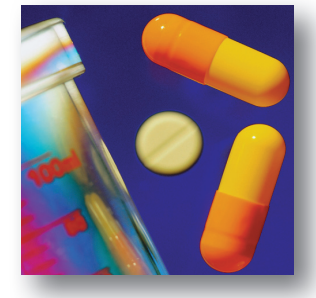

Phentermine/Topiramate Extended-Release Capsules (Qsymia) for Weight Loss

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INTRODUCTION

Obesity is a rapidly growing medical condition in the U.S. In 2010, approximately 35% of American adults were classified as obese.[1] The high prevalence of obesity has affected health care expenditures, with more than $99 billion spent in 1999, attributed to complications of the disease.[1] Obesity is associated with a higher incidence of and higher morbidity rates of several disease states (Table 1); it also has adverse effects on women's health, including complications during pregnancy and menstrual irregularities. Colon, breast, and endometrial cancer are found at higher incidence rates in obese patients, and overall mortality rates are increased by 50% to 100%.[2]

The most commonly used medications approved for weight loss include phentermine resin (Ionamin, UCB Pharma); phentermine HCl (Adipex-P, Gate), diethylpropion (Tenuate, formerly Sanofi-Aventis), and orlistat (Xenical, Roche/Genentech; nonprescription Alli, GlaxoSmithKline). Amphetamines, methylphenidate (Ritalin, CIBA/Novartis), sertraline (Zoloft, Pfizer), fluoxetine (Prozac, Eli Lilly), zonisamide (Zonegran, Elan/Eisai), and topiramate (Topamax, Janssen) have also been used in an off-label fashion for weight loss.[2–5]

Table 1 Disease States With High Morbidity Rates in Obese Patients

Hypertension
Dyslipidemia
Type-2 diabetes mellitus
Coronary heart disease
Stroke
Gallbladder disease
Osteoarthritis
Sleep apnea

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In 2010, Abbott's sibutramine (Meridia), an earlier adjunctive FDA-approved treatment, brought about weight reductions of 3.62 to 5.29 kg, but this medication was removed from the U.S. market because of associated cardiovascular events.[2–4] A meta-analysis showed that orlistat led to a weight loss of 2.2 to 3.31 kg, but diarrhea and flatulence were among the most common adverse effects.[5] Phentermine monotherapy at doses of 15 to 30 mg has been associated with a weight loss of 0.6 to 6.0 kg.

Another adjunctive agent, lorcaserin (Belviq, ADP-356, Arena/Eisai), approved in June 2012, brought about a weight loss of 4.5 to 5.8 kg during clinical trials.[5] (Lorcaserin's launch was delayed until June 2013 in order to resolve its classification as a Schedule IV substance.)

On July 17, 2012, the FDA approved a tablet combining phentermine plus extended-release topiramate (Qsymia, Vivus) for weight loss. Phentermine has been used for weight loss, and topiramate is an antiepileptic agent that has been commonly associated with weight loss as a side effect. The doses approved for weight reduction are lower than either agent when used for its current indications.

INDICATION

Qsymia (previously called Qnexa) is intended to be used as an adjunct to a reduced-calorie diet along with increased physical activity in patients with a body mass index (BMI) greater than 30 kg/m^2 or a BMI of 27 kg/m^2 or greater and who have at least one weight-related comorbidity (e.g., hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity).[6,7]

CHEMICAL AND PHYSICAL PROPERTIES

Phentermine, a centrally acting appetite suppressant, is designated chemically as α,α-dimethylphenethylamine HCl. Topiramate, an antiepileptic agent, is designated chemically as 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose sulfamate. The hard gelatin capsule contains immediate-release phentermine and extended-release topiramate beads.[6,7] Because earlier studies used the designation PHEN/TPM CR (controlled release), CR is used for the generic drug name in this article.

