New Drug Approvals

Phentermine/Topiramate for the Treatment of Obesity

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OBJECTIVE: To review the pharmacology, efficacy, and safety of phentermine/topiramate (PHEN/TPM) in the management of obese patients.

DATA SOURCES: MEDLINE (1966-July 2012) was searched using the terms weight loss, obesity, phentermine and topiramate, phentermine, topiramate, Qnexa, Qsymia, and VI-0521. Additionally, the new drug application and prescribing information for PHEN/TPM were retrieved.

STUDY SELECTION/DATA EXTRACTION: All studies considering the pharmacology, efficacy, and safety of PHEN/TPM were reviewed with a focus on efficacy and safety data from Phase 3 trials.

DATA SYNTHESIS: In 3 Phase 3 trials (EQUIP, CONQUER, and SEQUEL), treatment with PHEN/TPM consistently demonstrated statistically significant weight loss compared with placebo. After 56 weeks of treatment, percent weight loss achieved with PHEN/TPM was 10.6%, 8.4%, and 5.1% with 15/92 mg, 7.5/46 mg, and 3.75/23 mg, respectively ($p < 0.0001$). The 52-week extension study (SEQUEL) showed maintained weight loss over 2 years with 9.3% and 10.5% weight loss from baseline for 7.5/46 mg and 15/92 mg PHEN/TPM ($p < 0.0001$). A significantly higher proportion of patients achieved greater than 5%, 10%, or 15% weight loss with PHEN/TPM compared with placebo. Significant reductions in waist circumference, fasting triglycerides, and fasting glucoses were also attributable to PHEN/TPM. The drug was generally well tolerated in clinical trials. Adverse reactions occurring in 5% or more of study subjects included paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth.

CONCLUSIONS: PHEN/TPM is a new, once-daily, controlled-release, combination weight-loss product approved as an adjunct to diet and exercise for chronic weight management of obese or overweight patients with weight-related comorbidities. PHEN/TPM is modestly effective and a viable option for patients interested in losing weight, although long-term safety data are lacking.

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The current obesity epidemic affects more than 30% of adults and 17% of children and adolescents across the US, representing a major public health threat.[1,2] Additionally, 1 in 20 Americans has a body mass index (BMI) greater than 40 kg/m^2 and is thus classified as extremely obese.[3,4] Although some data suggest that the population prevalence of obesity may be slowing,[1] obesity remains one of the major causes of preventable death worldwide. Although the prevalence is similar for men and women, adults older than 60 years of age are more likely to be obese than are younger adults, and non-Hispanic whites have the lowest rate of obesity compared with other races and ethnicities.[4]

Despite the obesity epidemic, few long-term pharmacologic options are available for weight loss. Orlistat is the only product available in the US without

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restrictions on duration of therapy, but intolerable gastrointestinal adverse effects and reports of severe liver injury may limit its use.[5,6] Other prescription weight loss medications, including phentermine monotherapy, are Food and Drug Administration (FDA)–labeled for short-term use as monotherapy for obesity.[7]

Current pharmacologic options rarely achieve the initial treatment goal for obesity—a 10% reduction in weight over 6 months of therapy[3] and, of the available agents, phentermine can cause rebound weight gain.[8] Consequently, newer weight loss medications target 2 areas: initial treatment goals and maintenance of weight loss.[5] Two weight loss therapies recently approved by the FDA include lorcaserin, a selective 5-HT_{2c} agonist, and combination phentermine/topiramate (PHEN/TPM). FDA-approved on July 17, 2012, PHEN/TPM is a once-daily therapy combining low doses of phentermine and topiramate to promote weight loss while ostensibly reducing the risk of significant adverse effects when used at higher doses. PHEN/TPM is marketed in the US under the trade name Qsymia (VIVUS Inc.).[9] PHEN/TPM is approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult (≥18 years) obese patients (BMI ≥30 kg/m²) and overweight patients (BMI ≥27 kg/m²) with at least one weight-related comorbidity, including hypertension, type 2 diabetes, or dyslipidemia.[9] The purpose of this review is to describe the pharmacology, efficacy, and safety of PHEN/TPM and its role in the management of overweight and obese patients.

Pharmacology

PHEN/TPM is a fixed-dose, controlled-release, combination product containing immediate-release phentermine hydrochloride and extended-release topiramate. As a centrally acting sympathomimetic amine structurally related to amphetamine, phentermine increases norepinephrine release and, to a lesser extent, dopamine release.[7] As a result, phentermine works to suppress appetite, decrease food consumption, and increase heart rate secondary to increasing levels of catecholamines.[9] Tachyphylaxis and tolerance have been observed with phentermine use; the latter occurs in most patients and usually develops within a few weeks following initiation.[7]

The exact mechanism for weight loss with topiramate is unknown.[5,10] As a fructose monosaccharide, topiramate modulates voltage-gated ion channels, augments γ-aminobutyric acid (GABA) neurotransmitter activity at GABA-A receptors, antagonizes the AMPA/kainite subtype of the glutamate receptor, and inhibits carbonic anhydrase isoenzymes II and IV.[5,10] Reduced caloric intake was identified as a significant factor associated with topiramate-induced weight loss in humans.[11] However, animal studies suggest increased energy expenditure and decreased energy efficiency as contributors to weight loss with topiramate monotherapy.[12]

