Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Health Authority

New Obesity Drug Evaluations: Phentermine/Topiramate and Lorcaserin

Month/Year of Review: November 2012
Generic Name: Phentermine and topiramate extended-release
Generic Name: Lorcaserin Hydrochloride
PDL Class: Weight Loss Medications

End date of literature search: August 2012
Brand Name (Manufacturer): Qsymia® (Vivus, Inc.)
Brand Name (Manufacturer): Belviq® (Arena Pharmaceuticals, Inc.)
Dossier Received: Pending

FDA Approved Indications: [1]

Phentermine/topiramate 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 co-morbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Limitations of Use

- The effect of phentermine/topiramate on cardiovascular morbidity and mortality has not been established.
- The safety and effectiveness of phentermine/topiramate in combination with other products intended for weight loss, including prescription and over-the-counter drugs and herbal preparations have not been established.

Lorcaserin is a serotonin 2C receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of: [2]

- 30 kg/m2 or greater (obese), or
- 27 kg/m2 or greater (overweight) in the presence of at least one weight related co-morbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)

Limitations of Use:

- The safety and efficacy of co-administration of lorcaserin with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established.
- The effect of lorcaserin on cardiovascular morbidity and mortality has not been established.

Research Questions:

- Is there evidence for the efficacy and safety of phentermine/topiramate and lorcaserin for the long-term treatment of obesity?
- Is there any evidence that phentermine/topiramate and lorcaserin improves long term clinical outcomes such as prevention of type 2 diabetes and reduction of cardiovascular related morbidity and mortality?
- Are there any subgroup populations in which these drugs offer improved efficacy or safety?

Conclusions for phentermine/topiramate:

- There is insufficient evidence to make conclusions about phentermine/topiramate's effects on cardiovascular morbidity and mortality or long term maintenance of weight loss.
- There is moderate strength evidence that phentermine/topiramate 7.5mg/46mg demonstrated an increase in the number of patients who achieved a ≥5% weight loss at 56 weeks in overweight and obese patients compared to placebo (RR 2.9, 95% CI 2.6-3.3) and demonstrated a difference in mean weight loss of ≥5% compared to placebo, meeting both FDA efficacy requirements.
- There is low strength evidence that phentermine/topiramate caused a greater number of withdrawals due to adverse events than placebo.
- There is insufficient evidence to compare phentermine/topiramate with other currently available long-term weight loss agents, lifestyle modifications, and surgery options. There are currently no direct head-to-head comparison trials with other weight loss agents

Conclusions for lorcaserin:

- There is insufficient evidence to make conclusions about lorcaserin's effects on cardiovascular morbidity and mortality or long term maintenance or weight loss.
- There was moderate evidence showing that more patients on lorcaserin 10mg twice daily achieved ≥5% weight loss than placebo at 52 weeks in obese patients (RR 2.1, 95% CI 2.0-2.3) but did not demonstrate a difference in mean weight loss of ≥5% compared to placebo, meeting only one of the two FDA efficacy criteria.
- There is low evidence that lorcaserin does not cause FDA-defined valvulopathy; although the studies lacked large sample sizes and duration to fully detect long-term development and effects on cardiovascular outcomes.
- There is insufficient evidence to compare lorcaserin with other currently available long-term weight loss agents, lifestyle modifications, and surgery options. There are currently no direct head-to-head comparison trials with other weight loss agents

Recommendations for both phentermine/topiramate and lorcaserin:

- Cover for only OHP covered diagnoses
- As the treatment of obesity with medications is an OHP unfunded diagnosis, eliminate current prior authorization for weight loss medications.

Background:

Obesity is a chronic disease that is growing in prevalence in the United States and worldwide each year.[3] In the United States, more than 30% of males and females are considered obese, and in the state of Oregon, 1400 obesity related deaths occur each year, making obesity only second to tobacco as the state's leading cause of preventable death.[4,5] Under the Oregon Health Plan (OHP) medical treatment of obesity is limited to accepted intensive counseling on nutrition and exercise, provided by health care professionals, according to recommendations of the US Preventive Services Task Force. Pharmaceutical agents are not intended to be covered services for the treatment of obesity. Body mass index (BMI), taking into account a patient's height and weight, is considered a simple screening tool to tell if a patient is obese (Table 1). Research shows that waist circumference may be an acceptable alternative to BMI.[4, 6]

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Table 1: BMI Classifications

Classifications for BMI[6]	Body Mass Index (BMI)
Underweight	<18.5 kg/m^2
Normal weight	18.5-24.9 kg/m^2
Overweight	25-29.9 kg/m^2
Obesity (Class 1)	30-34.9 kg/m^2
Obesity (Class 2)	35-39.9 kg/m^2
Extreme obesity (Class 3)	≥40 kg/m^2

Long term consequences that result from obesity include many chronic diseases, such as diabetes, hypertension, high cholesterol, cardiovascular disease, arthritis, and sleep apnea. Mortality rates and risk of cardiovascular disease rise with increasing degrees of overweight and obesity; marked increases in risk of death occur when BMI levels reach 29 to 30 kg/m^2 or greater.[7] The Diabetes Prevention Program demonstrated that lifestyle interventions that can reduce body weight up to 7% lowers the 5-year risk of developing diabetes by 58%.[8] According to the 2007 Food and Drug Administration (FDA) Industry Guidance for Obesity Treatment, a product can be considered effective for weight management after one year of treatment, if either of the following occurs: 1) the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant, 2) or if the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.[4] The U.S. Preventative Services Task Force (USPSTF) found adequate evidence that a vigorous weight loss program involving multi-component behavioral interventions can lead to an average weight loss of 4 to 7 kg. This has been shown to improve glucose tolerance and other physiological risk factors for cardiovascular disease. Direct evidence about multiple interventions on reducing hospitalizations and mortality is lacking, and more trials on the long-term effects of weight reduction need to be conducted. Dietary changes, exercise, and behavioral modifications are considered first-line treatment for weight reduction according to the 2006 Canadian guidelines.[9]

The 2006 Canadian guidelines recommend pharmacological therapy when a patient has a BMI ≥30 kg/m^2 or if they have a BMI of 27-30 kg/m^2 with co-morbid conditions.[9] Medications should only be used in combination with lifestyle modifications, such as increased physical activity and dietary changes. Currently, orlistat (an intestinal fat absorption inhibitor) is the only long-term medication approved for obesity (data available for up to four years of treatment). Short-term medication options include phentermine or diethylpropion, but both have potential for abuse and should not be used longer than 12 weeks.[9,10] Attrition rates in studies evaluating weight loss medications are generally high, averaging above 30% according to a recent systematic review , possibly because of a high female representation, lack of weight related co-morbidities, and lack of an adequate lead-in period.[11] Surgery is reserved for patients who fail lifestyle modifications with or without drug therapy and who have a BMI>35 kg/m^2 with co-morbid conditions or a BMI>40 kg/m^2[2,3]

Phentermine/Topiramate

Clinical Efficacy (evidence table in Appendix 1):

Two double blind, placebo controlled, phase III, randomized controlled trials (EQUIP & CONQUER) and one double blind extension trial of CONQUER (SEQUEL) compared phentermine and topiramate continuous release at varying doses to placebo.[13–15] The majority of the patients included in all three trials were white females in their early forties and fifties. EQUIP included people who were considered severely obese (BMI ≥35) and were taking medications that included lipid lowering and antihypertensive agents. CONQUER and SEQUEL included patients who were overweight and obese (BMI 27-45), with two or more comorbidities

(hypertension, dyslipidemia, diabetes). The SEQUEL extension study included patients who completed the CONQUER study on treatment and complied with protocol requirements.