Clinical Pharmacology and Mechanism of Action

The exact mechanism of weight loss with phentermine is not elucidated in the FDA briefing, but from the package insert, it can be assumed that it acts as a sympathomimetic agent, which may suppress appetite as well as increase metabolism.[6–8] The mechanism by which topiramate exerts its weight loss effects is unknown. Proposed mechanisms of weight loss associated with topiramate include neurotransmitter-mediated appetite suppression and enhancement of satiety.[6,7,9]

Pharmacokinetics

Qsymia is well absorbed orally, with or without food. Peak concentrations (C_{max}) are reached in 6 hours for phentermine and 10 hours for topiramate. The half-life is 20 hours for phentermine and 65 hours for topiramate. There is a large volume of distribution.[6,7] Elimination is primarily via the urine.

Phentermine has limited hepatic metabolism through the cytochrome P450 (CYP) 3A4 isoenzyme.[6,7]

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CLINICAL EFFICACY

The EQUIP Trial (OB-302)[10]

A 56-week randomized, double-blind, parallel-group, placebo-controlled trial was conducted to compare placebo with phentermine/topiramate CR at 3.75/23 mg and 15/92 mg (Table 2). The trial consisted of a 4-week post-randomization titration period, followed by 52 weeks at the randomized treatment dose. A total of 1,267 patients were enrolled in 91 sites in the U.S. consisting of clinical practice sites, clinical trial sites, and academic centers. Patients between 18 and 70 years of age were included in the trial if they had a BMI of 35 kg/m^2 or greater, triglyceride levels of 200 mg/dL or below, blood pressure (BP) of 140/90 mm Hg or below, and a fasting plasma glucose level of 110 mg/dL or less.

Patients were permitted to take one antihyperlipidemic agent and/or up to two antihypertensive agents if required. Women of childbearing age were required to use contraception.

Exclusion criteria for EQUIP are presented in Table 3.

Patients were randomly assigned and stratified by sex in an allocation ratio of 2:1:2. This design was used to increase power of the safety analysis by having more patients receive placebo and a treatment group consisting of patients using the highest doses of phentermine/topiramate CR. All personnel were blinded to the treatment and placebo groups. Patients in each group were advised to reduce total daily caloric intake by 500 kilocalories (kcal) per day, increase water intake, and increase physical activity.

Primary outcomes were the percentage of change in body weight and the proportion of patients achieving at least a 5% weight reduction. A calibrated digital scale was used to measure changes in weight. Secondary outcomes measured included waist circumference, BP, blood glucose, triglycerides, total cholesterol, low-density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C). All measurements were performed by trained individuals and were analyzed in a single reference laboratory. Statistical analyses included an intention-to-treat and a modified intention-to-treat approach with the last observation carried forward (mITT/LOCF), and per protocol.

There were no significant differences at baseline between groups. Most of the patients were women (83%), and African-American patients represented 16% to 18% of those included. Patients in the treatment group lost significantly more weight than those receiving placebo regardless of the statistical analysis measurement used (all comparisons, $P < 0.0001$).

The percentage of weight loss in the high-dose group was significantly greater compared with low-dose phentermine/topiramate CR—1.6% for placebo, 5.1% for phentermine/topiramate 3.75/23 mg, and 10.9% for phentermine/topiramate CR 15/92 mg (mITT/LOCF). Patients achieving reductions of 5%, 10%, and 15% or more in weight were, respectively, 25.5%, 13.0%, and 5.9% for placebo; 59.1%, 27.7%, and 12.4% for 3.75/23 mg; and 83.5%, 67.7%, and 48.1% for 15/92 mg among those completing the trial (all comparisons, $P < 0.001$).

The high-dose treatment group experienced significant reductions in all secondary endpoint measurements compared with those receiving placebo. Low-dose treatment demonstrated decreases in all secondary measurements compared with placebo, although not all reductions were significant.

Doses of 3.75/23 mg and 15/92 mg were more effective than placebo over the course of 52 weeks. The authors suggest that the percentage of body weight lost was higher with the study drug than with currently marketed weight-loss medications, but they noted the need for head-to-head trials before this finding can be validated.