Pharmacokinetics

Clinical pharmacokinetic data for phentermine and topiramate are highlighted in Table 1. Notably, PHEN/TPM is not extensively metabolized by cytochrome P450 isoenzymes, has low plasma protein binding, and is predominantly cleared as unchanged drug in the urine.[9] Consequently, PHEN/TPM has minimal drug-drug interactions with a few notable exceptions. Non–potassium-sparing diuretics may potentiate hypokalemia when combined with PHEN/TPM.[9] Additionally, PHEN/TPM in combination with oral contraceptives may reduce contraceptive efficacy by decreasing ethinyl estradiol serum concentrations.[9]

Clinical Trials

MEDLINE (1966-July 2012) was searched using the terms weight loss, obesity, phentermine and topiramate, phentermine, topiramate, Qnexa, Qsymia, and VI-0521. Additionally, the new drug application and prescribing information for PHEN/TPM were retrieved. All studies considering the pharmacology, efficacy, and safety of PHEN/TPM were reviewed with a focus on efficacy and safety data from Phase 3 trials.

FDA-approval of PHEN/TPM for the treatment of obesity was based primarily on 3 clinical trials[12-14]: controlled release phentermine/topiramate in severely obese adults: a randomized, controlled trial (EQUIP)[12]; 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[13]; and 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.[14] These Phase 3 randomized, double-blind, placebo-controlled trials evaluated a combination of 3 fixed-dose formulations of PHEN/TPM in patients with or without various weight-related comorbidities.[5,12-14] Across these trials, the 3 PHEN/TPM doses studied were 3.75/23 mg (low-dose), 7.5/46 mg (mid-dose), and 15/92 mg (high-dose). In addition to pharmacotherapy, all patients received standardized diet and lifestyle modification counseling based on the LEARN (Lifestyle, Exercise, Attitudes, Relationship, and Nutrition) Program for Weight Management.[15] However, adherence to LEARN was not assessed. Furthermore, all patients were advised to increase daily physical activity, reduce caloric intake by 500-kcal/day, and increase water consumption.[12-15] If participants discontinued treatment for any reason, they were encouraged to remain in the study and complete monthly assessments.

The EQUIP and CONQUER studies consisted of a 2-week screening period, 4-week postrandomization titration period, and a 52-week treatment period. The aptly-named SEQUEL study was a 52-week extension of CONQUER.[5] In all 3 studies, the primary end points were percent weight loss from baseline and percentage of subjects achieving at least 5% weight loss from baseline to study completion; secondary end points varied.

OBESITY WITHOUT COMORBIDITIES

The EQUIP study evaluated low-dose and high-dose PHEN/TPM compared with placebo for a total treatment duration of 56 weeks (4-week titration phase; 52-week maintenance phase).[12] Study participants were 18-70 years of age with a BMI of 35 kg/m² or more and controlled triglycerides, blood pressure, and fasting plasma glucose. Study inclusion criteria and results are detailed in Table 2. Exclusion criteria were extensive and included the following: weight gain or loss greater than 5 kg within the past 3 months; history of eating disorders, previous bariatric surgery, glaucoma, and nephrolithiasis; thyroid dysfunction; chronic systemic glucocorticoid therapy; bipolar disorder or psychosis history, more than 1 lifetime episode of major depression, current depression of moderate or greater severity, presence or history of suicidal behavior or ideation with some intent to act, or antidepressant use that had not been stable for at least 3 months; stroke, myocardial infarction, life-threatening arrhythmia, or coronary revascularization within the past 6 months; unstable angina, congestive heart failure, or known or suspected clinically significant valvular heart disease; cholelithiasis within the past 6 months; use of any investigational medication or device within the past month.[5,12] Baseline characteristics for patients enrolled in EQUIP are presented in Table 3.

Overall, the placebo-subtracted percent weight loss was significant in both the low-dose and high-dose PHEN/TPM groups ($p < 0.0001$ for both comparisons with placebo). Participants receiving high-dose PHEN/TPM, low-dose PHEN/TPM, and placebo lost 10.9%, 5.1%, and 1.6% of body weight, respectively. The placebo-subtracted percentage of individuals with at least 5% weight loss and 10% weight loss was 49.4% and 39.8% for high-dose and 27.6% and 11.4% for low-dose PHEN/TPM, respectively.[12] Low-dose PHEN/TPM compared with placebo resulted in significant reductions in waist circumference, systolic blood pressure (SBP), and total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio.[12] Furthermore, compared with low-dose, high-dose PHEN/TPM resulted in significant reductions in waist circumference measurements, diastolic blood pressure (DBP) (Table 2), reduced total cholesterol to

Table 1. Clinical Pharmacokinetics of Phentermine/Topiramate[9]

Parameter	Phentermine	Topiramate
Absorption[a]		
C_{max}, ng/mL	49.1	1020
time to C_{max}, hours	6	9
AUC_{0-t}, ng•h/mL	1990	61600
Distribution[b]		
V_d, L	348	50.8 (central); 13.1 (peripheral)
plasma protein binding, %	17.5	15-41[c]
Metabolism[b]	Minor, primarily via CYP3A4	Not extensively metabolized
Excretion[b]		
clearance, L/h	8.79	1.17
half-life, hours	20	65
elimination, % (renal)	70-80	70
Impairment[a]		
hepatic		
mild (Child-Pugh score 5-6)	AUC ↑ 37%	No effect on AUC
moderate (Child-Pugh score 7-9)	AUC ↑ 60%	No effect on AUC
renal		
mild (CrCL 50-79 mL/min)	AUC ↑ 22%	AUC ↑ 25%
moderate (CrCL 30-49 mL/min)	AUC ↑ 45%	AUC ↑ 85%
severe (CrCL <30 mL/min)	AUC ↑ 91%	AUC ↑ 126%

AUC_{0-t} = area under the concentration time curve, zero to the last time with measurable concentration; C_{max} = maximum concentration; CrCl = creatinine clearance; V_d = volume of distribution.

