentermine and topiramate extended-release)

capsules, for oral use, CIV

Read this Medication Guide before you start taking Qsymia and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about Qsymia, talk to your healthcare provider or pharmacist.

What is the most important information I should know about Qsymia?

Qsymia can cause serious side effects, including:

- **Birth defects (cleft lip and cleft palate).** If you take Qsymia during pregnancy, your baby has a higher risk for birth defects called cleft lip and cleft palate. These defects can begin early in pregnancy, even before you know you are pregnant.

  Patients who are pregnant must not take Qsymia.

  Patients who can become pregnant should:

  1. Have a pregnancy test before taking Qsymia and every month while taking Qsymia.
  2. Use effective birth control (contraception) consistently while taking Qsymia. Talk to your healthcare provider about how to prevent pregnancy.

  If you become pregnant while taking Qsymia, stop taking Qsymia immediately and tell your healthcare provider right away. Healthcare providers and patients should report all cases of pregnancy to:

  - FDA MedWatch at 1-800-FDA-1088, and

  Because of the risk for birth defects (cleft lip and cleft palate), Qsymia is available through a restricted program called the Qsymia Risk Evaluation and Mitigation Strategy (REMS). Qsymia is only available through certified pharmacies that participate in the Qsymia REMS program. Your healthcare provider can give you information about how to find a certified pharmacy. For more information, go to www.QsymiaREMS.com or call 1-888-998-4887
- **Increases in heart rate.** Qsymia can increase your heart rate at rest. Your healthcare provider should check your heart rate while you take Qsymia. Tell your healthcare provider if you experience, while at rest, a racing or pounding feeling in your chest lasting several minutes when taking Qsymia.
- **Suicidal thoughts or actions.** Topiramate, an ingredient in Qsymia, may cause you to have suicidal thoughts or actions.

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

- **Serious eye problems** which include:
  - any sudden decrease in vision, with or without eye pain and redness,
  - a blockage of fluid in the eye causing increased pressure in the eye (secondary angle closure glaucoma).

These problems can lead to permanent vision loss if not treated. Tell your healthcare provider right away if you have any new eye symptoms.

Qsymia can have other serious side effects. See **"What are the possible side effects of Qsymia?"**

What is Qsymia?

- Qsymia is a prescription medicine that contains phentermine and topiramate extended-release that may help some obese adults or some overweight adults who also have weight-related medical problems lose weight and keep the weight off.
- Qsymia should be used with a reduced calorie diet and increased physical activity.
- It is not known if Qsymia changes your risk of heart problems or stroke or of death due to heart problems or stroke.
- It is not known if Qsymia is safe and effective when taken with other prescription, over-the-counter, or herbal weight loss products.
- It is not known if Qsymia is safe and effective in children under 18 years old.

- Qsymia is a federally controlled substance (CIV) because it contains phentermine and can be abused or lead to drug dependence. Keep Qsymia in a safe place, to protect it from theft. Never give your Qsymia to anyone else, because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take Qsymia?

Do not take Qsymia if you:

- are pregnant, planning to become pregnant, or become pregnant during Qsymia treatment.
- have glaucoma.
- have thyroid problems (hyperthyroidism).
- are taking certain medicines called monoamine oxidase inhibitors (MAOIs) or have taken MAOIs in the past 14 days.
- are allergic to topiramate, sympathomimetic amines such as phentermine, or any of the ingredients in Qsymia. See the end of this Medication Guide for a complete list of ingredients in Qsymia.

What should I tell my healthcare provider before taking Qsymia?

Before taking Qsymia, tell your healthcare provider about all of your medical conditions, including if you:

- have had a heart attack or stroke.
- have or have had an abnormal heart rhythm.
- have or have had depression, mood problems, or suicidal thoughts or behavior.
- have eye problems, especially glaucoma. See "**"Who should not take Qsymia?".**
- have a history of too much acid in the blood (metabolic acidosis) or a condition that puts you at higher risk for metabolic acidosis such as
    - chronic diarrhea, surgery, a diet high in fat and low in carbohydrates (ketogenic diet), weak, brittle, or soft bones (osteomalacia, osteoporosis, osteopenia), or decreased bone density
- have type 2 diabetes and take medicine to control your blood sugar.
- have kidney problems, kidney stones, or are getting kidney dialysis.
- have liver problems.
- have seizures or convulsions (epilepsy).
- are breastfeeding or plan to breastfeed. Qsymia can pass into your breast milk and may harm your baby. You and your healthcare provider should decide if you will take Qsymia or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Qsymia taken with other medicines may affect how each medicine works and may cause side effects.

Especially tell your healthcare provider if you take:

- **Birth control pills**. Tell your healthcare provider if your menstrual bleeding changes while you are taking birth control pills that contain both estrogen and progestin (combination oral contraceptives) and Qsymia.
- **Water pills** (diuretics) such as hydrochlorothiazide (HCTZ).
- **Any medicines that impair or decrease your thinking, concentration, or muscle coordination.**
- **Carbonic anhydrase inhibitors** such as ZONEGRAN (zonisamide), DIAMOX (acetazolamide) or NEPTAZANE (methazolamide).
- **Seizure medicines** such as valproic acid (DEPAKENE or DEPAKOTE).

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine. Do not start a new medicine without talking to your healthcare provider.

How should I take Qsymia?

- Your healthcare provider should start you on a diet and exercise program when you start taking Qsymia. Stay on this program while you are taking Qsymia.
- **Do not** change your dose without talking to your healthcare provider.
- Qsymia can be taken with or without food.
- If you miss a dose of Qsymia, wait until the next morning to take your usual dose of Qsymia. **Do not** double your dose.
- **To start treatment with Qsymia**
    - Take 1 **Qsymia 3.75 mg/23 mg capsule** (Figure A) 1 time each morning for the first 14 days.
    - After taking Qsymia 3.75 mg/23 mg capsule for 14 days, then take 1 **Qsymia 7.5 mg/46 mg capsule** (Figure B) 1 time each morning.
- **After taking Qsymia for 12 weeks**
    - Your healthcare provider should either tell you to stop taking Qsymia **or** increase your dose of Qsymia if you do not lose a certain amount of weight within the **first** 12 weeks of treatment at the recommended dose.
- **If your healthcare provider increases the dose of Qsymia**
    - Take 1 **Qsymia 11.25 mg/69 mg capsule** (Figure C) 1 time each morning for 14 days.

- After taking 14 days of Qsymia 11.25 mg/69 mg capsule, then take 1 **Qsymia 15 mg/92 mg capsule** (Figure D) 1 time each morning.

- **Stopping Qsymia treatment**

Your healthcare provider should tell you to stop taking Qsymia if you have not lost a certain amount of weight after an **additional** 12 weeks of treatment on the higher dose.

Do not stop taking Qsymia without talking to your healthcare provider. **Stopping Qsymia suddenly can cause serious problems, such as seizures.** Your healthcare provider will tell you how to stop taking Qsymia slowly.

Figure A
Qsymia (3.75 mg/23 mg)
Cap and body are purple with white printing

Figure B
Qsymia (7.5 mg/46 mg)
Cap is purple with white printing and the body is yellow with black printing

Figure C
Qsymia (11.25 mg/69 mg)
Cap and body are yellow with black printing

Figure D
Qsymia (15 mg/92 mg)
Cap is yellow with black printing and the body is white with black printing

If you take too much Qsymia, call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking Qsymia?

- **Do not get pregnant while taking Qsymia.** See **"What is the most important information I should know about Qsymia."**
- **Do not drink alcohol while taking Qsymia**. Qsymia and alcohol can affect each other causing side effects such as sleepiness or dizziness.
- **Do not drive a car, operate heavy machinery, or do other dangerous activities until you know how Qsymia affects you.** Qsymia can slow your thinking and motor skills, and may affect vision.

What are the possible side effects of Qsymia?
Qsymia can cause serious side effects, including:

- See **"What is the most important information I should know about Qsymia?"** at the beginning of this Medication Guide.
- **Mood changes and trouble sleeping.** Qsymia may cause depression or mood problems, and trouble sleeping. Tell your healthcare provider if symptoms occur.