Table 2 Percentage of Weight Loss by Dose and Clinical Trial*

Dose	EQUIP (OB-302)	CONQUER (OB-303)	SEQUEL (OB-305)
Placebo	1.6%	1.2%	1.8%
P/T 3.75/23 mg	5.1%	—	—
P/T 7.5/46 mg	—	7.8%	9.3%
P/T 15/92 mg	10.9%	9.8%	10.5%

*An intent-to-treat/last-observation-carried-forward approach was used.
P/T = phentermine/topiramate CR.

Table 3 Exclusion Criteria in the EQUIP Trial

Weight gain or loss of more than 5 kg within past 3 months
History of eating disorders
Previous bariatric surgery
Glaucoma
Nephrolithiasis
Thyroid dysfunction
Chronic systemic glucocorticoid therapy
Bipolar disorder or psychosis history
More than one lifetime episode of major depression
Current depression of moderate or greater severity
Presence of suicidal behavior or ideation with some intent to act
Antidepressant use that had not been stable for at least 3 months
Stroke, myocardial infarction, life-threatening arrhythmia
Coronary revascularization within past 6 months
Unstable angina, congestive heart failure
Suspected or known clinically significant cardiac valvulopathy
Cholelithiasis within past 6 months
Use of any investigational medication within the last month

The CONQUER Trial (OB-303)[11]

CONQUER was a 56-week randomized, double-blind, placebo-controlled trial that compared phentermine/topiramate CR 7.5/46 mg and 15/92 mg with placebo (see Table 2). A total of 2,487 patients were enrolled in 93 centers in the U.S. Patients were included if they were between 18 and 70 years of age, had a BMI between 27 and 45 kg/m^2, and had two or more weight-related comorbidities such as hypertension, dyslipidemia, diabetes or prediabetes, or abdominal obesity (Table 4). Exclusion criteria for the trial

are presented in Table 5.

Patients were randomly assigned, in a 2:1:2 ratio, to receive placebo, phentermine/topiramate CR 7.5/46 mg, or phentermine/topiramate CR 15/92 mg. Patients were stratified by sex and diabetic status. All patients were advised to implement lifestyle changes and adhere to a total daily caloric intake reduction of 500 kcal/day. Doses were started at 3.75/23 mg and titrated to the target dose over a period of 4 weeks.

Primary outcomes were percentage of change in body weight and the proportion of patients achieving at least a 5% reduction in weight. Secondary outcomes included absolute weight loss; the proportion of patients with a weight loss of more than 10%; changes in waist circumference; and changes in BMI, BP, lipids, fasting blood glucose levels, glycosylated hemoglobin (HbA_{1c}) and fasting insulin. Statistical analysis was accomplished via mITT/LOCF. Analysis of covariance (ANCOVA) was used to test for significance.

There were no significant differences in the groups at baseline. Women made up 70% of the patients, and 86% of patients were Caucasian. Treated patients lost significantly more weight than those receiving placebo. The average percentages of body weight loss were 7.8% with phentermine/topiramate CR 7.5/46 mg and 9.8% with 15/92 mg. The percentages of patients with a weight loss of 5% or more were 21% for placebo, 62% for the 7.5/46-mg dose and 70% for the 15/92-mg dose. The treatment groups showed significant improvements in all secondary outcome measures except reductions in diastolic BP and LDL-C levels.

Phentermine/topiramate CR 7.5/46 mg and 15/92 mg brought about more weight loss compared with placebo in patients with two or more weight-related comorbidities. However, the exclusion criteria (see Table 5) might limit stratification of the results to the general population.

The SEQUEL Trial (OB-305)[12]

A randomized, double-blind, placebo-controlled, 52-week extension of the CONQUER trial was conducted to de- termine the long-term efficacy and safety of phentermine/topiramate CR (see Table 2, page 449). Eligible patients from CONQUER continued with their treatment. Patients from CONQUER were excluded from the SEQUEL extension if their BMI was 22 kg/m^2 or below at the completion of the CONQUER trial; if they had not taken the study drug for more than 4 weeks at completion of the CONQUER trial; if they developed a condition that would interfere with compliance or attainment of study measures; or if they began participating in a formal weight-loss program.