[a]Data obtained following a single 15/92-mg dose of phentermine/topiramate.

[b]Data obtained from individual dosing of phentermine and topiramate.

[c]The fraction bound decreases as blood topiramate concentrations increase from 0.5 to 250 µg/mL.

HDL-C ratio, and reduced percent triglycerides, as well as increased HDL-C.[9]

Study limitations included a high dropout rate (40.1 %) and overrepresentation of female white participants, reducing study generalizability. However, the dropout rate in EQUIP is generally consistent with dropout rates in other pharmacotherapy trials for obesity (~30-50%). Of the 59.9% of participants who completed the study, only 53.7% took the drug for the full treatment course. Using the intention-to-treat last-observation-carried-forward (ITT-LOCF) analysis for missing data and failing to obtain final weight measurements for 40.1% of study participants may introduce bias when comparing randomized groups since the LOCF is based on an unrealistic assumption that weight will not change after the last measurement.[16] However, most weight loss occurs early and is often regained with time, particularly with agents that suppress appetite, such as phentermine and possibly topiramate. The most common reasons for discontinuation were loss to follow-up, withdrawal of consent, or adverse events. Discontinuations due to adverse events were more common in active treatment groups, with a higher frequency occurring with high-dose PHEN/TPM (see "Adverse Effects").

OVERWEIGHT OR OBESITY WITH WEIGHT-RELATED COMORBIDITIES

The CONQUER study and its 52-week extension study, SEQUEL, evaluated the safety and efficacy of mid-dose (7.5/46 mg) and high-dose (15/92 mg) PHEN/TPM compared with placebo in individuals with 2 or more weight-related comorbidities (eg, hypertension, dyslipidemia, type 2 diabetes, prediabetes, abdominal obesity). Unlike the EQUIP study, eligible patients had a BMI of 27 kg/m² or more and 45 kg/m² or less. However, in CONQUER, there was no designated lower limit on BMI for participants with type 2 diabetes at baseline.[2,11,12] Study inclusion criteria and results are detailed in Table 2. Exclusion criteria were similar to those in the EQUIP study with the exception of the following: use of phentermine or topiramate for weight loss or any other indication within 3 months prior to the study; type 1 diabetes or antidiabetic medications other than metformin; SBP greater than 160 mm Hg; DBP greater than 100 mm Hg or antihypertensive medication use that had not been stable for the preceding month; history of malignancy within 5 years; obesity of known genetic or endocrine origin; use of very-low-calorie diet or participation in a formal weight loss program in the 3 months prior to the study; smoking cessation within previous 3 months or plans to quit during the study period; history of drug/alcohol abuse within the preceding year; women who were pregnant, breastfeeding, or planning to conceive during the trial period. Prior to randomization, potential subjects were excluded for plasma bicarbonate level outside the normal range, aspartate aminotransferase and alanine aminotransferase greater than 2.5 times the upper limit of normal (ULN), fasting blood glucose greater than 240 mg/dL, serum triglycerides greater than 400 mg/dL, creatinine clearance less than 60 mL/min, thyroid stimulating hormone 1.5 times the ULN, or clinically significant abnormalities.[13] At the end of the CONQUER study, participants were automatically excluded from SEQUEL if they had a BMI of 22 kg/m² or less, had discontinued the study drug more than 4 weeks after 56 weeks of treatment, or had participated in another formal weight loss program during the interim between CONQUER completion and SEQUEL initiation.[14]

At the completion of CONQUER (56 weeks of therapy), the placebo-subtracted weight loss was significantly greater at both mid-dose and high-dose PHEN/TPM compared with placebo ($p < 0.0001$ for both comparisons to placebo).[13] The corresponding odds ratios for achieving at least 5% weight loss in the mid-dose and high-dose groups relative to placebo were 6.3 (95% CI 4.9-8.0; $p < 0.0001$) and 9.0 (95% CI 7.3-11.1; $p < 0.0001$), respectively. For patients completing the SEQUEL study, mean placebo-subtracted weight loss from baseline (week 0 of CONQUER) to 108 weeks was also significantly greater at both doses compared with placebo ($p < 0.0001$ for both comparisons with placebo).[14] In CONQUER, the corresponding odds ratios for achieving at least 10% weight loss in the mid-dose and high-dose PHEN/TPM groups compared with placebo were 7.6 (95% CI 5.6-10.2) and 11.7 (95% CI 8.9-15.4), respectively.[13] Furthermore, after 108 weeks of treatment (completion of SEQUEL), high-dose PHEN/TPM resulted in a significantly greater percentage weight loss compared with mid-dose in severely obese subjects (BMI ≥40 kg/m² and <45 kg/m²) at baseline ($p = 0.0016$ for the comparison between doses).[14] Both doses of PHEN/TPM also resulted in significant reductions in SBP, waist circumference measurement, total cholesterol, triglycerides, fasting plasma glucose, and improved insulin concentrations compared with placebo. In patients without type 2 diabetes at baseline, progression to type 2 diabetes was reduced by 54% and 76%, respectively, in subjects receiving mid-dose and high-dose PHEN/TPM compared with placebo.[14] For patients with prediabetes at baseline, the risk of progression to diabetes was reduced with both doses of PHEN/TPM compared with placebo, but only the comparison of high-dose PHEN/TPM with placebo was statistically significant, with a relative risk versus placebo of 0.47 (95% CI 0.25-0.88).[13] Furthermore, PHEN/TPM reduced the use of antidiabetic, antihypertensive, and lipid-lowering medications compared with placebo. These results remained essentially unchanged at 108 weeks in the SEQUEL extension study.