- **Concentration, memory, and speech difficulties.** Qsymia may affect how you think and cause confusion, problems with concentration, attention, memory, or speech. Tell your healthcare provider if symptoms occur.
- **Increases of acid in bloodstream (metabolic acidosis).** If left untreated, metabolic acidosis can cause brittle or soft bones (osteoporosis, osteomalacia, osteopenia), kidney stones, can slow the rate of growth in children, and may possibly harm your baby if you are pregnant. Metabolic acidosis can happen with or without symptoms. Sometimes people with metabolic acidosis will:
  feel tired
  not feel hungry (loss of appetite)
  feel changes in heartbeat
  have trouble thinking clearly

  Your healthcare provider should do a blood test to measure the level of acid in your blood before and during your treatment with Qsymia.
- **Low blood sugar (hypoglycemia) in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus.** Weight loss can cause low blood sugar in people with type 2 diabetes mellitus who also take medicines used to treat type 2 diabetes mellitus (such as insulin or sulfonylureas). You should check your blood sugar before you start taking Qsymia and while you take Qsymia.
- **Possible seizures if you stop taking Qsymia too fast.** Seizures may happen in people who may or may not have had seizures in the past if you stop Qsymia too fast. Your healthcare provider will tell you how to stop taking Qsymia slowly.
- **Kidney stones.** Drink plenty of fluids when taking Qsymia to help decrease your chances of getting kidney stones. If you get severe side or back pain, or blood in your urine, call your healthcare provider.
- **Decreased sweating and increased body temperature (fever).** People should be watched for signs of decreased sweating and fever, especially in hot temperatures. Some people may need to be hospitalized for this condition.

Common side effects of Qsymia include:

- numbness or tingling in the hands, arms, feet, or face (paraesthesia)
- dizziness
- change in the way foods taste or loss of taste (dysgeusia)
- trouble sleeping (insomnia)
- constipation
- dry mouth

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all of the possible side effects of Qsymia. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You can also report side effects to VIVUS at 1-888-998-4887.

How should I store Qsymia?

- Store Qsymia at room temperature between 59°F to 77°F (15°C to 25°C).

Keep Qsymia and all medicines out of the reach of children.

General Information about the safe and effective use of Qsymia.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Qsymia for a condition for which it was not prescribed. Do not give Qsymia to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about Qsymia. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Qsymia that is written for health professionals.

For more information, go to www.QsymiaREMS.com or call 1-888-998-4887.

What are the ingredients in Qsymia?

Active Ingredient: phentermine hydrochloride and topiramate extended-release

Inactive Ingredients: methylcellulose, sucrose, starch, microcrystalline cellulose, ethylcellulose, povidone, gelatin, talc, titanium dioxide, FD&C Blue #1, FD&C Red #3, FD&C Yellow #5 and #6, and pharmaceutical black and white inks.

VIVUS LLC

900 East Hamilton Avenue, Suite 550,
Campbell, CA 95008

US Patent Numbers: 7,056,890; 7,553,818; 7,659,256; 7,674,776; 8,580,298; 8,580,299; 8,895,057; 8,895,058; 9,011,905; and 9,011,906

Qsymia is a registered trademark of VIVUS LLC

ME-03-001-08

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Qsymia®
(phentermine and topiramate extended-release) capsules C

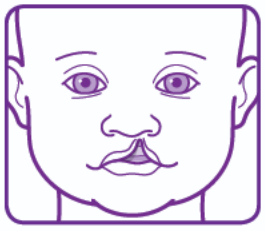
Risk of Birth Defects with Qsymia®

(phentermine and topiramate extended-release) capsules CIV

Please read the following important safety information about the use of Qsymia in patients who can become pregnant.

You are considered a patient who can become pregnant if this applies to you:

- You have never had a hysterectomy (uterus removed), surgical sterilization (tubes tied), or both ovaries removed and
- You have not gone through menopause. Menopause should be confirmed by your healthcare provider



cleft lip

1) Qsymia can increase the risk of a birth defect called cleft lip or cleft palate (as shown in the picture)

- These defects happen early in pregnancy, sometimes even before you know you are pregnant

2) You should have a pregnancy test taken BEFORE starting treatment with Qsymia and EVERY MONTH after that while on treatment

- Talk with your healthcare provider about when and where to have your pregnancy testing performed
- If you have a positive pregnancy test, or you miss a period, or you think you might be pregnant, you must not start Qsymia, or if you are already taking Qsymia, you should stop it immediately and tell your healthcare provider right away

3) While you are on Qsymia therapy, you should use effective birth control methods every time you have sex with a male

- Certain birth control methods are effective when used alone. Other birth control methods are not as effective by themselves, so you should use a second method of birth control

Talk to your healthcare provider to help decide what birth control options are best for you.

Please see the chart on the back to review birth control options.

Qsymia®
(phentermine and topiramate extended-release) capsules C

Your Birth Control Options

OPTION 1
Highly Effective Methods to Use Alone

One method from this list

- Intrauterine device (IUD) or intrauterine system (IUS)
  - Copper IUD
  - Levonorgestrel-releasing IUS
- Progestin implant
- Tubal sterilization
- Male partner's vasectomy

OR

OPTION 2
Acceptable Methods to Use Together

One method from this list

Hormonal Contraception

- Estrogen and progestin
  - Oral (the pill)
  - Transdermal patch
  - Vaginal ring
- Progestin only
  - Oral
  - Injection

+

One method from this list

Barrier Method

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)
- Male condom (with or without spermicide)

OR

OPTION 3
Acceptable Methods to Use Together

One method from this list

Barrier Method

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)

+

One method from this list

Barrier Method

- Male condom (with or without spermicide)

Keep in mind, even the most effective birth control methods can fail. But your chances of getting pregnant are lowest if the methods you choose are always used correctly and every time you have sex.

Please read the accompanying Qsymia® Medication Guide as it contains additional important safety information about your treatment. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about Qsymia, talk to your healthcare provider or pharmacist, contact VIVUS Medical Information at 1-888-998-4887, or visit the Web site www.QsymiaREMS.com.

VIVUS

Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. The FDA has required a REMS for Qsymia.

The purpose of the Qsymia REMS is to inform certified pharmacies and patients of reproductive potential about the:

- Increased risk of congenital malformation, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
- Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia
- Need to discontinue Qsymia immediately if pregnancy occurs

Full Prescribing Information

Materials for Patients

Risk of Birth Defects with Qsymia patient brochure

Medication Guide

These materials can be downloaded and printed.

Dispensed to Patients Through Certified Pharmacies

Qsymia is available only through certified pharmacies. Click Here to learn more.

For additional information, please contact VIVUS Medical Information at: 1-888-998-4887

Welcome to the Qsymia® (phentermine and topiramate extended-release) capsules CIV Pharmacy Training Program

The Qsymia REMS Pharmacy Training Program is designed to provide pharmacists with an understanding of the risks of Qsymia and the Pharmacy requirements under the REMS.

Enrollment in the Qsymia REMS Pharmacy Program is necessary to dispense Qsymia.

Before you can enroll in the Qsymia REMS Pharmacy Program, you must:

1. Review the Qsymia REMS Pharmacy Training Program
2. Successfully complete the Knowledge Assessment questions
3. Sign the acknowledgement statement on the enrollment form

Start the Qsymia Pharmacy Training Program

The Qsymia REMS Pharmacy Training Program and Knowledge Assessment questions can be downloaded using this link.

For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Indication and Patient Selection

Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m2 or greater (obese), 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

Limitations of use:

- The effect of Qsymia on cardiovascular morbidity and mortality has not been established
- 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

Next

For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Increased Risk of Teratogenicity

- Qsymia is contraind cated in pregnant patients because the use of Qsymia can cause fetal harm. Available data indicate an increase in oral clefts (cleft lip w th or w thout cleft palate) in infants exposed to topiramate, one of the components of Qsymia, during the first trimester of pregnancy

Studies evaluating the risk of major congenital malformations and/or oral clefts with exposure to topiramate, a component of Qsymia, during pregnancy include the following:

- The North American Anti-Epileptic Drug (NAAED) Pregnancy Registry (2010) analysis
- A retrospective evaluat on of a Wolters Kluwer claims database (January 2003-December 2010 from the United States)
- A retrospective observat onal study using 4 U.S. electronic healthcare databases (FORTRESS)
- A case-control study using data from the Slone Ep demiology Center Birth Defects Study (BDS, 1997-2009) and the Centers for Disease Control's (CDC's) National Birth Defects Prevention Study (NBDPS, 1996-2007)

The NAAED Pregnancy Registry suggested an estimated increase in risk for oral clefts of 9.60 (95% CI 3.60 - 25.70).

