Qsymia® (phentermine and topiramate extended-release capsules) for oral use, CIV
Pharmacy Training

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

- Increased risk of embryo-fetal toxicity with major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA) in a fetus 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 3 easy steps:

1. Designate an Authorized Representative to carry out the certification process and oversee implementation and compliance with the Qsymia REMS.

2. Read through the entirety of this Qsymia REMS Pharmacy Training and confirm you understand the content by completing the Knowledge Assessment questions.
   - For dispensing locations of corporate chain pharmacies, your training and knowledge assessment will be managed by your corporate Authorized Representative. Please contact your corporate Authorized Representative for instructions on completing your training and knowledge assessment.

3. Complete the Pharmacy Enrollment Form and fax the form to the Qsymia REMS Pharmacy Support Center at 1-855-302-6699 or email the form to VivusUSREMS.sm@ppd.com.

www.QsymiaREMS.com

Complete the Qsymia Pharmacy Training

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 embryo-fetal toxicity associated with Qsymia therapy.

The information presented in this training 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:

- 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 millitus, or dyslipidemia
- Pediatric patients aged 12 years and older with BMI in the 95th percentile or greater standardized for age and sex

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 drugs, over-the-counter drugs, and herbal preparations, have not been established.

Increased Risk of Embryo-Fetal Toxicity

- Qsymia is contraindicated in pregnant patients because the use of Qsymia can cause fetal harm and weight loss offers no clear benefit to a pregnant patient.
- Available data indicate an increased risk of major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA).

Studies evaluating the risk of major congenital malformations and/or oral clefts with exposure to topiramate during the first trimester of pregnancy include the following:

- The North American Anti-Epileptic Drug (NAAED) Pregnancy Registry (2010) analysis
- 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 UK Epilepsy and Pregnancy Register

The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was 12.5 (95% Confidence Interval [CI] 5.9-26.37) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a prevalence of oral clefts among infants exposed to topiramate monotherapy (3.2%) that was 16 times higher than the background rate in the UK (0.2%). An increase in oral clefts was observed with all dose strengths of topiramate.

These data show that exposure to topiramate in pregnancy is associated with a 2- to 5-fold increase in risk of oral clefts. The FORTRESS study found an excess risk of 1.5 (95% CI = -1.1 to 4.1) oral cleft cases per 1,000 infants exposed to topiramate during the first trimester. 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 topiramate).

Small for Gestational Age

- Data from the NAAED Pregnancy Registry and population-based birth registry cohort indicate that exposure to topiramate in utero is associated with an increased risk of SGA newborns (birth weight <10th percentile).
- In the NAAED Pregnancy Registry, 19.7% of topiramate-exposed newborns were SGA compared to 7.9% of newborns exposed to a reference AED and 5.4% of newborns of mothers without epilepsy and without AED exposure.
- In the medical Birth Registry of Norway, a population-based pregnancy registry, 25% of newborns in the topiramate monotherapy exposure group were SGA compared to 9% in the comparison group unexposed to AEDs; the long-term consequences of the SGA findings are not known.

Qsymia is only dispensed through Certified Pharmacies

To become a certified pharmacy, the Authorized Representative must:

- Carry out the certification process and oversee implementation and compliance with the Qsymia REMS on behalf of the pharmacy
- Complete the Pharmacy Training
- Complete the Pharmacy Enrollment Form and submit it to the Qsymia REMS
- Train all relevant staff involved in dispensing on the risks associated with Qsymia and the requirement to provide the Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure using the Pharmacy Training
- Establish processes and procedures to provide the Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure to each patient each time the drug is dispensed

Before dispensing, all pharmacy staff must:

- Provide the patient with the Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure through the processes and procedures established as a requirement of the Qsymia REMS

At all times, all pharmacy staff must:

- Not distribute, transfer, loan, or sell Qsymia
- Maintain records of standard operating procedures, training, and providing the Medication Guide and the *Risk of Birth Defects with Qsymia* patient brochure
- Maintain and submit annual compliance reports to the Qsymia REMS
- Comply with audits carried out by VIVUS to ensure that all processes and procedures are in place and are being followed
- Have a new Authorized Representative enroll in the Qsymia REMS by completing the Qsymia REMS Pharmacy Training and the Pharmacy Enrollment Form

The list of certified pharmacies will be updated within 5 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.