Study limitations included a lack of end point data for 31% of the study sample, restriction of the upper limit of BMI, a generally homogenous study population with mostly women (70%) and white (86%) participants, and lack of

Table 2. Efficacy of Phentermine/Topiramate in Clinical Trials

Study	Design	Inclusion Criteria	Treatment	Primary Efficacy Outcome	Secondary Efficacy Outcome[a]
OB-302 EQUIP[12] 56 weeks N = 1267	R, DB, PG, MC Phase 3 2:1:1 allocation ratio	Age 18-70 years; BMI ≥35 kg/m^2 Triglycerides ≤200 mg/dL, untreated or no more than 1 lipid-lowering medication BP ≤140/90 mm Hg, untreated or no more than 2 antihypertensive medications Fasting serum glucose level ≤110 mg/dL	Placebo (n = 514) PHEN/TPM CR 3.75/23 mg (n = 241) PHEN/TPM CR 15/92 mg (n = 512)	Placebo-subtracted weight loss at 56 weeks (%): 3.75/23 mg = 3.5 15/92 mg = 9.3 Pts. with at least 5% weight loss at 56 weeks (%): 3.75/23 mg = 44.9 15/92 mg = 66.7 Placebo = 17.3	WC (% change), mean: 3.75/23 mg = –5.6 (p = 0.0006) 15/92 mg = –10.9 (p < 0.0001 vs placebo and 3.75/23 mg) SBP (% change), mean: 3.75/23 mg = –1.8 (p = 0.0019 vs placebo) 15/92 mg = –2.9 (p < 0.0001 vs placebo; p = 0.2176 vs 3.75/23 mg) DBP (% change), mean: 3.75/23 mg = –0.1 (p = 0.4267 vs placebo) 15/92 mg = –1.5 (p = 0.0002 vs placebo; p = 0.0269 vs 3.75/23 mg) TG (% change), mean: 3.75/23 mg = 5.2 (p = 0.2639 vs placebo) 15/92 mg = –5.2 (p < 0.0001 vs placebo; p = 0.0027 vs 3.75/23 mg) Total cholesterol/HDL-C ratio (% change), mean: 3.75/23 mg = –0.22 (p = 0.0148 vs placebo) 15/92 mg = –0.35 (p < 0.0001 vs placebo; p = 0.023 vs 3.75/23 mg) HDL-C (% change), mean: 3.75/23 mg = 0.5 (p = 0.7057 vs placebo) 15/92 mg = 3.5 (p < 0.0001 vs placebo; p = 0.0008 vs 3.75/23 mg)
OB-303 CONQUER[13] 56 weeks N = 2487	R, DB, PG (3-arm), MC Phase 3 2:1:2 allocation ratio	Age 18-70 years; BMI ≥27 (no lower limit for pts. with T2DM), ≤45 kg/m^2 and ≥2 of the following at baseline: hypertension with SBP 140-160 mm Hg (130-160 mm Hg with DM), or DBP 90-100 mm Hg (85-100 mm Hg with DM), or taking ≥2 antihypertensive drugs to achieve control BP <140/90 mm Hg Hypertriglyceridemia with TG ≥200 mg/dL and ≤400 mg/dL or treated with ≥2 drugs to achieve TG <200 mg/dL Metabolic disorders with ≥1 of the following: fasting blood glucose level >100 mg/dL, glucose level >140 mg/dL at 2-hour OGTT, T2DM managed with lifestyle modifications or metformin monotherapy WC ≥102 cm for men or ≥88 cm for women	Placebo (n = 994) PHEN/TPM CR 7.5/46 mg (n = 498) PHEN/TPM CR 15/92 mg (n = 995)	Placebo-subtracted weight loss at 56 weeks (%): 7.5/46 mg = 6.6 15/ 92 mg = 8.6 Pts. with ≥5% weight loss at 56 weeks: 7.5/46 mg = 62.1 15/92 mg = 70.0 Placebo = 21.0	Weight loss (kg), mean: 7.5/46 mg = –8.1 (p < 0.0001 vs placebo) 15/92 mg = –10.2 (p < 0.0001 vs placebo) WC change (cm), mean: 7.5/46 mg = –7.6 (p < 0.0001 vs placebo) 15/92 mg = –9.2 (p < 0.0001 vs placebo) SBP change (mm Hg), mean: 7.5/46 mg –4.7 (p = 0.0008 vs placebo) 15/92 mg = –5.6 (p < 0.0001 vs placebo) Total cholesterol change (%), mean: 7.5/46 mg = –4.9 (p = 0.0345 vs placebo) 15/92 mg = –6.3 (p < 0.0001 vs placebo) TG change (%), mean: 7.5/46 mg = –8.6 (p < 0.0001 vs placebo) 15/92 mg = –10.6 (p < 0.0001 vs placebo) FPG change (mmol/L), mean: 7.5/46 mg = –0.01 (p = 0.0047 vs placebo) 15/92 mg = –0.07 (p < 0.0001 vs placebo) Fasting insulin change (pmol/L), mean: 7.5/46 mg = –24 (p = 0.0004 vs placebo) 15/92 mg = –27.6 (p < 0.0001 vs placebo)