An increase in oral clefts was observed with all dose strengths of topiramate.**Limitations of use:**

- The effect of Qsymia on cardiovascular morb dity and mortality has not been established
- 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

SUMMARY OF STUDIES EVALUATING
THE ASSOCIATION OF TOPIRAMATE IN
UTERO EXPOSURE AND ORAL CLEFTS

EPIDEMIOLOGY STUDY	ORAL CLEFTS		MAJOR CONGENITAL MALFORMATIONS	
	PREVALENCE/ ODDS RATIO	95% CI	ESTIMATED INCREASE IN RISK	95% CI
WOLTERS KLUWER[a]	1.47	0.36-6.06	1.12	0.81-1.55
FORTRESS[a]	2.22	0.78-6.36	1.21	0.99-1.47
SLONE/CDC	5.36	1.49-20.07	1.01	0.37-3.22

*Sponsored by the maker of Qsymia®
(phentermine and topiramate extended-release) capsules CIV.CI=confidence interval.

These data show that exposure to topiramate, a component of Qsymia, in pregnancy is associated with a 2- to 5-fold increase in risk of oral clefts.

Other data sources confirm the increased risk of oral clefts w th topiramate exposure during pregnancy (ie, animal studies and Adverse Event Reporting System data).

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For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Counseling Provided by HCPs for Patients of Reproductive Potential*

Qsymia can cause fetal harm.

Advise patients of reproductive potential that labeling recommends:

- Pregnancy testing pr or to beginning Qsymia and monthly during therapy. Specific documentation of the result is not required at the pharmacy level
- Use of effective contracept on consistently during Qsymia therapy because Qsymia can cause certain kinds of birth defects (oral clefts). Even patients who believe they cannot become pregnant should use effective contraception while taking Qsymia due to the potential for increased fertil ty associated with weight loss
- If a patient becomes pregnant while taking Qsymia, Qsymia should be discontinued immediately and the patient advised to notify their healthcare provider

Acceptable Contraception Methods for Patients of Reproductive Potential

Option 1
Highly Effective Methods to Use Alone

One method from this list
- Intrauterine device (IUD) or intrauterine system (IUS)
  - Copper IUD
  - Levonorgestrel-releasing IUS
- Progestin implant
- Tubal sterilization
- Male partner's vasectomy

OR

Option 2
Acceptable Methods to Use Together

One method from this list
Hormonal Contraception
- Estrogen and progestin
  - Oral (the pill)
  - Transdermal patch
  - Vaginal ring
- Progestin only
  - Oral
  - Injection

+

One method from this list
Barrier Method
- Diaphragm (with spermicide)
- Cervical cap (with spermicide)
- Male condom (with or without spermicide)

OR

Option 3
Acceptable Methods to Use Together

One method from this list
Barrier Method
- Diaphragm (with spermicide)
- Cervical cap (with spermicide)

+

One method from this list
Barrier Method
- Male condom (with or without spermicide)

*Patients of reproductive potential are patients who have NOT had a hysterectomy, bilateral oophorectomy, or med cally documented spontaneous ovarian failure, and have not gone through menopause. Menopause should be clinically confirmed by an individual's healthcare prov der.

Advise nursing mothers not to use Qsymia. Qsymia may be present in human milk because topiramate and amphetamines (phentermine has pharmacologic activity and a chemical structure similar to amphetamines) are excreted in human milk.

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For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Qsymia® (phentermine and topiramate extended-release) capsules ©

Risk Evaluation and Mitigation Strategy (REMS)

Qsymia is only dispensed through Certified Pharmacies

Under the REMS, Qsymia is only available through certified pharmacies. To become a certified pharmacy, an authorized or responsible pharmacy representative must agree to:

1. Refrain from reselling or transferring Qsymia to another pharmacy or distributor.
2. Train pharmacists and staff involved with the dispensing of Qsymia about the risks associated with Qsymia and the REMS requirement to provide a Medication Guide and Risk of Birth Defects with Qsymia patient brochure each time Qsymia is dispensed.
3. To be subject to and comply with surveys or audits (as applicable) to evaluate understanding of the risks associated with the use of Qsymia, and compliance with the requirements of the REMS.

The list of certified pharmacies will be updated within 1-2 business days after a new pharmacy is certified and eligible to dispense. Prescribers and patients will be able to use a "Certified Pharmacy Locator" tool to identify certified pharmacies in their area and can be found at www.QsymiaREMS.com

Please note that Qsymia is not available outside this network of certified pharmacies.

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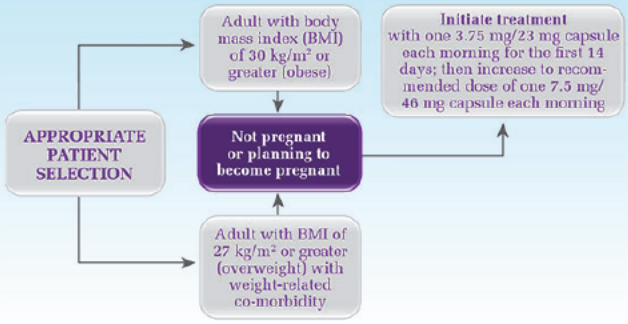
For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Dispensing Conditions

Qsymia must be dispensed with a Medication Guide and the Risk of Birth Defects with Qsymia patient brochure each time Qsymia is dispensed.

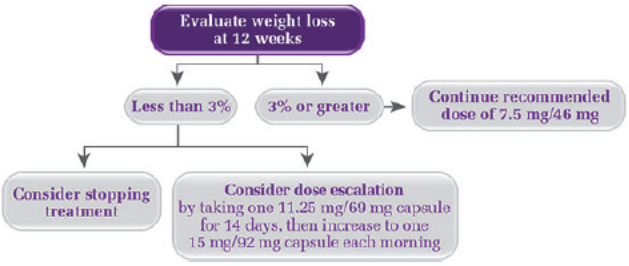


Please note that Qsymia is not available outs de this network of certified pharmacies.

Prescriber Dosing and Management Algorithm

- Prescriber needs to in tiate treatment by providing **two** prescriptions
  - one for 3.75 mg/23 mg 1 po qAM #14 (no refills) and
  - a second for 7.5 mg/46 mg 1 po qAM #30 (with refills potentially)

- Prescriber needs to escalate dose by prov ding **two** prescriptions
  - one for 11.25 mg/69 mg 1 po qAM #14 (no refills) and
  - a second for 15 mg/92 mg 1 po qAM #30 (w th refills potentially)



Only one Qsymia capsule to be taken daily, using sequence for dose escalations noted above.

Please see Qsymia Prescribing Information.

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For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Patient Counseling

1. The Medication Guide and patient brochure contain important information that patients should read and become familiar with.
2. Qsymia should be taken in the morning, with or without food.
3. Avoid taking Qsymia in the evening due to the possibility of insomnia.
4. Advise patients to start treatment with Qsymia as follows:
   - Take one Qsymia 3.75 mg/23 mg capsule once each morning for the first 14 days
   - After the first 14 days is complete, take one Qsymia 7.5 mg/46 mg capsule once each morning
   - Do not take Qsymia 3.75 mg/23 mg and Qsymia 7.5 mg/46 mg capsules together
5. If an increase in Qsymia dose is prescribed after medical evaluation, advise patients to increase the dose of Qsymia as follows:
   - Take one Qsymia 11.25 mg/69 mg capsule once each morning for 14 days
   - After the 14 days is complete, take one Qsymia 15 mg/92 mg capsule once each morning
   - Do not take Qsymia 11.25 mg/69 mg and Qsymia 15 mg/92 mg capsules together
6. Advise patients NOT to stop Qsymia without talking with their HCP as serious side effects such as seizures may occur.