The EQUIP trial (n=1267) was a 56-week fair-good quality trial (4-weeks post-randomization used for topiramate titration phase) looking at a titration dose of phentermine and topiramate (3.75mg/23mg) and the highest dose of the combination (15mg/92mg) compared to placebo. The co-primary outcomes were achieving weight loss ≥5% of baseline body weight, weight loss of ≥10% of body weight, and mean percent weight loss from baseline. In the intention to treat (ITT) population, significantly more patients in the treatment group achieved ≥5% loss of baseline body weight for both the high dose and titration dose compared to placebo (66.7%, 44.9%, and 17.3%, respectively; p-value<0.0001 for all comparisons),and achieved ≥10% loss (57%, 23.1%, and 11.1%; p-value <0.0001). Mean percent weight loss from baseline was also significantly greater with treatment compared to placebo (-10.9%, -5.1%, and -1.6%; p-value<0.0001) for phentermine/topiramate 15mg/92mg, 3.75mg/23mg versus placebo, respectively. Weight loss in the high dose group was accompanied by small, but statistically significant greater changes in blood pressure, glucose, triglycerides, and cholesterol compared to placebo. Overall attrition was 40%, with more patients in the placebo arm discontinuing drug than in the treatment arms. External validity is low due to majority of subjects being white females without many significant obesity-associated comorbid diseases. Also, the recommended initial maintenance dose of 7.5mg/46mg was not evaluated in this study.

The CONQUER trial (n=2448) was another fair to good quality, 56-week trial comparing a higher dose of phentermine/topiramate 15mg/92mg and lower dose of 7.5mg/46mg to placebo. Approximately 16% of patients had type 2 diabetes, 36% had hypertriglyceridemia, and 52% had hypertension, however those with significant cardiovascular disease were still excluded from the study. Both doses showed greater efficacy than placebo for each primary outcome. The mean percentage change in bodyweight between drug and placebo was statistically significant in both the 15mg/92mg group (-8.6%; 95% CI -9.3 to -8.0, p<0.001) and the 7.5mg/46mg group (-6.6%; 95% CI -7.4 to -5.8, p<0.0001). More patients in the treatment groups achieved a weight loss of at least 5% (RR 2.98; 95% CI 2.59, 3.41) and 10% (RR 5.07; 95% CI 3.94, 6.57) compared to placebo (p-value<0.0001 for all comparisons to placebo). Although there were few patients ≥65 years and few black patients, there was no significant difference in efficacy based on a subgroup analysis of sex, age, and race; although conclusions should not be drawn from this. The CONQUER trial lacks generalizability to the overall population.

SEQUEL was a 1-year extension of the CONQUER trial (108 weeks), using the patients who completed the CONQUER study on treatment, complied with protocol requirements, and agreed to continue as further participation was optional. Due to significant selection bias, results should be interpreted with caution, as the potential bias toward inclusion of only subjects with positive outcomes from CONQUER. A greater proportion of subjects in the 15mg/92mg treatment arm (85.5%) agreed to continue than both the 7.5mg/46mg arm (79.4%) and the placebo group (69.4%). There continued to be a significantly greater mean percentage change from baseline in body weight for the phentermine/topiramate 15mg/92mg and 7.5mg/46mg groups compared to placebo,(-10.5%, -9.3%, and -1.8%, respectively p-value<0.0001 for all comparisons). The number of patients achieving weight loss of at least 5% (RR 2.51; 95% CI 2.02, 3.07; low dose vs. placebo) and 10% (RR 2.31; 95% CI 1.51, 3.59; low dose vs. placebo) of body weight continued to be more for both treatment groups compared to placebo.

Clinical Safety:

In EQUIP, there was no statistically significant difference in severe adverse events (10.2%, 10.4%, and 8.0%; p-value=0.27) between phentermine 15mg/92mg (RR 1.27; 95% CI 0.85, 1.92), 3.75mg/23mg compared to placebo, respectively. Severe adverse events included cholelithiasis and myelogenous leukemia. There was a significant difference in withdrawals due to adverse events between the high dose of phentermine/topiramate 15mg/92mg and placebo (16% vs. 8.4%; p-value<0.001). The most common events included paresthesia, dry mouth, constipation, dysgeusia, depression, insomnia and irritability (p-values<0.0001).

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

The CONQUER trial reported no statistically significant difference in serious adverse events including nephrolithiasis and paresthesia (5% for phentermine/topiramate 15mg/92mg vs. 4% placebo; p-value=0.31), but did report a statistically significant difference in withdrawal rates (19% vs. 9% for 15mg/92mg vs placebo; p-value<0.0001, RR 2.16; 95% CI 1.70, 2.78). Dose related trends were noted for rates of dry mouth, constipation, dysgeusia, paraesthesia, insomnia, dizziness, anxiety, irritability, and disturbance in attention.

There were also no statistically significant differences in serious adverse events between the phentermine/topiramate 15mg/92mg and placebo in the SEQUEL trial (RR 1.03; 95% CI 0.41, 2.61, p=0.96) or in withdrawals due to adverse events (RR 1.41; 95% CI 0.54, 3.86; p=0.45). The most commonly reported adverse events were upper respiratory tract infection, constipation, paraesthesia, sinusitis, and dry mouth. The incidence of individual adverse events was lower in the second year (weeks 56-108) than in the first year (weeks 0-56).

Lorcaserin

Clinical Efficacy (Evidence table in Appendix 2):

FDA approval of lorcaserin was based on three fair quality phase III, double-blind, randomized, placebo-controlled trials (BLOOM, BLOOM-DM, and BLOSSOM).[16-18] BLOOM and BLOOSOM looked at lorcaserin in the non-diabetic population, while BLOOM-DM was conducted in the diabetic patients. The majority of the subjects for all of the trials were white women in their mid-40's to 50's that were relatively healthy. All patients in the trials were asked to participate in a standardized behavioral weight management program that recommended patients participate in 30 minutes of exercise daily and reduce their caloric intake by 600 kcal daily along with medication treatment. All studies had an overall high attrition rate and the primary data analysis was intention-to-treat (ITT) with last-observation-carried-forward (LOCF) imputation, which could yield misleading results if patients regained weight after withdrawing from the study. None of the studies met the first FDA efficacy criteria of achieving a difference in mean weight loss between drug and placebo of at least 5%, however the second criteria was met (percentage of subjects who lost at least 5 percent of body weight is at least 35%).

The Behavioral Modification and Lorcaserin for Overweight and Obesity Management trial (BLOOM) was a fair quality, 1-year trial that compared lorcaserin 10 mg twice daily versus placebo. Patients who remained in the trial were eligible to continue for a second year. Patients who were on placebo continued to receive it, while patients who had been receiving lorcaserin were randomized again in a 2:1 ratio to lorcaserin or placebo (not reported in evidence table). Endpoints at 52 weeks were analyzed using a modified intention-to-treat (MITT) with last observation carried forward (LOCF) imputation. There was a statistically significant difference between lorcaserin and placebo for all three co-primary endpoints: change in weight from baseline at year 1 (5.9+/-0.2kg vs. 2.2+/-0.1kg; p<0.0001), percent of subjects achieving ≥5% weight loss at week 52 (47.5% vs 20.3%; p-value<0.001), and percent of subjects achieving ≥10% weight loss at week 52 (22.6% vs. 7.7%; p-value<0.001). Although there was weight regain in all groups in year two, loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year two than those reassigned to receive placebo (67.9% vs. 50.3%, p<0.001).

The Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) study was a fair quality, 1-year trial comparing lorcaserin 10 mg BID and lorcaserin 10 mg QD to placebo in a randomized 2:1:2 ratio (n=4008). The co-primary outcomes included percent change in weight from baseline and proportion of participants achieving a weight loss ≥5% over one year. The percent change in weight at year 1 was -5.6%, -4.6%, and -2.7% for lorcaserin 10mg BID, lorcaserin 10mg QD, and placebo respectively (reported<0.001). The difference in mean weight loss between lorcaserin 10mg twice daily and placebo was 3%. The percentage of subjects achieving ≥5% weight loss was 47%, 42%, and 24% (p-value<0.001) for lorcaserin 10mg BID, lorcaserin 10mg QD, and placebo respectively. Although underrepresented, significant weight loss occurred in men, across BMI subgroups, and across racial subgroups. Study limitations included

an unclear method for appropriate allocation concealment and unclear method for patient and caregiver blinding, and exclusion of many preexisting conditions and serotonergic medications.

The Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) was a fair quality, 1-year trial that compared lorcaserin 10mg twice daily and lorcaserin 10mg daily with placebo in patients with type 2 diabetes. BLOOM-DM (n=524) enrolled patients that had ar HbA1c ranging from 7-10% and were currently taking metformin, a sulfonylurea, or both. The change in weight from baseline (-4.7kg vs. -1.6kg; p-value<0.001, mean difference 3%), number of patients with loss of ≥5% of body weight (37.5% vs.16.1%; p-value<0.001), and number with ≥10% of body weight (16.3% vs. 4.4%; p-value<0.001) were statistically significant comparing lorcaserin twice daily to placebo, respectively. Limitations of this study included unclear treatment randomization, unclear allocation concealment, and unclear blinding of outcome assessors.

Clinical Safety:

In the BLOOM trial, there was no statistically significant difference in FDA-defined valvulopathy between lorcaserin and placebo (2.7% vs 2.3% respectively; p-value=0.70, RR 1.1; 95% CI 0.69-1.85). There was also no significant difference in withdrawals due to adverse effects between the two groups (7.1% vs 6.7%; RR 1.06; 95% CI 0.82, 1.37). The most common adverse events reported in both trials were headache, upper respiratory infection, nasopharyngitis, dizziness, and nausea, and there were two patients that experienced serious cardiac disorders in the lorcaserin group (<1%). The BLOSSOM trial also did not demonstrate significant differences in rates of FDA-defined valvulopathy with percentages being 2.0%, 1.4%, and 2.0% for lorcaserin BID, QD, and placebo respectively. However, the statistical power of the echocardiographic safety analysis was limited. Discontinuations due to adverse events were similar between lorcaserin given twice daily and placebo (7.2%, vs. 4.6%).

In the BLOOM-DM trial, rates of hypoglycemia were more frequent in the lorcaserin groups compared to placebo (7.4% BID, 10.5% QD, and 6.3% placebo) and were higher among patients taking sulfonylureas over metformin. At 52 weeks, one patient in the placebo group (0.5%), two in the lorcaserin daily group (2.5%; p=0.187), and six in the lorcaserin twice daily group (2.9%; p=0.122) had echocardiographic FDA-defined valvulopathy that was not present at baseline, but the trial itself enrolled too few patients to provide a statistically significant population analysis specifically for the FDA-defined valvulopathy safety analysis. The most common adverse events in the lorcaserin group compared to placebo were headache, back pain, nasopharyngitis, and nausea.

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

References:

1. Qsymia Prescribing Information. QsymiaPI.pdf. Available at: http://www.vivus.com/docs/QsymiaPI.pdf. Accessed August 23, 2012.
2. Belviq Prescribing Information. BelviqPI.pdf. 2012. Available at: http://us.eisai.com/package_inserts/BelviqPI.pdf. Accessed August 14, 2012.
3. Bray GA. Overview of therapy for obesity in adults. Available at: http://www.uptodate.com/contents/overview-of-therapy-for-obesity-in-adults?source=search_result&search=obesity&selectedTitle=3%7E150#H1. Accessed August 14, 2012.
4. Moyer V. Annals of Internal Medicine | Screening for and Management of Obesity in Adults: U.S. Preventive Services Task Force Recommendation Statement. Available at: http://annals.org/article.aspx?articleid=1200996. Accessed August 14, 2012.
5. Buelow V, Ngo D. Oregon Overweight, Obesity, Physical Activity and Nutrition Facts. *Oregon Health Authority: Health Promotion and Chronic Disease Section*. 2012. Available at: http://public.health.oregon.gov/PreventionWellness/ PhysicalActivity/Pages/pubs.aspx. Accessed August 14, 2012.
6. Initiative NOE, Heart N, Lung, et al. *The Practical guide: identification, evaluation, and treatment of overweight and obesity in adults*. National Heart, Lung, and Blood Institute, 2002.
7. Padwal RS, Rucker D, Li SK, Curioni C, Lau DC. Long-term pharmacotherapy for obesity and overweight. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004094.pub2/abstract. Accessed August 17, 2012.
8. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 2002;346(6):393–403.
9. Lau DCW, Douketis JD, Morrison KM, et al. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *Canadian Medical Association Journal*. 2007;176(8):S1–S13.
10. National Guideline Clearinghouse. National Guideline Clearinghouse | World Gastroenterology Organisation Global Guideline: obesity. Available at: http://guideline.gov/content.aspx?id=15230&search=obesity. Accessed August 14, 2012.
11. Fabricatore AN, Wadden TA, Moore RH, et al. Attrition from randomized controlled trials of pharmacological weight loss agents: a systematic review and analysis. *Obes Rev*. 2009;10(3):333–341.
12. FDA News Release. Press Announcements - FDA approves Belviq to treat some overweight or obese adults. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm. Accessed August 14, 2012.
13. Allison DB, Gadde KM, Garvey WT, et al. Controlled-Release Phentermine/Topiramate in Severely Obese Adults: A Randomized Controlled Trial (EQUIP). *Obesity*. 2012;20(2):330–342.
14. 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 randomised, placebo-controlled, phase 3 trial. *Lancet*. 2011;377(9774):1341–1352.
15. Garvey 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(2):297–308.
16. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. *N. Engl. J. Med.* 2010;363(3):245–256.
17. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized Placebo-Controlled Clinical Trial of Lorcaserin for Weight Loss in Type 2 Diabetes Mellitus: The BLOOM-DM Study. *Obesity (Silver Spring)*. 2012;20(7):1426–1436.
18. Fidler MC, Sanchez M, Raether B, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. *J. Clin. Endocrinol. Metab.* 2011;96(10):3067–3077.

