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

Overview

FDA has required a Risk Evaluation and Mitigation Strategy (REMS) for Qsymia so that healthcare providers can be informed about the increased risk of teratogenicity associated with Qsymia therapy.

Purpose

The purpose of the REMS is to inform prescribers and females of reproductive potential (FRP) about the:

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

Complete the Qsymia Healthcare Provider Training Program in 2 easy steps:

1. Read through the entirety of this program.

2. Confirm you've read through and understand the program's content by faxing your completed assessment and registration information to VIVUS at 1-855-736-7329.

Step 1: Read through the entirety of the program

Before you consider prescribing 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 prescribing Qsymia, please read the accompanying Qsymia Prescribing Information and Qsymia Medication Guide.

Further information is also available on the Web site www.QsymiaREMS.com.

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 classified as **Pregnancy Category X**

- Qsymia is contraindicated in pregnant women 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 reports 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	
	PREVALENCE/ ODDS RATIO	95% CI
WOLTERS KLUWER[a]	1.47	0.36-6.06
FORTRESS[a]	2.00	0.71-5.68
SLONE/CDC	5.36	1.49-20.07

[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).

www.QsymiaREMS.com

Counseling for Females of Reproductive Potential*

Qsymia can cause fetal harm.

Advise females of reproductive potential that you recommend:

- Pregnancy testing prior to beginning Qsymia and monthly during therapy
- Use of effective contraception consistently during Qsymia therapy; even females who believe they cannot become pregnant should use effective contraception while taking Qsymia
- If you become pregnant while taking Qsymia, stop Qsymia immediately and notify your 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 Contraception Methods for Females of Reproductive Potential

OPTION 1 - Highly Effective Methods to Use Alone

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

OPTION 2 - Acceptable Methods to Use In Combination

Choose first method		Choose second method
Hormonal Contraception • Estrogen and progestin – Oral contraceptives – Transdermal patch – Vaginal ring • Progestin only – Oral – Injection	**and**	**Barrier Method** • Diaphragm (with spermicide) • Cervical cap (with spermicide) • Male condom (with or without spermicide)

OPTION 3 - Acceptable Methods to Use In Combination

Choose first method		Choose second method
Barrier Method • Diaphragm (with spermicide) • Cervical cap (with spermicide)	**and**	**Barrier Method** • Male condom (with or without spermicide)

*Females of reproductive potential are women 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.

Find patient education and other support tools at www.QsymiaREMS.com.

Dispensed to Patients Through Certified Pharmacies

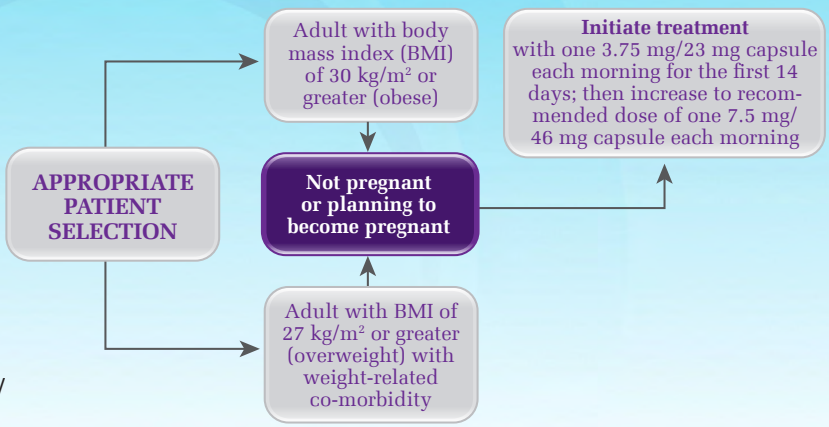
Qsymia is available only through certified pharmacies that provide a Qsymia Medication Guide and *Risk of Birth Defects with Qsymia* patient brochure with every prescription and refill as required by the REMS.

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

A full listing of the certified pharmacies can be found at: www.QsymiaREMS.com.

Dosage and Administration

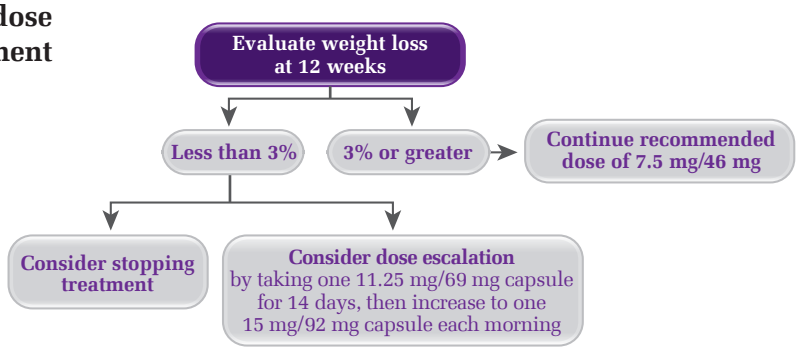
- Qsymia should be taken in the morning, with or without food
- Avoid dosing with Qsymia in the evening due to the possibility of insomnia
- For patients with moderate hepatic impairment or moderate/severe renal impairment, the Qsymia dose should not exceed the recommended dose of Qsymia 7.5 mg/46 mg (phentermine 7.5 mg/topiramate 46 mg extended-release)



- The suggested follow-up after administration of initial treatment is 2 to 8 weeks
- To initiate treatment: Start with one Qsymia 3.75 mg/23 mg (phentermine 3.75 mg/topiramate 23 mg extended-release) capsule each morning for the first 14 days; then increase to recommended dose of one Qsymia 7.5 mg/46 mg capsule each morning

Evaluate weight loss with the recommended dose of Qsymia, 7.5 mg/46 mg, at week 12 of treatment

If a patient has not lost at least 3% of baseline body weight on the recommended dose of Qsymia, 7.5 mg/46 mg, discontinue Qsymia or escalate the dose as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss at the Qsymia 7.5 mg/46 mg dose.