A total of 676 of 866 patients from 36 of the 93 sites were included in this extension trial. Primary outcomes were continued from CONQUER and included mean percentage weight loss and percentage of subjects achieving weight loss of 5% or more. Secondary outcomes included systolic and diastolic BP; triglycerides; HDL-C, LDL-C, and non–HDL-C levels; and HbA_{1c} in patients with type-2 diabetes mellitus. The mITT/LOCF strategy was used to analyze the data. There were no significant differences in baseline demographics among participants. The baseline groups were generally representative of the larger CONQUER trial.

Throughout the 52-week extension, treated patients showed a significantly greater percentage of weight loss compared with placebo patients. At week 108, rates of weight loss were 1.8% for placebo, 9.3% for 7.5/46 mg, and 10.7% for 15/92 mg. Significantly more treated patients lost 5%, 10%, 15%, and 20% or more weight compared with those receiving placebo.

Secondary outcomes did not differ significantly between placebo and treatment groups. However, the 15/92-mg dose led to significantly decreased triglyceride, HDL-C, and LDL-C levels compared with placebo, whereas the 7.5/46-mg dose significantly decreased only LDL-C levels compared with placebo. More patients required antihypertensive and antihyperlipidemic medications in the placebo group than in the treatment groups, although no statistical analyses were completed for this observation.

Overall, phentermine/topiramate CR 7.5/46 mg and 15/92 mg produced significant weight loss that was maintained throughout 108 weeks of treatment.

ADVERSE EFFECTS

The most common adverse drug events (ADEs) (in 10% of patients or more) that occurred significantly more often with any dose of phentermine/topiramate CR than with placebo were constipation, paresthesia, and dry mouth. Dysgeusia, insomnia, and dizziness occurred in more than 10% of patients who received the 15/92-mg dose.[6,7,10,11]

SEQUEL showed decreased rates of these common ADEs, but the trial included only patients who had taken phentermine/topiramate CR for the preceding 52 weeks. It is possible that patients who had experienced more ADEs did not continue to the SEQUEL extension; therefore, the assessment or reporting of ADEs would

Table 4 Comorbidities in the CONQUER Trial

Hypertension	
	Systolic blood pressure, 140–160 mm Hg
	Systolic blood pressure, 130–140 mm Hg in diabetes
	Diastolic blood pressure, 90–100 mm Hg
	Diastolic blood pressure 85–100 mm Hg in diabetes
	Or patient is taking at least two antihypertensive drugs
Hyperlipidemia	
	Triglycerides, 2.26–4.52 mmol/L
	Or patient is taking at least two lipid-lowering drugs
Glucose intolerance	
	Fasting blood glucose > 5.55 mmol/L
	Oral glucose tolerance test > 7.77 mmol/L
	Type-2 diabetes with only lifestyle changes or metformin (Glucophage) monotherapy
Waist circumference	
	102 cm for men
	88 cm for women

Table 5 Exclusion Criteria in the CONQUER Trial

A history of nephrolithiasis
Type-1 diabetes mellitus
Recurrent major depression
Suicidal behavior or ideation, current or past
Current substantial depressive symptoms
Current intake of antidepressant drugs

appear lower.[10,11] Other relatively common ADEs (affecting more than 5% of patients) in the low-dose treatment groups (7.5/46 mg) were dysgeusia and dizziness. Back pain and blurred vision were relatively common (affecting more than 5% of patients) with high-dose treatment (15/92 mg).[10–12]

Therapy discontinuation rates attributable to ADEs were similar between study groups in the SEQUEL trial; however, EQUIP and CONQUER showed dose-dependent discontinuation rates, as follows:[10–12]

- EQUIP: 8.4% for placebo, 11.3% for 3.75/23 mg, and 16% for 15/92 mg[10]
- CONQUER: 9%, for placebo, 12% for 7.5/46 mg, and 19% for 15/92 mg[11]

Adverse events leading to the discontinuation of treatment were similar in all three trials and included insomnia, irritability, anxiety, headache, attention disturbances, depression, dry mouth, and nephrolithiasis.[10–12] In the CONQUER trial, three cases of serious nephrolithiasis occurred in the 15/92-mg treatment group. One patient in the EQUIP trial who received phentermine/topiramate CR 3.75/23 mg experienced cholelithiasis, which resolved 1 week after treatment was interrupted.[10]