Appendix 1: COMPARATIVE CLINICAL EFFICACY FOR PHENTERMINE/TOPIRAMATE

Relevant Endpoints:

1) Reduction in morbidity and mortality due to cardiovascular events
2) Reduction of Type 2 diabetes
4) Withdrawals due to adverse events

Primary Study Endpoint:

1) Percent of body weight loss
2) Lost ≥5% of baseline body weight
3) Lost ≥10% of baseline body weight

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Ref./Study Design[a]	Drug Regimens	Patient Population	N	Outcomes/ Efficacy Results	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Allison D, et al.[13] RCT, DB, PC, PG, Phase III (EQUIP)	1. PHEN/TPM CR 15mg/92mg 2. PHEN/TPM CR 3.75mg/23mg 3. Placebo 56-week (4-week postrandomization titration period) Randomized in a 2:1:2 ratio	<u>Demographics:</u> Age ~42.7; female 83%; BMI 42.0kg/m^2; white ~80%; black 16-18%; weight 115kg <u>Inclusion Criteria:</u> Age 18-70; BMI≥35kg/m^2(no upper limit); TG≤200mg/dL with treatment of 0-1 lipid lowering med; BP≤140/90mmg/Hg with treatment of 0-2 antihypertensive medications; fasting BG≤110mg/dL <u>Exclusion Criteria:</u> Weight gain/loss >5 kg ≤3 months; history of eating disorders; bariatric surgery, thyroid dysfunction; chronic oral glucocorticoid therapy; bipolar disorder or psychosis; current moderate to severe depression, history of suicidal behavior or ideation, or antidepressant use that had not been stable for ≤3 months; stroke, myocardial infarction, unstable angina, congestive heart failure, or cardiac valvulopathy;	1. 512 2. 241 3. 514	<u>Lost≥5% of baseline body weight (ITT/MI):</u> 1. 381 (74.4%) 2. 123 (51.1%) 3. 127 (24.8%) 1 vs. 3: RR 3.01; 95% CI (2.60, 3.49) p-value<0.0001 2 vs. 3: RR 2.07; 95% CI (1.69, 2.51) p-value<0.0001 <u>Lost≥10% of baseline body weight (ITT/MI):</u> 1. 291 (57.0%) 2. 56 (23.1%) 3. 57 (11.1%) p-value<0.0001 1 vs. 3: RR 5.13; 95% CI (3.98, 6.66) p-value<0.0001 2 vs. 3: RR 2.09; 95% CI (1.47, 2.98) p-value<0.0001 <u>Mean percent weight loss from baseline (ITT/MI):</u> 1. -12.20% (-11.2 to -13.2) 2. -5.25% (-3.9 to -6.6) 3. -1.24% (-0.2 to -2.3) p-value <0.0001	ARR: 50% NNT: 2 ARR: 26% NNT: 4 ARR: 46% NNT: 2 ARR: 12% NNT: 8 N/A	<u>Severe Adverse Events:</u> 1. 52 (10.2%) 2. 25 (10.4%) 3. 41 (8.0%) 1 vs. 3: RR 1.27; 95% CI (0.85, 1.92) p-value=0.22 <u>Withdrawal due to adverse events:</u> 1. 82 (16.0%) 2. 27 (11.3%) 3. 43 (8.4%) 1 vs. 3: RR 1.91; 95% CI (1.33, 2.76) p-value<0.001 No deaths were reported	NS ARR: 8% NNH: 13	**Quality Rating: Fair-Good** **Internal Validity: RoB** <u>Selection:</u> Adequate randomization technique Unclear allocation concealment; groups similar at baseline <u>Performance:</u> Patients and caregivers blinded Study drug and placebo were visually indistinguishable <u>Detection:</u> All study participants, study physicians, site staff, and sponsor representatives were blinded; the independent data and safety monitoring board were unblinded <u>Attrition:</u> High attrition (~40% average), but comparable to previous weight loss trials and similar between arms; used six different analyses to adjust for high attrition rates; results were all showing similar effects of weight loss **External Validity:** <u>Recruitment:</u> Not reported; study conducted at 91 U.S. sites (clinical practices, clinical trial sites, and academic centers) <u>Patient Characteristics:</u> Mostly white females in their 40's; about 13% were using antidepressant; also were taking lipid lowering agents and antihypertensive medications <u>Setting:</u> All patients were provided with standardized lifestyle counseling (500 kcal diet decrease, increase water consumption, increase exercise)—may bias away from the null <u>Outcomes:</u> Asked to return monthly for follow-ups; all were surrogate outcomes; no long term outcomes were assessed (such as reduction in morbidity and mortality due to weight loss)

2. Gadde K, et al.[14] RCT, DB, PC, Phase III (CONQUER)	1. PHEN/TPM CR 15mg/92mg 2. PHEN/TPM CR 7.5mg/46mg 3. Placebo 56-week (4-week postrandomization titration period) Randomized in a 2:1:2 ratio	Demographics: Age~51; Female 70%; White 86%; African 11%; Weight ~102kg; BMI~36; BP ~128/80; HTN ~52%; Hypertriglyceridaemia ~36%; Type 2 DM ~68%; Three or more co-morbidities ~52% Inclusion Criteria: Patients age 18-70; BMI 27-45 kg/m^2; Systolic BP 130-160 Diastolic BP 85-100; taking at least 2 antihypertensive medications; concentration of triglycerides 2*26-4*52 mmol/L or using at least 2 lipid-lowering drugs; fasting BG ≥5*55 mmol/L, BG≥7*77 mmol/L at 2 hours after oral glucose load during oral glucose tolerance test, or diagnosed type 2 DM managed with lifestyle changes or metformin monotherapy Exclusion Criteria: BP≥160/100 mmHg; type 1 DM; use of antidiabetic drug other than metformin history of nephrolithiasis, major depression; suicidal behavior with intention to act; current substantial depressive symptoms; No tricyclic antidepressants or monoamine oxidase inhibitors	1. 994 2. 498 3. 993	Lost≥5% of baseline body weight (ITT/LOCF): 1. 687 (70%) 2. 303 (62%) 3. 204 (21%) 1 vs. 3: RR 3.36; 95% CI (2.98, 3.80) p-value<0.0001 2 vs. 3: RR 2.98; 95% CI (2.59, 3.41) p-value<0.0001 Lost≥10% of baseline body weight (ITT/LOCF): 1. 467 (48%) 2. 182 (37%) 3. 72 (7%) 1 vs. 3: RR 6.47; 95% CI (5.14, 8.13) p-value<0.0001 2 vs. 3: RR 5.07; 95% CI (3.94, 6.57) p-value<0.0001 Mean percentage weight loss from baseline (ITT/LOCF): 1. Absolute change -10.2 kg (LSM: -9.8%) 95% CI (-10.4, -9.3); p-value<0.0001 2. -8.1kg (LSM: -7.8%) 95% CI (-8.5, -7.1); p-value<0.0001 3. -1.4kg (LSM: -1.2%) 95% CI (-1.8, -0.7)	ARR: 49% NNT: 2 ARR: 41% NNT: 2 ARR: 40% NNT: 2 ARR: 30% NNT: 3 N/A	Serious Adverse Events: 1. 50 (5%) 2. 15 (3%) 3. 40 (4%) 1 vs. 3: RR 1.25; 95% CI (0.82, 1.92) p-value=0.28 Withdrawal due to adverse events: 1. 191 (19%) 2. 58 (12%) 3. 88 (9%) 1 vs. 3: RR 2.16; 95% CI (1.70, 2.78) p-value<0.0001 One placebo-treated patient died as a result of cardiopulmonary arrest	NS ARR: 10% NNH: 10	**Quality Rating: Fair -Good** **Internal Validity: RoB** Selection: Adequate randomization assignment (computer generated algorithm implemented through an interactive voice response system to assign patients according to random allocation sequence); adequate allocation sequence; groups similar at baseline Performance: Investigators (physicians)* and patients were blinded. Detection:; unclear if outcome assessors were blinded Attrition: High attrition rate (overall 38%), but similar to previous weight loss trials and more in placebo arm. **External Validity:** Recruitment: Not reported; conducted at 93 centers in the U.S. Patient Characteristics: Patients were mostly white females with an average weight of 102 kg; they had more co-morbidities to start (over 50% with three or more) and were on one or more medications to control the co-morbidities; not used in advanced DM (controlled with metformin only) Setting: All patients were provided with standardized lifestyle counseling (500 kcal diet decrease, increase water consumption, increase exercise)—may bias away from the null Outcomes: Asked to return monthly for follow-ups; all were surrogate outcomes; no long term outcomes were assessed (such as reduction in morbidity and mortality due to weight loss)