OB-303 Extension Trial, OB-305 SEQUEL[14] Weeks 56-108 N = 676	R, DB, PG, (3 arm), MC Phase 3 2:1:2 allocation ratio	CONQUER inclusion/exclusion criteria: BMI ≥27 kg/m² and ≤45 kg/m² and ≥2 weight-related comorbidities; pts. were excluded from extension if BMI ≤22 kg/m², if study drug had been discontinued for >4 weeks after CONQUER study end, and if they had participated in another formal weight-loss program in the interim	PTS. continued randomly assigned treatments from CONQUER Placebo (n = 227) PHEN/TPM CR 7.5/46 mg (n = 153) PHEN/TPM CR 15/92 mg (n = 295)	Placebo-subtracted weight loss, week 108 (%): 7.5/46 mg = 7.5 15/92 mg = 8.7 Pts. with ≥5% weight loss from baseline to week 108: 7.5/46 mg = 75.2 15/92 mg = 79.3 Placebo = 30.0	Weight loss change (%), mean: 7.5/46 mg = −9.3 15/92 mg = −10.5 (p < 0.0001 for both doses vs placebo) WC change (cm), mean: 7.5/46 mg = −9.8 15/92 mg = −10.6 (p < 0.0001 for both doses vs placebo) FPG change (mg/dL), mean: 7.5/46 mg = 0.1 (p = 0.0872 vs placebo) 15/92 mg = −1.2 (p = 0.0048 vs placebo) Fasting insulin change (*m*IU/mL), mean: 7.5/46 mg = −5.3 (p = 0.0051 vs placebo) 15/92 mg = −5.2 (p = 0.0012 vs placebo)

BMI = body mass index; BP = blood pressure; CR = controlled release; DB = double-blind; DBP = diastolic blood pressure; FPG = fasting plasma glucose; MC = multicenter; OGTT = oral glucose tolerance test; PG = parallel-group; PHEN/TPM = phentemine/topiramate; R = randomized; SBP = systolic blood pressure; TG = triglycerides; T2DM = type 2 diabetes mellitus; WC = waist circumference.
[a]Selected secondary outcomes that were significantly different between phentermine/topiramate doses or between either phentermine/topiramate dose and placebo.

active comparator groups.[11,12] Like EQUIP, limited heterogeneity of the study population affects the generalizability of findings. Additionally, although the CONQUER and SEQUEL study findings showed a reduction in concomitant use of drugs for comorbid conditions, patients with type 2 diabetes did not have advanced disease, again limiting the generalizability of the findings. Furthermore, not all CONQUER subjects were eligible for enrollment in SEQUEL because of limitations in enrollment based on study center; only participants from high-enrolling centers were given the option (36 of 93 centers in CONQUER). Since patients were allowed an option for continuation, a bias for inclusion of subjects with positive treatment outcomes may have been introduced. Furthermore, for unknown reasons, a higher percentage of subjects in the high-dose arm were lost to follow-up, resulting in an underestimation of reasons for drop-out including potential adverse events or lack of efficacy. Finally, some patients treated with metformin were likely included in the studies; however, neither study addressed the impact of metformin on additional weight loss when compared with PHEN/TPM.

Dosing Recommendations

FDA-approved dosage forms for PHEN/TPM include 3.75/23 mg (low dose), 7.5/46 mg (mid dose), 11.25/69 mg (three-quarter dose), and 15/92 mg (high dose), but the low-dose and three-quarter dose PHEN/TPM are for titration purposes only.[9] PHEN/TPM is given as a single daily dose in the morning, with or without food. To prevent insomnia, evening doses should be avoided.

The recommended starting dose is PHEN/TPM 3.75/23 mg daily for 14 days, subsequently increasing to a recommended 7.5/46-mg daily dose. Dosing should not exceed 7.5/46 mg daily in patients with moderate or severe renal impairment (estimated CrCl <50 mL/min) or moderate or severe hepatic impairment (Child-Pugh score ≥7).

For patients not achieving clinically significant weight loss of at least 3% after 12 weeks, PHEN/TPM may be increased to 11.25/69 mg for 14 days, followed by 15/92 mg daily if needed. If, after 12 weeks of taking PHEN/TPM 15/92 mg daily, 5% weight loss is not achieved, PHEN/TPM should be discontinued gradually by taking a dose every other day for 1 week to minimize the possibility of precipitating seizures from rapid topiramate withdrawal.[9] The mechanism of precipitant seizures is unclear.