Substantial reductions in serum bicarbonate levels were observed in the CONQUER trial, affecting one placebo patient, one patient receiving 7.5/46 mg, and seven patients receiving 15/92 mg.[11] Overall, substantial serum bicarbonate reductions represented an incidence rate of less than 1% for each treatment group.[7,10–12]

In CONQUER, hypokalemia also occurred in three patients receiving placebo (fewer than 1%), in seven patients receiving 7.5/46 mg (1%), and in 30 patients receiving 15/92 mg (3%).[11] Other serious ADEs reported in EQUIP were chest pain, pulmonary embolism, and myelogenous leukemia.[10] Only myelogenous leukemia occurred in the treatment group receiving 15/92 mg and was identified after 6 months of therapy.

No increased risks of major cardiovascular severe ADEs were noted,[7,10–12] and no significant effects on the corrected QT interval were observed.[7] No significant psychomotor effects were documented. The incidence of cognitive dysfunction was low and dose-related. Of these instances, attention and memory deficits were the most commonly reported.[7] There was an association with an increased incidence of mild-to-moderate psychiatric ADEs, but serious depression and anxiety were not reported. No suicidal attempts or ideation was observed.[6,7]

DRUG INTERACTIONS

Topiramate is a mild inducer of CYP 3A4 isoenzymes and a weak inhibitor of organic anion/cation transporters. These interactions are considered minimal, and dosage adjustments should not be necessary. The effectiveness of oral contraception might be decreased during phentermine/topiramate CR therapy. Metformin (Glucophage, Bristol-Myers Squibb) levels may be increased, but dosage adjustments are not considered necessary. The antiseizure agents carbamazepine (Carbatrol, Shire) and phenytoin (Dilantin, Pfizer) may reduce plasma levels of topiramate by approximately 40% to 48%.[7] Overall, phentermine/topiramate CR has a limited drug-interaction profile.[6,7]

CONTRAINDICATIONS

Phentermine/topiramate CR (Qsymia) is contraindicated in pregnancy and is designated as a Pregnancy Category X drug.[7] However, topiramate is considered Pregnancy Category D as a single agent for migraines or epilepsy and phentermine is classified as Pregnancy Category C drug when used alone.[8,9] When used during the first trimester of pregnancy for epilepsy, topiramate resulted in an increased risk of oral cleft formation.

The potential risk for teratogenic harm to the fetus has generated the creation of a Risk Evaluation and Mitigation Strategy (REMS) system for Qsymia. Health care professionals must complete a training program, and only certain pharmacies may dispense this agent. Women of childbearing age must use contraception and must be assessed for pregnancy status on a regular basis. If pregnancy occurs, the medication must be discontinued and the patient should be counseled regarding risks to the fetus.[7]

Because of reports of acute myopia and secondary angle-closure glaucoma with phentermine, phentermine/topiramate CR is contraindicated in glaucoma. Additional contraindications include hyperthyroidism and the concomitant use of monoamine oxidase (MAO) inhibitors or their use within 14 days.[7–9]

WARNINGS

Phentermine/topiramate CR carries a warning for increased heart rate, particularly in patients with known cardiac disease. Warnings generally associated with antiepileptic drugs, such as topiramate, include an increased risk of suicidal thoughts and behaviors.[9] Changes in mood and increased anxiety have occurred with the combination, and the risk is higher in patients with a history of depression.[7] These changes usually resolve spontaneously or upon discontinuation of the product.

Because metabolic acidosis may occur with treatment,[7] it is recommended that serum electrolytes, including bicarbonate, be monitored routinely. Elevated serum creatinine levels may occur during treatment, peak at about 4 to 8 weeks, and then gradually decline; however, the elevation persists compared with baseline levels.