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For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Important Safety Information

Qsymia is contraindicated in pregnancy; in patients with glaucoma; in hyperthyroidism; in patients receiving treatment or within 14 days following treatment w th monoamine ox dase inhib tors (MAOIs); or in patients with hypersens tivity or diosyncrasy to sympathomimet c amines, topiramate, or any of the inactive ingredients in Qsymia.

Qsymia can cause fetal harm. Patients of reproductive potential should have a pregnancy test before treatment and monthly thereafter and use effective contraception consistently during Qsymia therapy. If a patient becomes pregnant while taking Qsymia, treatment should be discontinued immediately, and the patient should be informed of the potential hazard to the fetus.
Qsymia can cause an increase in resting heart rate. Regular measurement of resting heart rate is recommended for all patients taking Qsymia, especially patients w th cardiac or cerebrovascular disease or when initiating or increasing the dose of Qsymia. Qsymia has not been studied in patients with recent or unstable cardiac or cerebrovascular disease and therefore use is not recommended.

Topiramate, a component of Qsymia, increases the risk of suicidal thoughts or behav or in patients taking these drugs for any indication. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Qsymia in patients who experience suic dal thoughts or behaviors. Qsymia is not recommended in patients with a history of suicidal attempts or active suicidal deat on.

Acute angle closure glaucoma has been reported in patients treated w th topiramate, a component of Qsymia. Symptoms include acute onset of decreased visual acuity and/or eye pain. Symptoms typically occur within 1 month of initiating treatment with topiramate but may occur at any time during therapy. The primary treatment to reverse symptoms is immediate discontinuation of Qsymia.

Qsymia can cause mood disorders, including depression, and anxiety, as well as insomnia. Qsymia can cause cogn tive dysfunction (e.g., impairment of concentration/attention, diff culty w th memory, and speech or language problems, part cularly word-finding diff culties). Since Qsymia has the potential to impair cognitive funct on, patients should be cautioned about operating hazardous machinery, including automobiles.

Hyperchloremic, non-anion gap, metabol c acidosis has been reported in patients treated with Qsymia. If metabolic acidosis develops and persists, considerat on should be given to reducing the dose or discontinuing Qsymia.

Qsymia can cause an increase in serum creatinine. If persistent elevations in creatinine occur while taking Qsymia, reduce the dose or discontinue Qsymia.

Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated w th insulin and/or insulin secretagogues (e.g., sulfonylureas). Qsymia has not been studied in combinat on w th insulin. A reduction in the dose of antidiabetic medications wh ch are non-glucose-dependent should be cons dered to mitigate the risk of hypoglycemia.

The most commonly observed s de effects in controlled clin cal studies, ≥5% and at least 1.5 times placebo, include paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

To report negative side effects, contact VIVUS LLC at 1-888-998-4887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Qsymia® (phentermine and topiramate extended-release) capsules C

Risk Evaluation and Mitigation Strategy (REMS)

Additional Information and Tools

Additional information and tools can be found at www.QsymiaREMS.com

- Risk of Birth Defects with Qsymia patient brochure
- Qsymia Prescribing Information
- Qsymia Medication Guide

For more information on Qsymia or the Qsymia REMS Pharmacy Program, or for information on Pharmacy Certification, contact Qsymia REMS Phamacy Support Center at 1-855-302-6698 or visit www.QsymiaREMS.com.

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For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

Qsymia® (phentermine and topiramate extended-release) capsules C

Risk Evaluation and Mitigation Strategy (REMS)

IMPORTANT PROGRAM UPDATE

Beginning March 25, 2022, the Qsymia REMS program and www.qsymiarems.com will be updated to accommodate the removal of the current "switch" pharmacy management system. For questions or further information please email REMS@vivus.com.

Information for Pharmacists

Qsymia is only available through certified pharmacies. Certified pharmacies must follow the requirements of the Qsymia REMS program.

Steps for pharmacy certification:

1. Successful completion of Pharmacy Training Program and knowledge assessment
2. Completion of appropriate Pharmacy Enrollment form-acknowledging and agreeing to pharmacy requirements
   - **Corporate Entity of Retail Chain Pharmacy–** Authorized Pharmacy Representative (responsible for internally coordinating and overseeing the Qsymia REMS program for their organization)
   - **Independent Retail Pharmacies–** Authorized Pharmacy Representative (responsible for internally coordinating and overseeing the Qsymia REMS program requirements)
   - **Mail Order Pharmacies–** Authorized Pharmacy Representative (responsible for internally coordinating and overseeing the Qsymia REMS program requirements)

Search for Certified Pharmacies

Search now.

Qsymia REMS Pharmacy Support Center

Phone: 1-855-302-6698

Full Prescribing Information

Materials for Pharmacists

Pharmacy Training Program

- Pharmacy Enrollment Form
- Corporate Chain Pharmacies
- Independent Pharmacies
- Mail Order Pharmacies

Medication Guide

Risk of Birth Defects with Qsymia patient brochure

These materials can be downloaded and printed.

For assistance, please contact the Qsymia REMS Pharmacy Support Center at 1-855-302-6698

VIVUS®

Qsymia® (phentermine and topiramate extended-release) capsules C

Risk Evaluation and Mitigation Strategy (REMS)

Search for a Certified Pharmacy near you

Enter your zip code to locate a certified pharmacy within 20 miles of your zip code.

Enter your ZIP Code [ ] Search

Qsymia is also available by mail order through the Qsymia Home Delivery Network:

medvantx
P: 1-844-777-9642
F: 1-844-678-8444

Walgreens
P: 1-877-487-8800
F: 1-800-332-9581

Walmart Pharmacy
P: 1-800-273-3455
F: 1-800-406-8976

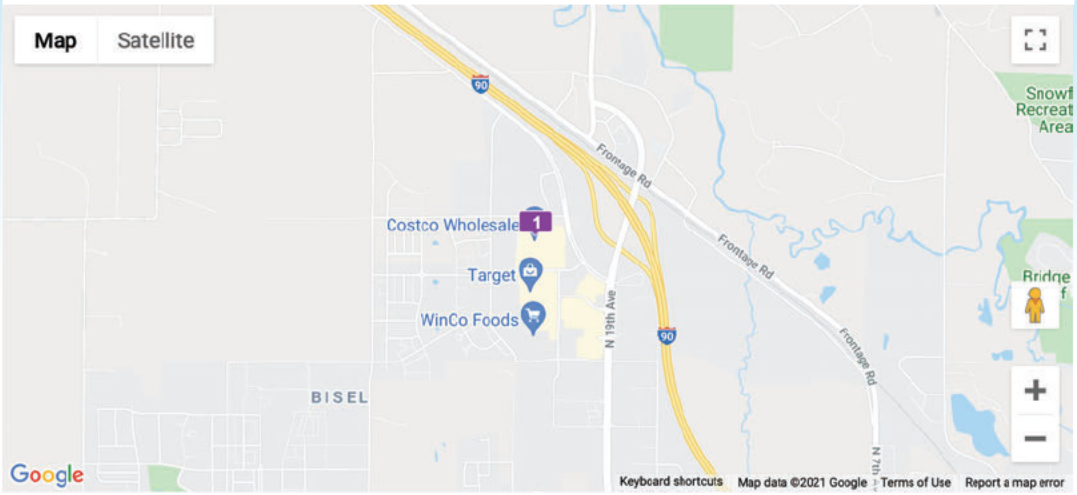
For additional information, please contact VIVUS Medical Information at: 1-888-998-4887

VIVUS®

Search for a Qsymia® Certified Pharmacy Retail Location

Sort by: (•) Distance ( ) Pharmacy Name **Search Again**

10 Pharmacies near 59718



1 **COSTCO PHARMACY** < 1 mile Directions
2505 CATRON ST
BOZEMAN, MT 59718
Phone: 406-585-7575

2 **COSTCO PHARMACY** 1.4 miles Directions
1400 N 19TH AVE
BOZEMAN, MT 59718
Phone: 406-586-3550

3 **COSTCO PHARMACY** 1.8 miles Directions
1500 N 7TH AVE
BOZEMAN, MT 59715
Phone: 406-585-8753

4 **COSTCO PHARMACY** 2.0 mile Directions
1126 N 7TH AVE
BOZEMAN, MT 59715
Phone: 406-587-8570

5 **COSTCO PHARMACY** 2.1 miles Directions
910 N. 7th Ave.
Bozeman, MT 59715
Phone: 406-587-0608