Adverse Effects

In general, PHEN/TPM was well tolerated in Phase 3 clinical trials, with the most commonly reported adverse effects being dry mouth, dizziness, constipation, insomnia, dysgeusia, and paresthesia (Table 4).[12-14] Rates of discontinuation due to adverse events were greater with high-

dose PHEN/TPM and appear to be dose-related. The most common reasons for discontinuation were blurred vision, headache, and irritability.[9]

In monotherapy weight loss studies, topiramate has been associated with dose-dependent neuropsychiatric adverse events, mainly memory and mood events such as depression. Consequently, during clinical trials for PHEN/TPM, depressive symptoms were assessed using the Patient Health Questionnaire 9 (PHQ-9), and suicide ideation and behavior were assessed using the clinician-administered Columbia Suicide Severity Rating Scale (C-SSRS). Across all 3 trials, depressive symptoms tended to improve over time and no significant increase in suicide risks was identified.[12-14]

Like other carbonic anhydrase inhibitors, topiramate can decrease serum concentrations of bicarbonate and potassium, increasing the risk of hypokalemia and nephrolithiasis.[13] In the CONQUER trial, 3 serious adverse events of

Table 3. Baseline Characteristics for Phase 3 Clinical Trials

Characteristic	EQUIP (OB-302)[12]	CONQUER (OB-303)[13]	SEQUEL (OB-305)[14]
Age (years), mean (SD)	42.7 (11.6)	51.1 (10.4)	52 (10.3)
Female, %	2.8	70	66.7
Race, %			
white	9.9	86	85.8
African American	17.7	12	12.7
BMI (kg/m^2), mean (range)	42 (35.0-78.7)	36.6 (32-41)	36.1 (31.4-40.8)
Other factors	Personal Health Questionnaire-9 score, mean 2.8	Comorbidities: hypertension[a]: 52.4% hypertriglyceridemia[b]: 36.1% impaired glucose tolerance or impaired fasting glucose (including T2DM): 68% T2DM[c]: 15.8% abdominal obesity[d]: 98.3% ≥Comorbidities: 51.3%	Comorbidities: hypertension[a]: 50.5% hypertriglyceridemia[b]: 34.1% T2DM[c]: 21.5% metabolic syndrome: 66.8%

BMI = body mass index; T2DM = type 2 diabetes mellitus.

[a]Defined as systolic blood pressure 140-160 mm Hg or diastolic blood pressure 90-100 mm Hg, or controlled (<140/90 mm Hg) with 2 or more antihypertensive drugs.

[b]Defined as fasting triglycerides greater than 200-400 mg/dL or receiving treatment with 2 or more lipid-lowering agents.

[c]Defined as fasting blood glucoses >100 mg/dL, blood glucoses greater than 140 mg/dL 2 hours after an oral glucose tolerance test, or diagnosed T2DM managed with lifestyle changes or metformin monotherapy. For SEQUEL, T2DM was defined as fasting blood glucoses ≥126 mg/dL or 2-hour blood glucoses ≥200 mg/dL after oral-glucose-tolerance tests.

[d]Defined as waist circumference of at least 102 cm for men and at least 88 cm for women.

Table 4. Adverse Events with a Frequency of 5% or More in Any PHEN/TPM Group

	EQUIP[12]		CONQUER[13]		SEQUEL[14]	
Event	PHEN/TPM CR 3.75/23 (n = 240)	PHEN/TPM CR 15/92 (n = 511)	PHEN/TPM CR 7.5/46 (n = 153)	PHEN/TPM CR 15/92 (n = 295)	PHEN/TPM CR 7.5/46 (n = 153)	PHEN/TPM CR 15/92 (n = 295)
General, n (%)						
paresthesia	10 (4.2)	96 (18.8)	21 (13.7)	62 (21.0)	1 (0.7)	10 (3.4)
dry mouth	16 (6.7)	87 (17.0)	21 (13.7)	59 (20.0)	1 (0.7)	4 (1.4)
constipation	19 (7.9)	72 (14.1)	25 (16.3)	62 (21.0)	11 (7.2)	12 (4.1)
upper respiratory tract infection	38 (15.8)	63 (12.3)	23 (15.0)	55 (18.6)	26 (17.0)	45 (15.3)
headache	25 (10.4)	61 (11.9)	8 (5.2)	28 (9.5)	4 (2.6)	12 (4.1)
dysgeusia	3 (1.3)	43 (8.4)	18 (11.8)	39 (13.2)	1 (0.7)	3 (1.0)
Psychiatric, n (%)						
depression	8 (3.3)	24 (4.7)	14 (3)	39 (4)	(3.9)	(8.1)
anxiety	7 (2.9)	19 (3.7)	9 (2)	41 (4)	(6.5)	(9.5)
Cognitive, n (%)						
attention disturbance	1 (0.4)	18 (3.5)	10 (2)	35 (4)		

CR = controlled release; PHEN/TPM = phentermine/topiramate.

nephrolithiasis occurred in participants treated with high-dose PHEN/TPM.[13] To monitor for hypokalemia and reduce the risk for nephrolithiasis, a blood chemistry profile should be collected at baseline before initiating PHEN/TPM and periodically thereafter.

Because the area under the curve of PHEN/TPM can be increased by mild hepatic and renal impairment, careful monitoring of hepatic and renal function is warranted. If PHEN/TPM is used in persons with mild or worse than mild hepatic or renal function, careful monitoring of adverse events is needed.

In addition to blood chemistry profiles, regular measurement of resting heart rate during treatment with PHEN/TPM is recommended.[9] The phentermine component of high-dose PHEN/TPM increased resting heart rate by 1.2 beats/min in the EQUIP study compared with placebo ($p = 0.0830$) and by 1.7 beats/min in the CONQUER and SEQUEL studies ($p < 0.0001$ vs placebo).[12-14] The clinical significance of increased heart rate is unknown, especially in patients with chronic cardiac conditions. Regardless, patients should be educated to inform health care providers if they experience heart palpitations while resting.