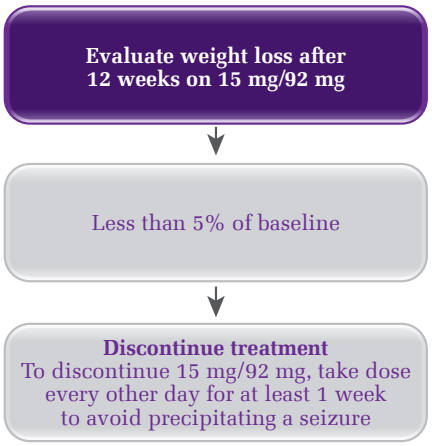


To escalate the dose: Increase to one Qsymia 11.25 mg/69 mg (phentermine 11.25 mg/topiramate 69 mg extended-release) capsule each morning for 14 days, followed by dosing one Qsymia 15 mg/92 mg (phentermine 15 mg/topiramate 92 mg extended-release) capsule each morning.

Evaluate weight loss following dose escalation to Qsymia 15 mg/92 mg after 12 weeks of treatment

If a patient has not lost at least 5% of baseline body weight on Qsymia 15 mg/92 mg, discontinue Qsymia, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

To discontinue Qsymia 15 mg/92 mg, have the patient take a dose every other day for at least 1 week prior to stopping treatment altogether, due to the possibility of precipitating a seizure with abrupt cessation of dosing.



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Step 2: Confirm you've read through and understand the Qsymia REMS by answering 5 assessment questions found on the next page.

Fax your completed assessment and registration information to VIVUS at 1-855-736-7329.

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

- **Healthcare Provider Counseling Tool for Females of Reproductive Potential**
- **Prescriber Dosing and Management Checklist**
- ***Risk of Birth Defects with Qsymia* patient brochure**
- **Dear Healthcare Provider Letter**
- **Qsymia Prescribing Information**
- **Qsymia Medication Guide Certified**
- **Certified Pharmacy Locator on www.QsymiaREMS.com**

For more information, contact VIVUS Medical Information at 1-888-998-4887 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. Females of reproductive potential should have a negative 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.

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, Inc. at 1-888-998-4887 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Healthcare Provider Training Program

Complete the following information (Please Print)

First Name | NPI #

Last Name | DEA #

Are you a: ☐ MD ☐ DO ☐ PA ☐ NP

I am a Kaiser Permanente Healthcare Provider: ☐

Date of Birth (M M D D Y Y Y Y) | Telephone (Optional)

E-mail

Address 1 | State

Address 2 | ZIP

City

Assessment Questions

To complete the process and confirm that you have been trained on the Qsymia REMS, fax this completed form to VIVUS at 1-855-736-7329.

		True	False
1	The major risk for females of reproductive potential (FRP) being treated with Qsymia is that of teratogenicity (birth defects), specifically the risk of cleft lip with or without cleft palate.	☐	☐
2	If a patient hasn't achieved 3% weight loss following 12 weeks of treatment on the recommended dose of Qsymia, 7.5 mg/46 mg (phentermine 7.5 mg/ topiramate 46 mg extended-release), discontinuation of therapy or dose escalation should be considered.	☐	☐
3	Women taking Qsymia should use contraception unless they have had infertility or trouble getting pregnant in the past.	☐	☐
4	If I don't think a patient is at risk for pregnancy, I don't need to discuss contraception.	☐	☐
5	If a woman thinks she is pregnant, she should continue taking Qsymia until the pregnancy is confirmed.	☐	☐

Please review the Qsymia Prescribing Information and Qsymia Medication Guide before prescribing.

1 of 5

True or False: The major risk for females of reproductive potential (FRP) being treated with Qsymia 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, 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 hasn't achieved 3% weight loss following 12 weeks of treatment on the recommended dose of Qsymia, 7.5 mg/46 mg (phentermine 7.5 mg/topiramate 46 mg extended-release), discontinuation of therapy or dose escalation should be considered.

The correct answer is TRUE.

If a patient has not lost at least 3% of baseline body weight on Qsymia 7.5 mg/46 mg, discontinue Qsymia or escalate the dose as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss at the Qsymia 7.5 mg/46 mg dose.

3 of 5

True or False: Women taking Qsymia should use contraception unless they have had infertility or trouble getting pregnant in the past.

The correct answer is FALSE.

ALL women, except those who have gone through menopause or undergone surgical sterilization, should be advised to consistently use effective contraception, even women who have had difficulty getting pregnant in the past.

4 of 5

True or False: If I don't think a patient is at risk for pregnancy, I don't need to discuss contraception.

The correct answer is FALSE.

It is important to have this conversation with all patients. It is important to know whether a patient is:

- Trying to get pregnant and not using contraception, in which case do not prescribe Qsymia
- Sexually active and what contraception she is using, in which case reinforce the importance of consistent use of effective contraception
- Surgically sterilized or has gone through menopause that has been clinically confirmed, in which case no contraception is required

It is important to have this conversation with all patients, so that if there is a female of reproductive potential in the house, the patient knows to keep Qsymia in a secure location and not share it with anyone else.

5 of 5

True or False: If a woman thinks she is pregnant, she should continue taking Qsymia until the pregnancy is confirmed.

The correct answer is FALSE.

If a woman believes she might be pregnant, she should stop taking Qsymia immediately and contact her healthcare provider.