6 **COSTCO PHARMACY** 2.4 miles Directions
1525 W MAIN ST
BOZEMAN, MT 59715
Phone: 406-587-9252

7 **COSTCO PHARMACY** 2.6 miles Directions
200 S 23RD AVE
BOZEMAN, MT 59718
Phone: 406-587-8800

8 **COSTCO PHARMACY** 4.0 miles Directions
925 HIGHLAND BLVD STE 2000
BOZEMAN, MT 59715
Phone: 406-585-5030

9 **COSTCO PHARMACY** 6.9 miles Directions
6999 JACKRABBIT LN
BELGRADE, MT 59714
Phone: 406-388-1696

10 **COSTCO PHARMACY** < 24.4 miles Directions
2120 PARK ST S
LIVINGSTON, MT 59047
Phone: 406-222-1188

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For additional information, please contact VIVUS Medical Information at: 1-888-998-4887

Privacy Policy

Privacy Policy

Effective November 15, 2021

Data We Collect and Use

Information you provide during registration or in response to questionnaires

Information that may be collected automatically

How We Use Personal Data

How We Share Your Personal Data

Additional Information for California Residents

Cookies and Other Tools

Interest-based Advertising and the Advertising Option Icon

Security Policies

Your Privacy Choices and Updates

Individual Rights

Retention Period

Cross Border Transfers

Children's Privacy

Contact Us

Updates to Our Privacy Policy

Other Links & Resources

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BILLING

We use a third-party payment processor to bill you through a payment account linked to your account on the services for use of the services. The processing of payments will be subject to the terms, conditions and privacy policies of the payment processor in addition to this agreement. We are not responsible for errors by the payment processor. By choosing to use the services, you agree to pay us, through the payment processor, all charges at the prices then in effect for any use of such services in accordance with the applicable payment terms and you authorize us, through the payments processor, to charge your chosen payment provider (your "Payment Method"). You agree to make payments using that selected Payment Method. We reserve the right to correct any errors or mistakes that it makes even if it has already requested or received payment.

The terms of your payment will be based on your Payment Method and may be determined by agreements between you and the financial institution, credit card issuer or other provider of your chosen Payment Method. If not, through the payment processor, do not receive payment from you, you agree to pay all amounts due upon demand.

Other Links & Resources

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Qsymia®
(phentermine and topiramate extended-release) capsules CIV

Risk of Birth Defects with Qsymia®
(phentermine and topiramate extended-release) capsules CIV

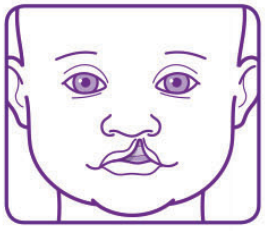
Please read the following important safety information about the use of Qsymia in patients who can become pregnant.

You are considered a patient who can become pregnant if this applies to you:

- You have never had a hysterectomy (uterus removed), surgical sterilization (tubes tied), or both ovaries removed and
- You have not gone through menopause. Menopause should be confirmed by your healthcare provider

1) Qsymia can increase the risk of a birth defect called cleft lip or cleft palate (as shown in the picture)

- These defects happen early in pregnancy, sometimes even before you know you are pregnant



cleft lip

2) You should have a pregnancy test taken BEFORE starting treatment with Qsymia and EVERY MONTH after that while on treatment

- Talk with your healthcare provider about when and where to have your pregnancy testing performed
- If you have a positive pregnancy test, or you miss a period, or you think you might be pregnant, you must not start Qsymia, or if you are already taking Qsymia, you should stop it immediately and tell your healthcare provider right away

3) While you are on Qsymia therapy, you should use effective birth control methods every time you have sex with a male

- Certain birth control methods are effective when used alone. Other birth control methods are not as effective by themselves, so you should use a second method of birth control

Talk to your healthcare provider to help decide what birth control options are best for you.

Please see the chart on the back to review birth control options.

Qsymia®
(phentermine and topiramate extended-release) capsules [C]

Your Birth Control Options

OPTION 1
Highly Effective Methods to Use Alone

One method from this list

- Intrauterine device (IUD) or intrauterine system (IUS)
  - Copper IUD
  - Levonorgestrel-releasing IUS
- Progestin implant
- Tubal sterilization
- Male partner's vasectomy

OR

OPTION 2
Acceptable Methods to Use Together

One method from this list

Hormonal Contraception

- Estrogen and progestin
  - Oral (the pill)
  - Transdermal patch
  - Vaginal ring
- Progestin only
  - Oral
  - Injection

+

One method from this list

Barrier Method

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)
- Male condom (with or without spermicide)

OR

OPTION 3
Acceptable Methods to Use Together

One method from this list

Barrier Method

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)

+

One method from this list

Barrier Method

- Male condom (with or without spermicide)

Keep in mind, even the most effective birth control methods can fail. But your chances of getting pregnant are lowest if the methods you choose are always used correctly and every time you have sex.

Please read the accompanying Qsymia® Medication Guide as it contains additional important safety information about your treatment. This information does not take the place of talking to your healthcare provider about your medical condition or treatment. If you have any questions about Qsymia, talk to your healthcare provider or pharmacist, contact VIVUS Medical Information at 1-888-998-4887, or visit the Web site www.QsymiaREMS.com.

VIVUS®

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONIKA A HOUSTOUN
03/08/2022 11:48:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022580Orig1s020

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	022580
Supplement Number	Supplement-20 (sequence 0589), amended (sequence 0607, 0608, 0610, and 0613)
Date Received	July 30, 2021, December 22, 2021, January 6, 2022, January 21, 2022, email correspondence January 27, 2022 and February 18, 2022
OSE RCM #	2021-1502
Reviewer Name(s)	Ingrid N. Chapman, PharmD, BCPS[a] Kate Oswell, MA, Health Communications Analyst
Team Leader	Naomi Boston, PharmD
Associate Director of REMS Design and Evaluation	Laura Zendel, PharmD, BCPS
Review Completion Date	March 1, 2022
Subject	Review of proposed Major REMS Modification
Established Name	phentermine and topiramate extended-release
Trade Name	Qsymia
Name of Applicant	Vivus, LLC
Therapeutic Class	Anorectic and antiepileptic
Formulation(s)	Capsules (phentermine and topiramate extended-release) for oral administration in the following dosages: 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg

[a] At the time of the completion of this review Dr. Chapman was on extended leave from the Agency.

Table of Contents

EXECUTIVE SUMMARY

This is a review of the proposed modification to the Risk Evaluation and Mitigation Strategy (REMS) for Qsymia (phentermine and topiramate extended-release), NDA 022580/S-020, submitted by Vivus LLC on July 30, 2021, and amended December 22, 2021, January 6, 2022, January 21, 2022, January 27, 2022 and February 18, 2022.

Qsymia was approved with a REMS on July 17, 2012. Qsymia is a combination of phentermine, a sympathomimetic amine anorectic, and topiramate extended-release, an antiepileptic drug, indicated as 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: 30 kg/m2 or greater (obese) 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. The REMS for Qsymia is to mitigate the risk of congenital malformations, specifically orofacial clefts.

The most recent REMS modification was approved on March 31, 2021 to replace gender-specific language in the REMS document and REMS materials with gender-neutral language. This modification aligned the REMS document and REMS materials with changes previously made to the Qsymia prescribing information.

The REMS currently consists of a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU includes: training will be provided to healthcare providers who prescribe Qsymia and pharmacies that dispense Qsymia will be specially certified.

The Applicant's proposed modifications to the REMS include the following:

- Proposed alternative to the switch system: pharmacies would collect prescriber data and send this information to the Applicant monthly
- Identify not-yet-trained prescribers only after 30 days (stop the 60-day and 90-day escalation).
- Completion of Qsymia patient exposure reporting
- Completion of stakeholder knowledge and understanding surveys
- Completion of the Pharmacy materials distribution survey
- Pharmacy compliance reports be reduced to occur annually versus quarterly
- Convert the REMS document to conform to the FDA standardized REMS format; Draft Reference Format and Content of a REMS Document, Guidance for Industry, October 2017
- Eliminate the pharmacy enrollment form. The applicant is proposing that pharmacies will now call the Applicant's new independent pharmacy distributor to complete enrollment
- Name change: VIVUS Inc. to VIVUS LLC

In addition, the following modifications were communicated to the Applicant during the review:

- Removal of ETASU A based on data from previous assessments and surveys showing adequate knowledge on the risk of Qsymia for healthcare providers.