Other safety considerations for PHEN/TPM include misuse, abuse, and overdose potential, given phentermine's structural similarity to amphetamine.[5,7] PHEN/TPM is a Schedule IV drug under the FDA Controlled Substances Act, meaning abuse of the drug may lead to limited physical dependence or psychological dependence.

PHEN/TPM is contraindicated in patients with glaucoma or hyperthyroidism, as well as during pregnancy and during or within 14 days following monoamine oxidase inhibitor use.[9] Due to an increased risk for cleft lip and cleft palate during the first trimester of pregnancy, the FDA recently classified PHEN/TPM in pregnancy category X.[10] In each Phase 3 trial, 2 forms of birth control were required for women of childbearing age. Even with strict study requirements, 15 pregnancies were reported in women exposed to PHEN/TPM in the EQUIP study and 2 in the SEQUEL study.[12-14] Of these pregnancies, there were 3 spontaneous abortions, 3 elective abortions, and 9 healthy live births. Congenital malformations were not observed.

A Risk Evaluation and Mitigation Strategy (REMS) is in place for PHEN/TPM to discuss appropriate contraception and pregnancy test requirements, as well as to educate women on immediate discontinuation and reporting should pregnancy occur.[5] A pregnancy test is required at baseline before starting PHEN/TPM and monthly thereafter for all females of childbearing age, defined as those who have not had a hysterectomy, bilateral oophorectomy, or medically documented spontaneous ovarian failure, and have not completed menopause.[9,17] Menopause should be confirmed clinically by a health care provider. More information about prescribing requirements, REMS training, and PHEN/TPM prescribing requirements is available at www.qsymia.com/hcp/.

Formulary Considerations

To date, no clinical trials have directly compared PHEN/TPM with other weight-loss medications. Consequently, any comparison of pharmacotherapy-induced weight loss across trials has inherent limitations, most notably differences in trial design, length, and patient populations. With these limitations in mind, some general comparisons can be made between PHEN/TPM and other weight-loss agents.

When compared with other long-term weight-loss options, PHEN/TPM has generally resulted in similar or superior weight reductions after 1 year of therapy. Specifically, orlistat 120 mg 3 times daily for 1 year resulted in a 9.6% weight loss compared with 5.6% with placebo ($p < 0.001$), for a placebo-subtracted weight loss of 4%. The proportion of patients achieving 5% or more weight loss was also greater with orlistat (73%) compared with placebo (45%; $p < 0.001$).[18] Lorcaserin 10 mg twice daily for 1 year resulted in 5.8% (±7.8%) weight loss compared with 2.2% (±3.9%) with placebo ($p < 0.001$), for a placebo-subtracted weight loss of approximately 3.6%, on average. The proportion of patients achieving 5% or more weight loss with lorcaserin and placebo was 48% and 20%, respectively ($p < 0.001$).[19] In comparison with orlistat and lorcaserin, the percent placebo-subtracted weight loss achieved with PHEN/TPM may be modestly superior after 1 year of treatment at approximately 9% for high-dose and approximately 7% for mid-dose. Notably, baseline weight was generally similar among these trials (mean baseline weight approximately 100-103 kg), except for the EQUIP study (mean baseline weight approximately 115 kg). Furthermore, across Phase 3 clinical trials, the percentages of participants who achieved 5% or more weight loss with PHEN/TPM were 69%, 62%, and 27.6% for high-dose, mid-dose, and low-dose, respectively.[12-14] PHEN/TPM may also be associated with fewer adverse effects compared with lorcaserin.[19,20]

The average wholesale price (AWP) per unit for PHEN/TPM varies from $4.80 for 3.75/23-mg capsules and $7.35 for 15/92-mg capsules.[21] By comparison, Adipex-P (phentermine) AWP per unit is approximately $2.00 to $2.50, and the AWP per unit of regular-release topiramate at doses of 25-100 mg varies between approximately $2.00 and $7.00, depending on package size. PHEN/TPM contains extended-release topiramate, which is not available as monotherapy. The AWP per unit of orlistat is $5.40 for 120-mg capsules and AWP information for lorcaserin is currently unavailable.

Summary

PHEN/TPM should be avoided or carefully initiated and monitored in patient populations excluded in clinical trials until further postmarketing safety data become available. Furthermore, caution should be exercised when prescrib-

ing PHEN/TPM for the elderly or for patients with mild to moderate hepatic or renal impairment. PHEN/TPM has not been studied in patients on insulin or sulfonylureas. Consequently, as patients lose weight, antidiabetic and antihypertensive regimens may need to be adjusted to prevent potential hypoglycemia or hypotension.

Future studies evaluating the efficacy and safety of PHEN/TPM in the elderly and in men, as well as in patients with significant depression, cardiac, or cerebrovascular disease are needed. Head-to-head trials comparing long-term pharmacologic interventions (ie, lorcaserin, PHEN/TPM, orlistat) and surgical interventions (eg, lap banding, bariatric surgery) may further guide practitioners.

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EXTRACTO

Fentermina/Topiramato (Qsymia) Para el Tratamiento de Obesidad

SM Smith, M Meyer, KE Trinkley

Ann Pharmacother 2013;47:340-9.