3. Garvey W, et al.[15] RCT, DB, PC, Phase III extension of CONQUER (SEQUEL)	1. PHEN/TPM CR 15mg/92mg 2. PHEN/TPM CR 7.5mg/46mg 3. Placebo 52-week extension Randomized in a 2:1:2 ratio	Demographics: Age~51; Female ~65%; White ~85%; African ~12%; Weight ~102kg; BMI~36; BP ~128/80; HTN ~52%; Hypertriglyceridaemia ~35%; Type 2 DM ~20%; Metabolic syndrome ~67% Inclusion Criteria: Patients age 18-70; BMI 27-45 kg/m^2 as well as ≥2 weight-related co-morbidities, as previously described in CONQUER; female subjects of childbearing potential were required to continue contraception (double-barrier method, stable hormonal contraception + single barrier, or tubal ligation) Exclusion Criteria: BMI≤22 at CONQUER completion; not taking study drug continuously fo >4weeks at the end of CONQUER; developing a condition during CONQUER that would interfere with compliance or attainment of study measures, or participating in another formal weight-loss progran	1. 295 2. 154 3. 227	Lost≥5% of baseline body weight (ITT/LOCF/MI): 1. 235 (79.7%) 2. 114 (74.3%) 3. 67 (28.9%) 1 vs. 3: RR 2.70; 95% CI (2.22, 3.27) p-value<0.0001 2 vs. 3: RR 2.51; 95% CI (2.02, 3.07) p-value<0.0001 Lost≥10% of baseline body weight (ITT/LOCF/MI): 1. 156 (53%) 2. 78 (50.6%) 3. 26 (11.6%) 1 vs. 3: RR 4.61; 95% CI (3.17, 6.90) p-value<0.0001 2 vs. 3: RR 2.31; 95% CI (1.51, 3.59) p-value<0.0001 Mean percentage change from baseline in body weight (least-square mean using multiple imputation; 95% CI): 1. -11.2% (-12.2, -10.3) 2. -10.3% (-11.6, -9.0) 3. -2.5% (-3.4, -1.6) p-value<0.0001 compared with placebo for all comparisons	 ARR: 50% NNT: 2 ARR: 45% NNT: 2 ARR: 41% NNT: 2 ARR: 15% NNT: 7 N/A	Serious Adverse Events: 1. 12 (4.1%) 2. 4 (2.6%) 3. 9 (4.0%) 1 vs. 3: RR 1.03; 95% CI (0.41, 2.61) p-value=0.95 Withdrawal due to adverse events: 1. 13 (4.4%) 2. 7 (4.5%) 3. 7 (3.1%) 1 vs. 3: RR 1.43; 95% CI (0.54, 3.91) p-value=0.43 No deaths reported	 NS NS	**Quality Rating: Poor-Fair** **Internal Validity: RoB** Selection: Patients included who consented from CONQUER; those who completed and complied with previous study (may introduce bias away from the null). Performance: Investigators (physicians)* and patients were blinded Detection: Unclear if outcome assessors were blinded Attrition: Lower overall attrition compared to previous studies (average ~15%); potentially due to compliant patients from CONQUER and similar between all arms. **External Validity:** Recruitment: Patients from the CONQUER study were chosen to continue in the SEQUEL study; 36 sites from the CONQUER study were selected for the extension study based on their high initial enrollment numbers and rates of retention Patient Characteristics: Same as the CONQUER study (see above), but considered more compliant individuals overall; smaller sample size Setting: All patients continued to receive standardized lifestyle counseling (500 kcal diet decrease, increase water consumption, increase exercise)—may bias away from the null Outcomes: Asked to return monthly for follow-ups; all were surrogate outcomes; no long term outcomes were assessed (such as reduction in morbidity and mortality due to weight loss)

RCT: Randomized Controlled Trial; DB: Double-blind; PC: Placebo Controlled; PG: Parallel Group; PHEN/TPM CR: controlled-release phentermine/topiramate; HTN: Hypertension; BP: Blood pressure; BG: Blood glucose; DM: Diabetes mellitus; MITT: Modified-intention-to-treat; LOCF: last-observation-carried-forward; MI: multiple imputation; *Vivus medical information was contacted to clarify what was meant by investigators; they consider investigators (physicians) to be care givers

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Appendix 2:COMPARATIVE CLINICAL EFFICACY FOR LORCASERIN

Relevant Endpoints:

1) Reduction in morbidity and mortality due to cardiovascular events
2) Reduction in incidence of type 2 diabetes
3) FDA-defined valvulopathy
4) Withdrawals due to adverse events
5) Long term maintenance of weight loss

Primary Study Endpoint:

4) Percent change in weight from baseline at 1 year
5) Percent of subjects achieving ≥5% weight loss at week 52
6) Percent of subjects achieving ≥10% weight loss at week 52

Ref./Study Design[a]	Drug Regimens	Patient Population	N	Outcomes/ Efficacy Results	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Smith S, et al. RCT, DB, PC[16] (BLOOM)	1. Lorcaserin (L) 10 mg BID 2. Placebo (P) BID Year 1: 1:1 ratio 2-year study; patients re-randomized in the second year in a 2:1 ratio	Demographics: White 67.9%; Black 18.7%; Hispanic 11.4%; Female 82.9% Mean Age: 43.8±0.3 Weight: 100.4±0.4 kg BMI: 36.2 BP: ~120/76 Total Cholesterol (mg/dL): ~195 HbA1c%: 5.66±0.01 Inclusion Criteria: Age 18 to 65 years; BMI of 30 to 45 or of 27 to 45 with 1+ co-existing condition (HTN, dyslipidemia, CV disease, impaired glucose tolerance, or sleep apnea) Exclusion Criteria: Moderate or more severe mitral regurgitation or aortic regurgitation (i.e. valvulopathy), DM, >140mmHg systolic BP, >90mmHg diastolic BP, depression or other psychiatric disease within the past 2 years, pregnanc and lactation	L: 1593 P: 1584 MITT1: L: 1538 P: 1499	% of subjects achieving ≥5% weight loss at week 52 (MITT): L: 731 (47.5%) P: 304 (20.3%) RR 2.3, 95% CI (2.09, 2.62) p-value<0.001 % of subjects achieving ≥10% weight loss at week 52 (MITT): L: 347 (22.6%) P: 115 (7.7%) RR 3.0, 95% CI (2.8, 4.4) p-value<0.001 Weight as a % change from baseline body weight at Year 1 L: -5.9±0.2 kg P: -2.2±0.1 kg Mean Difference: -3.7; 95% CI (-4.1, -3.3); p-value<0.0001	ARR: 27% NNT: 4 ARR: 15% NNT: 7 N/A	Outcome: FDA-defined Valvulopathy at week 52* L: (34/1278) 2.7% P: (28/1191) 2.3% RR 1.1, 95% CI (0.69, 1.85 p-value 0.70 Withdrawal due to adverse events: L: 113 (7.1%) P: 106 (6.7%) RR 1.06; 95% CI (0.82, 1.37); p-value=0.68	NS NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: Adequate generation of randomizatic sequence; adequate allocation concealment (treatment kits with randomization numbers we used); groups were similar at baseline; sample s was adequate Performance: Patients and investigators blinded Detection: Unclear if outcome assessors blinded Attrition: High overall attrition (lorcaserin 37.2% and placebo 40.6%): large percentage of withdrawal was from subject decision; used MI analysis with LOCF(potential bias away from the null) **External Validity:** Recruitment: Not reported; conducted at 98 academic and private trial sites Patient Characteristics: Mostly healthy, white, obese females in their 40's Setting: All patients enrolled in a standardized behavioral weight management program Outcomes: 1-year duration with high attrition a LOCF (bias weight reduction over gain); all surrogate endpoints measured as outcomes, nc clinically relevant long-term outcomes