- [redacted] (b) (4)
- The need to keep all pharmacy enrollment forms that are applicable as part of the REMS program.

The Agency evaluated the Applicant's proposed REMS modifications along with collective data from the last 10 REMS assessment periods to evaluate the necessity for continued voluntary prescriber training (ETASU A) as a requirement in this REMS Program. Based on these data, we concluded that the voluntary training can be removed as an element of this REMS. Stakeholders, particularly prescribers who are not yet trained are aware of the risks of Qsymia, and there has not been a large uptake in the training program since the Qsymia REMS has been approved, therefore, ETASU A is not necessary to ensure safe use. Removing ETASU A would also decrease the burden of the pharmacy requirement to submit prescriber data to the Applicant monthly, however, the pharmacies would continue to ensure that the patient materials are included with each prescription. The determination to remove ETASU A was communicated to the Applicant on December 17, 2021.

The Division of Risk Management (DRM) finds the Qsymia REMS as submitted on July 30, 2021 and amended on February 18, 2022 to be acceptable. The Applicant's proposals to reduce the frequency of compliance reporting, update the REMS Document to the standardized format, and incorporate their new name, Vivus LLC in all applicable places and to remove ETASU A are acceptable.

The modified REMS will consist of a MG, ETASU (pharmacy training and certification), an implementation system, and a timetable for submission of assessments of the REMS. Because of the removal of ETASU A, the goal of the REMS is now focused on informing pharmacies and patients of the risks as pharmacies are required to dispense the MG and the patient brochure with each Qsymia prescription. The modified goal of the Qsymia REMS is to inform certified pharmacies and patients of reproductive potential about:

1. The increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy.
2. The importance of pregnancy prevention for patients of reproductive potential receiving Qsymia; and
3. The need to discontinue Qsymia immediately if pregnancy occurs.

In addition to the MG and Risk of Birth Defects with Qsymia Patient Brochure, the REMS materials will also include online and print pharmacy training modules, pharmacy enrollment forms for mail order pharmacies, corporate entities and independent retail pharmacies, and a REMS website.

There are no changes to the Timetable for submission of assessments of the REMS, and they will remain as originally approved on July 17, 2012.

The REMS Assessment Plan has been changed to remove all references to prescriber training, certification, knowledge and understanding surveys, and assessment protocols. Certified pharmacy compliance, assessments and distributor assessments will remain as part of the Assessment Plan.

1 Introduction

This is a review of the proposed modification to the REMS for Qsymia (phentermine and topiramate extended-release), NDA 022580/S-020, submitted by Vivus LLC on July 30, 2021.

The Applicant's proposed modifications to the REMS include the following:

- Proposed alternative to the switch system: pharmacies will now collect prescriber data and send this information to the Applicant monthly.
- Completion of Qsymia patient exposure reporting
- Completion of stakeholder knowledge and understanding surveys
- Completion of the Pharmacy materials distribution survey
- Identify not-yet-trained prescribers only after 30 days (stop the 60-day and 90-day escalation).
- Pharmacy compliance reports be reduced to occur annually versus quarterly.
- Convert the REMS document to conform to the FDA standardized REMS format; Draft Reference Format and Content of a REMS Document, Guidance for Industry, October 2017
- Eliminate the pharmacy enrollment form. The applicant is proposing that pharmacies will now call the Applicant's new independent pharmacy distributor to complete enrollment
- Name change: VIVUS Inc. to VIVUS LLC

2 Background

2.1 PRODUCT INFORMATION

Qsymia (phentermine and topiramate extended-release) is a combination sympathomimetic amine anorectic and antiepileptic indicated as 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:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

The recommended dosage and administration is as follows:

- phentermine 3.75 mg/topiramate 23 mg ER: one capsule by mouth daily in the morning for 14 days; then increase to
- phentermine 7.5 mg/topiramate 46 mg ER: one capsule by mouth daily in the morning
- Discontinue or escalate dose if 3% weight loss is not achieved after 12 weeks on 7.5 mg/46 mg dose.
- Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg.
- Discontinue 15 mg/92 mg dose gradually to prevent possible seizure.
- Do not exceed 7.5 mg/46 mg dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment

The serious risk associated with Qsymia for which a REMS is necessary to ensure the benefits outweigh the risks includes the increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy.

The goal of the Qsymia REMS is to inform prescribers and patients of reproductive potential about:

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

The Qsymia REMS consists of a MG, ETASU, an implementation system, and a timetable for submission of assessments. The ETASU includes training will be provided to healthcare providers who prescribe phentermine and topiramate ER; and pharmacies that dispense phentermine and topiramate ER will be specially certified.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history relevant to this review:

- 07/17/2012: The Agency approved Qsymia (phentermine and topiramate ER), NDA 022580, as 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 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) when accompanied by weight related co-morbidities such as hypertension, type 2 diabetes mellitus, or dyslipidemia.
- 07/30/2021: The Applicant submitted NDA 022580/S-020 which proposes a REMS major modification to replace the switch system, convert the REMS document format, eliminate the pharmacy enrollment forms, provide the Applicant's name change, and various changes to assessment data requirements and compliance reporting.
- (b) (4)
- 12/22/2021: The Applicant responded to the Agency's comments on 12/17/2021 regarding the REMS document and materials.

- (b) (4)
- 1/06/2022: The Applicant responded to clarifying questions regarding pharmacy operations under the modified REMS, as well as to comments on the need to keep pharmacy enrollment forms in the REMS program and to keep a pharmacy-locator link on the REMS website.
- (b) (4)
- 1/26/2022: Comments were sent to the Applicant regarding the REMS document; the time frame was updated to annual compliance reporting in the REMS document, and edits to the REMS Assessment Plan was sent to the Applicant.
- (b) (4)
- 2/11/2022: Comments sent back to the Applicant regarding the REMS Assessment Plan and minor changes on the REMS Document to align with the assessment plan.
- 2/18/2022: The Applicant responded with the final, agreed upon REMS, REMS materials, and REMS Assessment Plan.

3 Review of Proposed REMS Modifications

On July 30, 2021 the Applicant submitted a multitude of proposed REMS modifications that primarily involve changes to the operation of the Qsymia REMS due to discontinuation of the switch system, updates to the REMS document and REMS materials due to corporate restructuring, and revising the REMS document to align it with the format used in the Draft Guidance for Industry, Format and Content of a REMS Document, October 2017.[1] The summary of modifications and the Applicant's rationale for these proposed modifications are as follows:

Switch provider replacement and data collection requirements: The pharmacy management switch system was implemented; to 1) facilitate data collection of healthcare providers who prescribed Qsymia, and to target prescribers who had not taken the voluntary training provided in the Qsymia REMS that inform them of the risk of Qsymia and 2) Assure distribution of patient safety materials (MG and *Risk of Birth Defects with Qsymia* patient brochure). (b) (4) (b) (4). To replace this service, the Applicant is proposing to establish a system for pharmacies to collect Qsymia prescriber data and provide this data to Vivus monthly. The pharmacies will continue to be responsible for ensuring that the MG and *Risk of Birth Defects with Qsymia* patient brochure is dispensed with each prescription.

Qsymia patient data collection: Since the inception of the Qsymia REMS in 2012, the Applicant has been required to submit data on patient exposure to Qsymia. The Applicant reports that the majority of patients dispensed Qsymia have been greater than 46 years old, and 80% have been female. The Applicant is proposing to eliminate this assessment since these data have been consistent for the past 10 reporting cycles.

Prescriber training: The Applicant is proposing to decrease their identification and outreach of prescribers who have not taken advantage of the voluntary Qsymia prescriber training from an escalation period of 30, 60 and 90 days, to only 30 days. The Applicant cites that the additional escalation periods at 60 and then 90 days for identification and outreach of not-yet trained providers are ineffective in increasing prescriber uptake of the Qsymia prescriber training program result in only 2.3% for trained providers.