OBJETIVO: Revisar la farmacología, eficacia y seguridad de fentermina/topiramato (PHEN/TPM) en el manejo de pacientes obesos.

FUENTES DE DATOS: Se realizó una revisión de la literatura mediante el sistema de base de datos MEDLINE (1966-julio 2012) utilizando los términos; pérdida de peso, obesidad, fentermina y topiramato, fentermina, topiramato, Qnexa, Qsymia, y VI-0521. También se estudió la información sometida para solicitar la aprobación de el uso como una nueva droga y la información de prescripción del producto.

SELECCIÓN DE ESTUDIOS Y DATOS: Se revisaron todos los estudios que consideraron la farmacología, eficacia y seguridad de PHEN/TPM enfocando en los datos de eficacia y seguridad de los estudios fase III.

SÍNTESIS DE LOS DATOS: En tres estudios fase III (EQUIP, CONQUER, y SEQUEL), el tratamiento con PHEN/TPM demostró en forma uniforme una pérdida de peso estadísticamente significativa comparada con el placebo. Después de 56 semanas de tratamiento, el porciento de pérdida de peso que se logró con PHEN/TPM fue de 10.6%, 8.4%, y 5.1% con las dosis de 15/92 mg, 7.5/46 mg y 3.75/23 mg, respectivamente ($p < 0.0001$). La extensión del estudio, que fue de 52 semanas (SEQUEL), demostró que la pérdida de peso se mantuvo sobre 2 años, y que el peso se redujo entre 9.3% y 10.5% con las dosis de 7.5/46 mg y 15/92 mg de PHEN/TPM ($p<0.0001$). Un número significativamente más alto de pacientes tratados con PHEN/TPM obtuvo una pérdida de peso mayor de 5%, 10% o 15% comparado con el placebo. Se obtuvieron reducciones significativas en la circunferencia de la cintura, concentraciones de triglicéridos, y de glucosa en ayunas, las cuales se relacionaron a PHEN/TPM. PHEN/TPM fue generalmente bien tolerado en los estudios clínicos. Las reacciones adversas que ocurrieron en >5% de los pacientes estudiados incluyeron parestesias, mareos, boca seca, disguesia o alteración en el sentido del gusto, insomnio, y estreñimiento.

CONCLUSIONES: PHEN/TPM es un nuevo producto de combinación para bajar de peso, que se administra una vez al día, se libera en forma controlada y se aprobó como tratamiento adjunto a dieta y ejercicio para

el manejo crónico de peso en pacientes obesos o en sobrepeso con comorbilidades relacionadas al peso. PHEN/TPM es moderadamente efectivo y es una opción viable para pacientes interesados en perder peso, aunque la información sobre seguridad, a largo plazo, se desconoce.

Traducido por Mirza Martínez

RÉSUMÉ

Phentermine/Topiramate (Qsymia) Pour le Traitement de l'Obésité

SM Smith, M Meyer, KE Trinkley

Ann Pharmacother 2013;47:340-9.

OBJECTIF: Revoir la pharmacologie, l'efficacité et l'innocuité du phentermine/topiramate (PHEN/TPM) dans le traitement de l'obésité.

SOURCE DES DONNÉES: La banque de données MEDLINE (1966 à juillet 2012) a été utilisée en utilisant les mots clés perte de poids, obésité, phentermine/topiramate, phentermine, topiramate, Qnexa, Qsymia, et VI-0521. De plus, l'information sur la demande d'homologation du PHEN/TPM a été utilisée dans cette évaluation.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Toutes les études qui ont évalué la pharmacologie, l'efficacité et l'innocuité du PHEN/TPM ont été revues en mettant l'accent sur l'efficacité et l'innocuité dans les études de phase III.

ANALYSE DE DONNÉES: Dans les études de phase III (EQUIP, CONQUER et SEQUEL), le traitement avec le PHEN/TPM a démontré une perte de poids statistiquement significative lorsque comparé au placebo. Après 56 semaines de traitement, le pourcentage de perte de poids observé avec le PHEN/TPM était de 10.6%, 8.4% et 5.1% avec 15/92 mg, 7.5/46 mg et 3.75/23 mg respectivement ($p < 0.0001$). Le prolongement de l'étude (SEQUEL) à 52 semaines a démontré que la perte de poids est maintenue sur une période de 2 ans par rapport aux valeurs initiales avec perte de poids de 9.3% et 10.5% avec une posologie de 7.5/46 mg et de 15/92 mg de PHEN/TPM respectivement ($p < 0.0001$). Lorsque comparé au placebo, un nombre de significativement plus élevé de patients traités avec PHEN/TPM a atteint une perte de poids 5%, 10%, ou 15%. Une réduction significative du tour de taille, des triglycérides et glycémies à jeun a été associée à l'utilisation du PHEN/TPM. Ce médicament était généralement bien toléré dans les études cliniques. Les effets indésirables signalés chez plus de 5% des patients incluaient la paresthésie, les étourdissements, la dysgueusie, l'insomnie, la constipation et la bouche sèche.

CONCLUSIONS: Le PHEN/TPM est une préparation à libération contrôlée administré une fois par jour pour le maintien chronique de surpoids chez les patients obèses avec comorbidités de l'obésité et ce, en complément à la diète et l'exercice. Le PHEN/TPM a une certaine efficacité et représente une option intéressante chez les patients intéressés à perdre du poids même si les données à long terme sont manquantes.

Traduit par Louise Mallet