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

3. Fidler M, et al. RCT, DB, PC PG[18] (BLOSSOM)	1. Lorcaserin 10 mg BID 2. Lorcaserin 10 mg QD 3. Placebo 52-week study randomized in a 2:1:2 ratio	Demographics: Age ~43; Female ~80%; White ~67%; Black ~20%; Hispanic ~10%; Weight 100kg; BMI ~35; HTN 23%; Dyslipidemia 27% Inclusion Criteria: Age 18-65 year olds; BMI between 30-45 kg/m2 or between 27 and 29.9 kg/m2 with co-morbidity (HTN, dyslipidemia, CV disease, impaired glucose tolerance, or sleep apnea, and ability to participate in exercise program) Exclusion Criteria: Recent CV events; major surgeries; medical conditions that would prevent food or exercise change; DM; BP>150/95mm/Hg; TG>499mg/dL; SSRI within 1 year; previous bariatric surgery; recent weight-loss drugs (within 1 month for OTC, 3 months for prescription) or low calorie diet; or change in weight o at least 5 kg within 3 months. *Did not exclude patients based on echocardiographic results	1. 1602 2. 801 3. 1601 MITT: 1. 1561 2. 771 3. 1541	% of subjects achieving ≥5% weight loss at week 52 (MITT): 1. 737 (46%) 2. 296 (37%) 3. 384 (24%) 1 vs. 3*: RR 1.91; 95% CI (1.73, 2.12); p-value<0.001 % of subjects achieving ≥10% weight loss at week 52 (MITT): 1. 353 (22.6%) 2. 134 (17.4%) 3. 150 (9.7%) p-value<0.001 1 vs. 3*: RR 2.32; 95% CI (1.95, 2.77) Co-Primary End-point ITT with LOCF: Weight as a % change from baseline body weight at Year 1: 1. -5.6% (-5.9 to -5.3%) 2. -4.6% (-5.0 to -4.1%) 3. -2.7% (-3.1 to -2.4%) No p-values were reported *RR not reported for group 2, as it is not an approved dose.	ARR: 22% NNT: 5 ARR: 13% NNT: 8 N/A	Outcome: FDA-defined Valvulopathy that was no present at baseline at week 52* 1. 24/1208 (2.0%) 2. 8/622 (1.4%) 3. 23/1153 (2.0%) Withdrawal due to adverse events: 1. 115 (7.2%) 2. 50 (6.2%) 3. 73 (4.6%) 1 vs. 3*: RR 1.57; 95% CI (1.18, 2.09) Serious adverse events 1. 49 (3.1%) 2. 27 (3.4%) 3. 36 (2.2%) 1 vs. 3*: RR 1.36; 95% CI (0.8-2.12) 1 death in placebo group due to asthma attack *RR not reported for group 2, as it is not an approved dose.	NS ARR: 3% NNH: 38 NS	**Quality Rating: Fair** **Internal Validity: RoB** Selection: unclear treatment allocation concealment, adequate randomization techniqu (randomization code generated programmatica by statistician not directly involved with study) Performance: Stated double-blinding, but did n specifically mention care giver and patient blinc or use of matching placebo for daily dosing grou Detection: outcome assessors blinded for echocardiography analysis Attrition: High attrition rates (>40%), but simila other weight loss trials; high number of patient requesting to withdraw from study, use of LOCF **External Validity:** Recruitment: Not reported; study was conducte 97 U.S. research centers Patient Characteristics: Majority were women (~80%); white (~67%); included patients with H (BP<150/95), dyslipidemia, CV disease, impaire glucose tolerance, and sleep apnea Setting: All patients were instructed to reduce caloric intake by 600 kcal and participate in 30 minutes of exercise daily; Returned at 2 and 4 weeks post-randomization, then on a monthly b Outcomes: 1-year study with high attrition and LOCF imputation; only reported true IIT for % weight change and ≥5% weight loss; reported MITT for ≥10% weight loss; mostly surrogate endpoints; no morbidity/mortality data or reduction in hospitalizations

2. O'Neil P, et al. RCT, DB, PC[17] (BLOOM-DM)	1.Lorcaserin 10 mg BID 2. Lorcaserin 10 mg QD 3. Placebo 52-week study randomized in a 1:1:1 ratio	Demographics: Age ~53; women 54%; weight ~104kg; BMI ~36; white 58.7%; African Americans 22.3%; HbA1c 8.1%; Metformin 92%; Sulfonylurea 50%; both medications 42% Inclusion Criteria: Type 2 DM treated with metformin, a SFU, or both; HbA1c at visit between 7-10%; 18-65 years old with BMI 27-45 kg/m^2; were able to participate in moderate intensity exercise program Exclusion Criteria: Use of insulin, exenatide o pramlintide (body weight effects); prior bariatric surgery; depression or other psychiatric disorder; cardiopulmonary problems (stroke, MI, unstable angina); TSH or T4 abnormalities; TG>499mg/dL; LDL>160mg/dL; SCr>1.5 times upper limit of norma	1. 256 2. 95 3. 252 MITT: 1. 251 2. 94 3. 248	% of subjects achieving ≥5% weight loss at week 52 (MITT): 1. 94 (37.5%) 2. 42 (44.7%) 3. 40 (16.1%) 1 vs. 3* RR 2.32; 95% CI (1.67, 3.22) p-value <0.001 % of subjects achieving ≥10% weight loss at week 52 (MITT): 1. 41 (16.3%) 2. 17 (18.1%) 3. 11 (4.4%) 1 vs. 3*: RR 3.68; 95% CI (1.94, 7.0) p-value <0.001 Weight as a % change from baseline body weight at Year 1 1. -4.5±0.4 2. -5.0±0.5 3. -1.5±0.4 p-value<0.001 *RR not reported for group 2, as it is not an approved dose	ARR: 21% NNT: 5 ARR: 12% NNT: 8 N/A	FDA-defined Valvulopathy that was not present at baseline at week 52* 1. 6 (2.9%) 2. 2 (2.5%) 3. 1 (0.5%) p=0.06 1 vs. 3: RR 5.97; 95% CI (0.72, 49.17) Withdrawal due to adverse events: 1. 22 (8.6%) 2. 6 (6.3%) 3. 11 (4.3%) 1 vs. 3: RR 1.97; 95% CI (0.97, 3.97) Hypoglycemia 1. 19 (7.4%) 2. 10 (10.5%) 3. 16 (6.3%) 1 vs. 3: RR 1.16; 95% CI (0.58, 2.32); p-value=0.66 Serious adverse events 1. 16 (6.3%) 2. 8 (8.4%) 3. 17 (6.7%) 1 vs. 3: RR 0.93; 95% CI (0.46, 1.90); p-value=0.83 No deaths occurred	NS NS NS NS	**Quality Rating: Fair (-)** **Internal Validity: RoB** Selection: Unclear randomization techniques; unclear allocation concealment; groups were similar at baseline Performance: Patients and investigators blinded Detection: Unclear if outcome assessors were blinded Attrition: Included MITT analysis with LOCF; in t study, a smaller population was used compare t the previous study, so small changes in data wil have a large effect on the outcome (bias potent away from the null); had high attrition rates (21 37%) with more patients in the placebo group t treatment arms. **External Validity:** Recruitment: Not reported; conducted in 58 academic and private research sites in U.S. Patient Characteristics: Diabetes population wit HbA1c between 7-10% and only either metform or sulfonylurea or both (no insulin which could potentially increase hypoglycemia side effect); women comprised just over half of the populati small sample size; older (~54 years old) Setting: All patients enrolled in a standardized behavioral weight management program; Retur at 2 and 4 weeks post-randomization, then on a monthly basis Outcomes: 1-year duration with high attrition a LOCF (bias weight reduction over gain); all surrogate endpoints; no clinically relevant long-term outcomes (reported weight loss, cholester blood pressure, etc.)