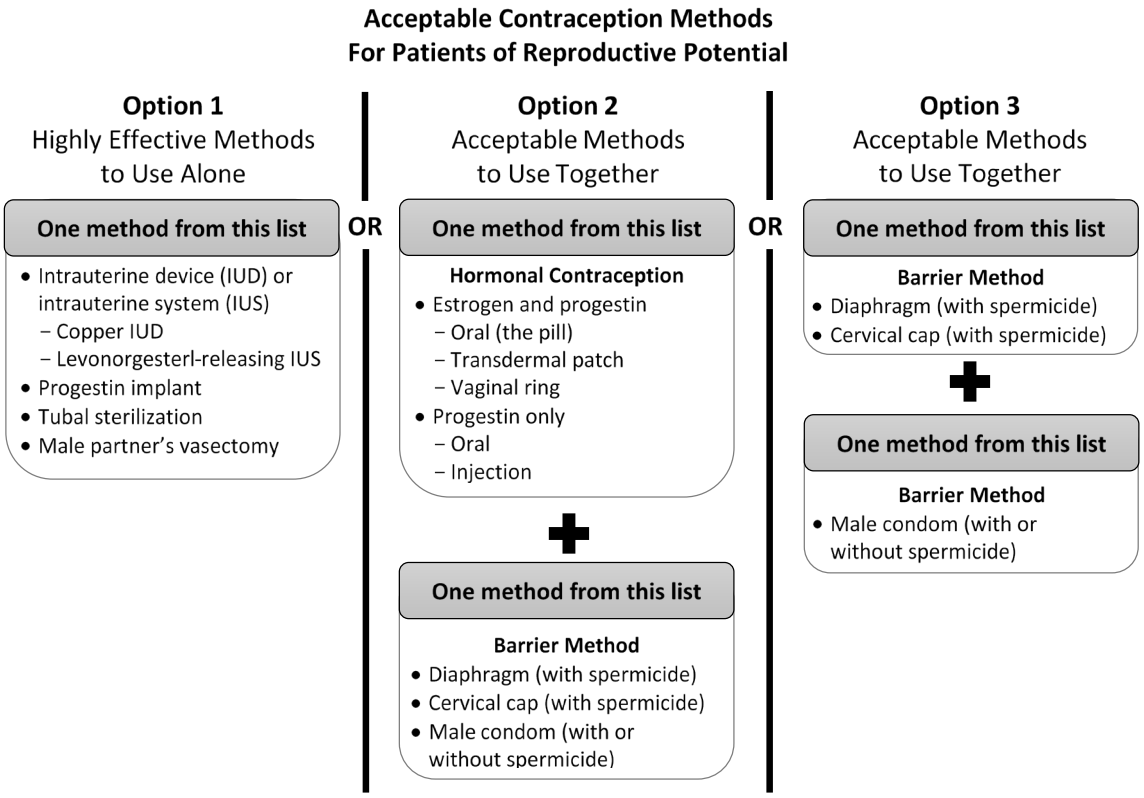
Please note that Qsymia is not available outside this network of certified pharmacies.

Counseling 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.

www.QsymiaREMS.com

Counseling for All Patients

- The Medication Guide and patient brochure contain important information that patients should read and become familiar with.
- Qsymia should be taken in the morning, with or without food.
- Avoid taking Qsymia in the evening due to the possibility of insomnia.
- 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
- 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
- Advise patients NOT to stop Qsymia without talking with their healthcare provider as serious side effects such as seizures may occur.

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 about Qsymia, contact VIVUS Medical Information at 1-888-998-4887 or visit www.Qsymia.com.

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

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 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. 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.

Visual field defects (independent of elevated intraoccular pressure) have been reported in clinical trials and in postmarketing experience in patients receiving topiramate. In clinical trials, most of these events were reversible after topiramate discontinuation.

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.

Qsymia can cause slowing of linear growth. Consider dosage reduction or discontinuation if pediatric patients are not growing or gaining height as expected.

Qsymia can cause serious skin reactions and should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related.

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.

www.QsymiaREMS.com

Confirm Understanding through the Knowledge Assessment

Completing the Qsymia REMS Pharmacy Training

Confirm that you've read through and understand the Qsymia Pharmacy Training by completing the Knowledge Assessment questions and required Pharmacy Enrollment Form.

Knowledge assessment questions (choose True or False):

		True	False
1	The major risk for patients of reproductive potential (PRP) is that of embryo-fetal toxicity, including but not limited to the risk of cleft lip with or without cleft palate and of being small for gestational age.	☐	☐
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 redistributing, transferring, loaning, or reselling 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.	☐	☐

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Pharmacy Knowledge Assessment Answers

1 of 5

True or False: The major risk for patients of reproductive potential (PRP) is that of embryo-fetal toxicity, including but limited to the risk of cleft lip with or without cleft palate and of being small for being small for gestational age.

The correct answer is TRUE.

The major risk for patients of reproductive potential (PRP) is that of embryo-fetal toxicity, including but not limited to the risk of cleft lip with or without cleft palate and of being small for gestational age.

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 redistribute, transfer, loan, or resell 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.

Pharmacy Knowledge Assessment Answers (Continued)

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.

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