Dose-related cognitive impairment is associated with the use of phentermine/topiramate CR, especially with rapid dose titrations. Patients with diabetes who lose weight while taking antidiabetic medications have an increased risk of hypoglycemia.[7]

DOSAGE AND ADMINISTRATION

The initial dose of phentermine/topiramate CR for adults is 3.75/23 mg daily for 14 days. The dose should then be increased to 7.5/46 mg daily for 90 days. If a higher dose is needed after 90 days, the dose can be increased to 11.25/69 mg daily for 14 days, followed by 15/92 mg daily thereafter.[7]

The maximum recommended dose in patients with renal impairment is 7.5/46 mg daily. Although phentermine levels are increased in those with mild-to-moderate hepatic impairment, doses above 7.5/46 mg/day may be considered. The FDA has designated Qsymia as a Schedule IV drug because phentermine is a Schedule IV agent with abuse potential related to amphetamines.[7,8] Topiramate is not considered to have abuse potential.[9] Both agents could produce negative withdrawal reactions if they are discontinued suddenly. Rapid tapering or discontinuation should be monitored to prevent complications.[7]

CONCLUSION

Phentermine/topiramate CR (Qsymia) was the first weight-loss drug to be launched in the U.S. in 13 years. The capsules combine a previously FDA-approved weight-loss medication with an approved antiepileptic agent known for weight loss as a side effect. This combination works synergistically to cause weight loss at lower doses compared with the individual products used alone, thereby reducing adverse effects. The types of adverse effects demonstrated in clinical trials were similar to those of the single products. The most notable adverse reactions of the individual products include cardiovascular and cognitive dysfunction. There were no serious cardiovascular events during the trials, and discontinuation of treatment attributable to cognitive dysfunction rarely occurred. Because of the risk of teratogenicity, the patient, prescriber, and certified pharmacy must all comply with the FDA-mandated REMS program for this medication.

Trials have demonstrated the clinical efficacy of phentermine/topiramate CR in all recommended doses. The expected cost is about $130 to $210 per month. For those with insurance coverage, the average co-pay is $50 or $60.[13]

Currently, no studies have compared the efficacy and safety of this combination product with either active ingredient alone as monotherapy or with other available weight-loss agents. Qsymia may represent another safe and effective adjunctive treatment to be considered in the management of obese and overweight patients with comorbid medical conditions who would benefit from weight loss.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of obesity in the United States, 2009–2010. National Center for Health Statistics. *NCHS Data Brief*, January 2012, No. 82.
2. Pi-Sunyer FX, Becker DM, Bouchard C, et al. Obesity Education Initiative. *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report.* Bethesda, Md.: National Institutes of Health. NIH Pub. No. 98-4083. September 1998. Available at: www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf. Accessed April 29, 2013.
3. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: A systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. *J Am Diet Assoc* 2007;107:1755–1767.
4. James WP, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363(10):905–917.
5. Li Z, Maglione M, Tu W, et al. Meta-analysis: Pharmacologic treatment of obesity. *Ann Intern Med* 2005;142:532–546.
6. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. *VI-0521 (Qnexa) Advisory Committee Briefing Document*. Mountain View, Calif.: Vivus, Inc.; July 15, 2010.
7. Qsymia (phentermine and topiramate extended-release) capsules, prescribing information. Mountain View, Calif.: Vivus, Inc.; July 2012 (revised April 2013).
8. Adipex-P (phentermine HCl), prescribing information. Sellersville, Pa.: Teva; January 2012.
9. Topamax (topiramate), prescribing information. Titusville, N.J.: Janssen; February 13, 2012.
10. Allison DB, Gadde KM, Garvey WT, et al. Controlled-release phentermine/topiramate in severely obese adults: A randomized controlled trial (EQUIP). *Obesity (Silver Spring)* 2012;20(2):330–342.
11. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): A randomized, placebo-controlled, phase 3 trial. *Lancet* 2011;377:1341–1352.
12. Garvery WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): A randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012;95:297–308.
13. Doheny K. Weight loss pill Qsymia 'gaining traction.' WebMD, December 26, 2012. Available at: www.webmd.com/diet/news/20121224/qsymia-gaining-traction. Accessed May 14, 2013. ■