RCT: Randomized Controlled Trial; DB: Double-blind; PC: Placebo Controlled; PG: Parallel Group; HTN: Hypertension; CV: Cardiovascular; BP: Blood pressure; DM: Diabetes mellitus; TG: Triglycerides; SSRI: Selective serotonin reuptake inhibitor; OTC: over-the-counter, MITT: Modified-intention-to-treat; LOCF: last-observation-carried-forward

*Echocardiographic analyses used all patients with an echocardiogram at baseline and at least one post-baseline time point, with LOCF imputation

Appendix 3: Specific Drug Information for phentermine/topiramate

CLINICAL PHARMACOLOGY[1]

The mechanism of action for both drugs is not fully known. Phentermine is a sympathomimetic amine and is thought to stimulate increased hypothalamic release of norepinephrine, resulting in reduced appetite and decreased food consumption. Topiramate, a fructose monosaccharide derivative, is thought to have a combined pharmacologic effect, including augmenting the activity of the neurotransmitter gamma-aminobutyrate, modulation of voltage-gated ion channels, inhibition of AMPA/kainite excitatory glutamate receptors, or inhibition of carbonic anhydrase. In combination, it can help suppress appetite and enhance satiety.

PHARMACOKINETICS[1]

Parameter	Result (Phentermine)	Result (Topiramate)
Oral Bioavailability	Not reported	Not reported
Elimination	70-80% in urine unchanged	70% in urine unchanged
Half-Life	~20 hours	~65 hours
Metabolism	P-hydroxylation; N-oxidation CYP3A4 metabolism	Hydroxylation; hydrolysis; glucuronidation

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE FORM:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Titration Doses: 3.75 mg/ 23 mg 11.25mg/ 69mg	Oral	QD morning	Capsule	Moderate CrCl<50mL/min Severe CrCl<30mL/min NTE: 7.5mg/46mg once daily	Moderate hepatic impairment (Child-Pugh score 7 - 9) NTE: 7.5 mg/46 mg once daily	Not recommended under 18 years of age	Use caution (minimal data over age 65)	-With or without food -Start with low dose for 14 days, then increase to recommended doses (either 7.5mg/46mg or 15mg/92mg depending o titration phase) -Used for titration purposes
Normal Doses: 7.5mg/ 46mg 15mg/ 92mg	Oral	QD morning	Capsule	Moderate CrCl<50mL/min Severe CrCl<30mL/min NTE: 7.5mg/46mg once daily	Moderate hepatic impairment (Child-Pugh score 7 - 9) NTE: 7.5 mg/46 mg once daily	Not recommended under 18 years of age	Use caution (minimal data over age 65)	-With or without food -Evaluate weight loss after 12 weeks witl the 7.5mg/46mg dose (patient should lo at least 3% of body weight to continue o escalate dose) -Patient should lose at least 5% of body weight after 12 weeks at high dose (15mg/92mg) or else discontinue treatm

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Discontinue medication by taking a dose every other day for at least 1 week prior to stopping treatment altogether (potential of precipitating a seizure in norma subjects if abrupt withdrawal)

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

- Risk Evaluation and Mitigation Strategy (REMS) requirement put in place to inform prescribers and female patients of reproductive potential about:
    - The increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to phentermine/topiramate during the first trimeste of pregnancy
    - The importance of pregnancy prevention for females of reproductive potential receiving phentermine/topiramate
    - The need to discontinue phentermine/topiramate immediately if pregnancy occurs
- Requirements: dispense medication guide with prescription; prescriber training required; dispensed by certified pharmacies

Contraindications:

- Pregnancy (topiramate shown to increase risk of oral clefts in first trimester of pregnancy; category X)
- Glaucoma (topiramate has been reported to cause acute myopia and secondary angle closure glaucoma)
- Hyperthyroidism
- During or within 14 days following administration of monoamine oxidase inhibitors
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines

Warnings and Precautions:

- Fetal Toxicity: Phentermine/topiramate can cause fetal harm. Data from pregnancy registries and epidemiology studies indicate that a fetus exposed to topiramate in the first trimester of pregnancy has an increased risk of oral clefts (cleft lip with or without cleft palate).

- Increase in heart rate: A higher percentage of phentermine/topiramate-treated overweight and obese adults experienced heart rate increases from baseline of more than 5, 10, 15, and 20 beats per minute (bpm) compared to placebo-treated overweight and obese adults. Regular monitoring of resting heart rate is recommended while on phentermine/topiramate. Clinical significance of a heart rate elevation with phentermine/topiramate treatment is unclear, especially for patients with cardiac and cerebrovascular disease (such as patients with a history of myocardial infarction or stroke in the previous 6 months, life-threatening arrhythmias, or congestive heart failure).

- Suicidal behavior and ideation: Antiepileptic drugs (AEDs), including topiramate, a component of phentermine/topiramate, increase 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 phentermine/topiramate in patients who experience suicidal thoughts or behaviors.

- Acute myopia and secondary angle closure glaucoma: Has been reported in patients treated with topiramate. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure, possible mydriasis; symptoms can occur within the first month

of initiating treatment or anytime during therapy. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. The primary treatment to reverse symptoms is immediate discontinuation of phentermine/topiramate.

- Mood and sleep disorders: Patients with a history of depression may be at increased risk of recurrent depression or other mood disorders while taking phentermine/topiramate. The majority of these mood and sleep disorders resolved spontaneously, or resolved upon discontinuation of dosing.

- Cognitive impairment: Rapid titration or high initial doses of phentermine/topiramate may be associated with higher rates of cognitive events such as attention, memory and language/word-finding difficulties. Since phentermine/topiramate has the potential to impair cognitive function, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain phentermine/topiramate therapy does not affect them adversely. If cognitive dysfunction persists consider dose reduction or withdrawal of phentermine/topiramate for symptoms that are moderate to severe, bothersome, or those which fail to resolve with dose reduction.

- Metabolic acidosis: Hyperchloremic, non-anion gap, metabolic acidosis (decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) has been reported in patients treated with phentermine/topiramate. Conditions or therapies that predispose to acidosis (i.e., renal disease, severe respiratory disorders, status epilepticus, diarrhea, surgery or ketogenic diet) may be additive to the bicarbonate lowering effects of topiramate. Concomitant use of phentermine/topiramate and a carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide) may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. The effect of phentermine/topiramate on growth and bone-related sequelae has not been systematically investigated in long-term, placebo-controlled trials. Measurement of electrolytes including serum bicarbonate prior to starting phentermine/topiramate and during treatment is recommended. In clinical trials, the peak reduction in serum bicarbonate occurred by week 4 and in most subjects there was a correction of bicarbonate by week 56, without any change to study drug. However, if persistent metabolic acidosis develops while taking phentermine/topiramate, reduce the dose or discontinue the medication.