Pharmacy compliance reporting: Certified mail order and corporate entities of retail chain pharmacies are the pharmacies that dispense Qsymia. These pharmacies are required to submit compliance reports on a quarterly basis. Based on stakeholder feedback, the Applicant is proposing that the frequency of these reports be reduced to occur on an annual basis versus quarterly basis.

Qsymia assessment reporting requirements: The Applicant is proposing changes to some of the assessment reporting requirements based on proposed changes in the current REMS modification.

Pharmacy enrollment: The Applicant is proposing to eliminate pharmacy enrollment forms and have any new pharmacy call Vivus Medical Information to become certified and enrolled in the program.

Vivus corporate restructuring: The Applicant has undergone corporate restructuring as of July 15, 2021 from Vivus Inc to Vivus LLC and propose that the REMS Document and REMS materials are updated to reflect this change.

Qsymia REMS Document: The Applicant has revised the REMS document to align with the format and content of a REMS as described in the 2017 Draft Format and Content of a REMS Document, Guidance for Industry.

3.1 Current Requirements for the Approved REMS

The Applicant makes training available to prescribers online via the Qsymia REMS website and through medical liaisons during prescriber visits, professional society meetings and at medical educational venues in print and electronic format. Certified pharmacies are required to provide a MG and *Risk of Birth Defects with Qsymia* Patient Brochure with each prescription. The Applicant maintains a database of all healthcare providers who have completed the training. On monthly basis, the Applicant compares the database of trained and not-yet trained healthcare providers identified from the switch system. The Applicant provides outreach of at least 95% of not-yet trained prescribers within 30 days, and then again at 60 days and 90 days.

The Qsymia REMS Program contains the following REMS materials:

- Dear Healthcare Provider Letter
- Dear Medical Society Letter
- Healthcare Provider Counseling Tool for Females of Reproductive Potential
- Online and Print Qsymia REMS Healthcare Provider Training
- Online and Print Qsymia REMS Pharmacy Training Module
- Pharmacy Enrollment forms: Corporate Entity of Retail Chain, Independent and Mail Order
- Medication Guide
- *Risk of Birth Defects with Qsymia* Patient Brochure
- REMS Website

3.2 Removal of ETASU A

The Applicant removed ETASU A and all associated materials per the Agency's December 17, 2021 communication. The associated materials for ETASU A included:

- Online and Print Training Modules for Healthcare Providers
- Healthcare Counseling Tool for Patients of Reproductive Potential
- Prescriber Dosing and Management Checklist
- Dear Healthcare Provider Letter
- Dear Medical Society Letter

Reviewer Comment:

DRM and DDLO evaluated the Applicant's proposed REMS modifications along with collective data from the last 10 REMS assessment periods to evaluate the need for continuing to require that the applicant make prescriber training available in the Qysmia REMS. The Qsymia REMS does require the pharmacist to verify that the prescriber has completed training prior to dispensing; completion of training is

voluntary for the prescriber. Data from the last 10 assessment reporting periods has shown that less than 15% of prescribers took the training, and this number has decreased to less than 8% over the past nine reporting periods.[2] Furthermore, the Applicant reports that additional outreach of not yet trained providers after 30 days results in an uptake of 2.3% of additional trained prescribers.[1] While the 10th assessment did not include surveys, data from the 9th REMS Assessment showed that there were similarities in the knowledge of the three objectives for the risks amongst trained prescribers and not yet trained prescribers.[3] In the first objective, informing prescribers and females of reproductive potential about the increased risk of congenital malformations, specifically orofacial clefts in infants exposed to Qsymia during the first trimester of pregnancy, the overall mean score was 78%, with 89% of trained prescribers versus 77% of untrained prescribers met this objective. While the difference between trained and untrained prescribers met statistical significance, it still showed that a significant portion of untrained prescribers were knowledgeable about the increased risk of congenital malformations. In the second objective, informing prescribers and females of reproductive potential about the importance of pregnancy prevention for females of reproductive potential receiving Qsymia, the overall mean score was 98%, with 100% of trained prescribers versus 98% of untrained prescribers meeting this objective. The third objective, informing prescribers and females of reproductive potential about the need to discontinue Qsymia immediately if pregnancy occurs, the overall mean score was 94%, with 96% of trained prescribers versus 93.5% of untrained prescribers meeting this objective.

Based on these data, DRM and DDLO conclude that both trained and untrained prescribers had adequate knowledge of the risks and that the requirement for the Applicant to make training available was no longer necessary to ensure the benefits outweigh the risks of Qsymia; therefore, ETASU A can be removed as an element of this REMS. Removing ETASU A would also decrease the burden of the pharmacy requirement to submit prescriber data to the Applicant monthly, however, the pharmacies would continue to ensure that the patient materials are given with each prescription. In addition, removing ETASU A would remove the REMS materials associated with prescriber training, as well as surveys and assessment reporting for prescribers.

3.3 REMS Goals

With the removal of ETASU A, the goal of the Qsymia REMS has been changed to the following:

The goal of the Qsymia REMS is to inform certified pharmacies and patients of reproductive potential about:

1. The increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy.
2. The importance of pregnancy prevention for patients of reproductive potential receiving Qsymia.
3. The need to discontinue Qsymia immediately if pregnancy occurs.

Reviewer Comment:

The goal was changed to remove certified prescribers as ETASU A, prescriber training, was removed as an element of the REMS. Certified Pharmacies were added to the goal as the REMS now only includes ETASU B, pharmacy certification. The goal of the REMS is now focused on informing pharmacies of the

risks as it will be the pharmacy's responsibility to inform patients by dispensing the MG and the patient brochure with each Qsymia prescription.

3.4 Qsymia REMS Document:

The Applicant updated the REMS document to align with the format used in the October 2017 draft Guidance for Industry: Format and Content of a REMS.

Reviewer Comment: *The updated REMS document is acceptable. With regard to Vivus corporate restructuring, we agree with their proposed changes to update the REMS document and REMS materials with the new corporate entity name from Vivus Inc to Vivus LLC. We have no additional comments.*

3.5 REMS Requirements

3.5.1 Participant Requirements and Materials

Only the participants or their associated materials that are part of the REMS and impacted by this modification are addressed in the following sections of the review.

3.5.1.1 Pharmacies that dispense

Pharmacy Requirements: With the removal of ETASU A, the pharmacy requirements of ensuring that processes and procedures are in place to collect prescriber data, are no longer necessary and have been removed.

Reviewer Comment:

We agree with the removal of the pharmacy requirements that no longer apply due to removal of ETASU A. Pharmacies are still responsible for dispensing the MG and Patient Brochure with each Qsymia prescription. On December 30, 2021 we sent clarifying questions regarding the pharmacy operations of the proposed modified REMS Programs, including how the pharmacies will distribute the patient materials with each prescription, as this was one of the functions of the former switch system. The Applicant responded that the corporate retail pharmacies maintain the required internal programs to systemically direct that the Medication Guide and Patient Brochure be provided to patients each time that Qsymia is dispensed and have committed to comply with these Qsymia REMS program requirements. Any pharmacy that does not have the internal systems in place to commit to the REMS requirements will be required to either develop a system that will function to comply or log into the QsymiaREMS.com website while processing a Qsymia prescription to obtain those documents to distribute with Qsymia dispensing.[4]

Pharmacy enrollment forms: The following pharmacy enrollment forms have been maintained as part of the REMS:

- Corporate Entity Pharmacy Enrollment Form
- Independent Retail Pharmacy Enrollment Form
- Mail Order Pharmacy Enrollment Form

Reviewer Comment:

In the Applicant's proposal, they state they have contracted and certified an independent mail-order pharmacy (MedVantx) to distribute Qsymia, and therefore proposes to no longer utilize pharmacy enrollment forms. Instead, any new pharmacy must call Vivus Medical Information to become certified to dispense. The Applicant further states that Qsymia is available universally and all corporate and independent pharmacies enrolled in the Qsymia REMS program are certified to dispense. On December 30, 2021 we sent communication to the Applicant stating that we do not agree with removing the pharmacy enrollment forms, because these forms contain pertinent attestations that must be documented and kept on file with this ETASU REMS Program. We also inquired whether currently certified pharmacies that dispense Qsymia will have to recertify in the REMS following the proposed modification, and whether the Applicant plans to remove Qsymia from these pharmacies in order to have Qsymia only dispensed from MedVantx. On January 6, 2022, the Applicant responded, stating that the pharmacy enrollment forms for corporate entities of retail chain pharmacies and independent pharmacies will be reinstated into the REMS Program, and will be available via the Qsymia REMS website under the tab "Information for Pharmacies." The Applicant also stated that MedVantx is the certified mail order pharmacy that they have contracted to deliver Qsymia to patients, and therefore enrollment forms for these entities are no longer available.[4] Additionally, the Applicant responded that certified and compliant pharmacies will not be required to renew certification or re-train pharmacy staff, and they do not intend to prohibit currently certified and compliant pharmacies from dispensing Qsymia. MedVantx will remain as one of the options available for patients to obtain Qsymia.[4] On January 20, 2022 we communicated to the Applicant that although they have contracted with a specific mail order pharmacy, because mail order pharmacies are an option, then the mail order pharmacy form must be retained as part of the REMS. On January 21, 2022 the Applicant responded their agreement and reinstated the Mail Order Pharmacy Enrollment Form.

3.6 REMS Assessment Timetable

The timetable for submission of assessments of the REMS remains the same as that approved on July 17, 2012.

4 Supporting Document

All references to prescribing training and certification have been removed from the REMS Supporting Document due to removal of ETASU A. In addition, reference to the Applicant's current name, Vivus LLC has been incorporated in the REMS Supporting Document. The following are updates to the reporting requirements of surveys and pharmacy compliance reporting:

(b) (4)

Pharmacy compliance reporting: The Applicant states that since the approval of the Qsymia REMS in 2012, there have only been 10 occurrences of non-compliance reported; the last issue being reported in 2019. The Applicant states that feedback from pharmacies is that the reminders and frequency of these reports are burdensome. We agree with the Applicant that these pharmacy compliance reports can be reduced to annually.

5 Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval Letter.

The REMS Assessment Plan has been changed to remove all references to prescriber training, certification, knowledge and understanding surveys, and assessment protocols. Certified pharmacy compliance, assessments and distributor assessments will remain as part of the Assessment Plan.

The revised REMS Assessment Plan must include, but is not limited to, the following:

Program Implementation and Operations

Program Implementation and Operations (per reporting period and cumulatively)

1. Pharmacy Enrollment Statistics
    a. Number and type (mail order, chain, independent) of pharmacies certified
    b. Number of chain dispensing locations certified

2. REMS Compliance
    a. Number and type of pharmacy decertified and the reason for decertification
    b. Summary of annual compliance reports provided to VIVUS by corporate chains, mail order pharmacies, and contracted distributors
        i. Copy of the audit plan for each stakeholder including the criteria for non-compliance (noncompliance plan)
        ii. Number of audits expected and performed

iii. Summary report of deviations found, associated corrective and preventative actions and status of corrective actions

c. Report on the periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21CFR 208.24 and *Risk of Birth Defects with Qsymia* patient brochure

i. Pharmacist Materials Distribution Survey (beginning with the 11-year (12^{th}) REMS assessment)

1. Assessment of pharmacists' compliance with the Qsymia REMS dispensing requirements, specifically the provision of a Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure with each dispensing of Qsymia

3. Patient Demographics and Prescription Data

a. Patient Demographics

i. Unique number of patients received Qsymia stratified by gender

ii. Unique number of patients of reproductive potential receiving Qsymia stratified by age groups (12-17, 18-29, 30-39, 40-49, and $\geq$50)

iii. Average duration of Qsymia treatment among patients of reproductive potential

b. Prescription Data

i. Provide a table that includes the following for the overall population and another table for patients of reproductive potential :

1. Total number of unique patients
2. Number and percentage of total prescriptions dispensed
3. Number and percentage of total prescriptions dispensed for new and refill
4. Number and percentage of total prescriptions dispensed by dosage strength

Knowledge (per reporting period and cumulatively)

1. Patients of reproductive potential (beginning with the 11-year (12^{th}) REMS assessment)

a. Assessment of patients of reproductive potential understanding of:

i. Increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy

ii. Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia therapy

iii. Need to promptly discontinue Qsymia therapy in the event of a pregnancy

b. Assessment of the receipt, reading, and understanding by patients of reproductive potential of the Qsymia Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure

c. Assessment of patients of reproductive potential receipt of counseling about pregnancy prevention and effective contraceptive use including:

i. Counseling provider (i.e., prescriber, office nurse, pharmacist)

ii. Duration of time spent counseling

iii. Frequency of patient counseling (each visit while receiving Qsymia; first time prescribed Qsymia

2. Pharmacists (beginning with the 11-year (12th) REMS assessment)
   a. Assessment of pharmacists' understanding of:
      i. Increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
      ii. Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia therapy
      iii. Need to promptly discontinue Qsymia therapy in the event of a pregnancy
   b. Assessment of pharmacists' awareness and understanding of the need to provide a Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure with every Qsymia prescription dispensed

Health Outcomes and/or Surrogates of Health Outcomes

Periodic REMS assessment reports will include for each reporting period and cumulatively:

1. Safety Surveillance
   a. Summary of pregnancy cases associated with Qsymia, including the source of the report, pregnancy outcome, and cases of congenital malformations for each exposed pregnancy
   b. Overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy is meeting the goal or whether one or more such goals or such elements should be modified

6 Discussion

As stated above in section 3.2, DRM and DDLO recommend that ETASU A, voluntary prescriber training, be removed from the Qsymia REMS Program based on the most recent assessment reports that provide support that despite low uptake of the training by prescribers, there is adequate knowledge of the importance of pregnancy prevention, and the need to discontinue Qsymia immediately if pregnancy occurs by both trained and untrained prescribers. Collective review of the previous 10 REMS assessment periods show low uptake of prescriber training. On December 10, 2021 a meeting with the REMS Oversight Committee (ROC) was held to discuss DRM and DDLO's proposal for the removal of the voluntary ETASU A under S-020 REMS modification, and (b) (4)

(b) (4)

Pharmacies that dispense Qsymia must be specially certified (ETASU B) and dispense a MG and *Risk of Birth Defects with Qsymia* Patient Brochure with each prescription. The timetable for submission of assessments will remain at the time the REMS was originally approved.

The Qsymia REMS Program contains the following materials:

- Online and Print Pharmacy Training Program
- Pharmacy Enrollment Forms: Independent Pharmacy Enrollment Form, Corporate Entity of Retail Chain Pharmacy Enrollment Form, Mail Order Pharmacy Enrollment Form
- Medication Guide
- *Risk of Birth Defects with Qsymia* Patient Brochure
- REMS Website

The REMS Supporting Document and REMS Assessment Plan has been aligned to meet the revised changes in this REMS modification. The final REMS document and REMS Materials are appended at the end of this document. As per correspondence from the Applicant received on January 26, 2022[5], the Applicant states that there is a ribbon that appears on the REMS website that states changes to the REMS program will be forthcoming. In addition, the Applicant stated in this communication that there will be communication going to all pharmacies once this modification is approved. The Applicant also states that the REMS will be implemented with 90 days of the approval of this REMS modification.

7 Conclusions and Recommendations

DRM has reviewed the Applicant's submission of the above contents submitted on July 30, 2021, amended on December 22, 2021, January 6, 2022, January 21, 2022, January 27, 2022 and February 18, 2022 and have no further comments. DRM recommends approval of the REMS Modification for Qsymia last amended on February 18, 2022 and appended to this review.

The timetable for submission of assessments of the REMS remains the same as that approved on July 17, 2012.

The REMS Assessment Plan, as summarized in the REMS Supporting Document has been revised to be consistent with the REMS modification for Qsymia and will be included in the REMS Modification Approval Letter.

8 References

[1] Qsymia REMS modification summary and rationale for REMS Modification. Vivus LLC. July 30, 2021

[2] Boston N. Qsymia REMS Oversight Committee meeting presentation, Decmber 10, 2021

[3] Kiruthi W. Ninth year REMS Assessment Report. October 2020

[4] Qsymia NDA 022580 REMS Correspondence, submitted by Vivus LLC, January 6, 2022

[5] Email correspondence received from Vivus, Maryam Azizi to FDA , Martin White, January 26, 2022

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/s/

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