- Elevation in creatinine: Peak increases in serum creatinine were observed after 4 to 8 weeks of treatment. On average, serum creatinine gradually declined but remained elevated over baseline creatinine values. Elevations in serum creatinine often signify a decrease in renal function, but the cause for phentermine/topiramate -associated changes in serum creatinine has not been definitively established. Therefore, measurement of serum creatinine prior to starting phentermine/topiramate and during treatment is recommended. If persistent elevations in creatinine occur while taking phentermine/topiramate, reduce the dose or discontinue the medication.

- Potential risk of hypoglycemia in patients with Type 2 Diabetes and on an anti-diabetic medication: 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). Phentermine/topiramate has not been studied in combination with insulin. Measurement of blood glucose levels prior to starting and during treatment is recommended in patients with type 2 diabetes. Decreases in medication doses for antidiabetic medications which are nonglucose-dependent should be considered to mitigate the risk of hypoglycemia. If a patient develops hypoglycemia after starting phentermine/topiramate, appropriate changes should be made to the antidiabetic drug regimen.

- Potential risk of hypotension in patients treated with antihypertensive medications: In hypertensive patients being treated with antihypertensive medications, weight loss may increase the risk of hypotension, and associated symptoms including dizziness, lightheadedness, and syncope. Measurement o blood pressure prior to starting phentermine/topiramate and during treatment is recommended in patients being treated for hypertension. If a patient

develops symptoms associated with low blood pressure after starting phentermine/topiramate, appropriate changes should be made to the antihypertensive drug regimen.

- CNS depression with concomitant CNS depressants including alcohol: Avoid concomitant use of phentermine/topiramate with alcohol because it can potential CNS depression or other centrally mediated effects such as dizziness, drowsiness, light-headedness, impaired coordination, and somnolence.

- Potential seizures with abrupt withdrawal of phentermine/topiramate: It has been shown in patients taking topiramate that abrupt withdrawal can increase the risk for seizures in individuals without a history of seizures or epilepsy. If the medication is immediately terminated, appropriate monitoring is recommended. Patients who are discontinuing the 15mg/92mg dose of phentermine/topiramate, gradual tapering is recommended to alleviate seizure risk.

- Patients with renal impairment: Both phentermine and topiramate are renally cleared, so exposure increases with moderate or severe renal impairment. It has not been studied in patients in end-stage renal disease on dialysis, and the medication should be avoided.

- Patients with hepatic impairment: In patients with mild or moderate hepatic impairment, exposure compared to healthy volunteers was higher, and the dose should be adjusted accordingly. It has not been studied in patient with severe hepatic impairment and should be avoided.

- Kidney stones: Topiramate inhibits carbonic anhydrase activity and promotes kidney stone formation by reducing urinary citrate excretion and increasing urine pH. Avoid the use of the medication with other drugs that inhibit carbonic anhydrase. Also, the use of topiramate by patients on a ketogenic diet may result in a physiological environment that increases the likelihood of kidney stone formation. Increase in fluid intake is recommended.

- Oligohydrosis and Hyperthermia: Topiramate has been shown to decrease sweating and increase body temperature. Patients treated with phentermine/topiramate should be advised to monitor for decreased sweating and increased body temperature during physical activity, especially in hot weather. Caution should be used when it is prescribed with other drugs that predispose patients to heat-related disorders, which include carbonic anhydrase inhibitors and anticholinergic activity.

- Hypokalemia: Mechanism is through carbonic anhydrase activity inhibition, and monitoring potassium levels should be done, especially if used in combination with non-potassium-sparing diuretics.

- LABS: Bicarbonate, creatinine, potassium, and glucose labs should be collected at baseline and periodically during treatment.

Table 1:[1] Adverse Reactions Reported in Greater than or Equal to 2% of Patients and More Frequently with than Placebo During 1-Year Treatment-Overall Study Population				
System Organ Class Preferred Term	Placebo (N=1561) %	Phentermine/topiramate 3.75mg/23mg (N=240) %	Phentermine/topiramate 7.5mg/46mg (N=498) %	Phentermine/topiramate 15mg/92mg (N=1580) %

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Nervous System Disorders				
Paresthesia	1.9	4.2	13.7	19.9
Headache	9.3	10.4	7.0	10.6
Dizziness	3.4	2.9	7.2	8.6
Dysgeusia	1.1	1.3	7.4	9.4
Psychiatric Disorders				
Insomnia	4.7	5.0	5.8	9.4
Gastrointestinal Disorders				
Constipation	6.1	7.9	15.1	16.1
Dry Mouth	2.8	6.7	13.5	19.1
Nausea	4.4	5.8	3.6	7.2
Metabolism and Nutrition Disorders				
Hypokalemia	0.4	0.4	1.4	2.5
Infections and Infestations				
Upper Respiratory Tract Infection	12.8	15.8	12.2	13.5
Nasopharyngitis	8.0	12.5	10.6	9.4
Urinary Tract Infection	3.6	3.3	5.2	5.2

Potential Drug Interactions:

- Monoamine oxidase inhibitors
- Oral contraceptives
- CNS depressants including alcohol
- Non-potassium sparing diuretics
- Antiepileptic drugs
- Carbonic Anhydrase Inhibitors

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Appendix 4: Specific Drug Information for lorcaserin

CLINICAL PHARMACOLOGY[2]

Lorcaserin hydrochloride is a selective serotonin 2C receptor agonist for oral administration used for chronic weight management. Lorcaserin is believed to decrease food consumption and promote satiety by selectively activating 5-HT2C receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus. The exact mechanism of action is not known. Lorcaserin at the recommended daily dose selectivity interacts with 5-HT2C receptors as compared to 5-HT2A and 5-HT2B receptors, other 5-HT receptor subtypes, the 5-HT receptor transporter, and 5-HT reuptake sites.

PHARMACOKINETICS[2]

Parameter	Result
Oral Bioavailability	Peak plasma 1.5-2 hours after oral dose; unknown absolute bioavailability in humans
Elimination	Urine ~92.3%; feces ~2.2%
Half-Life	~11 hours; ss=3 days (BID dosing); accumulation ~70%
Metabolism	Extensive liver metabolism

DOSE & AVAILABILITY[2]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10 mg	Orally	Twice daily	20 mg/day Tablets	No adjustment needed; not recommended in severe renal dysfunction (CrCl<30mL/min) or ESRD	No adjustment needed in mild to moderate impairment; use caution in severe impairment	Not established	No change unless renally impaired	-Can be taken with or without food -Evaluate response to therapy in 12 weeks and if patient has not lost at lea 5% of body weight, discontinue medication

DRUG SAFETY[2]

Serious (REMS, Black Box Warnings, Contraindications):

- Contraindication: Pregnancy (category X)

Warnings and Precautions:

- Serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions
  - Possible when given with concomitant medications that can increase serotonin
  - Has not been shown to cause serotonin syndrome or NMS

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

- Valvular heart disease
    - Has not been studied in congestive heart failure or hemodynamically-significant valvular heart disease
- Cognitive impairment possible
- Psychiatric disorders
    - Events of euphoria, hallucination, and dissociation seen at supratherapeutic doses
    - Possible abuse/dependence potential
- Potential risk of hypoglycemia in patients with type 2 diabetes mellitus on antidiabetic therapy
    - Shown to increase hypoglycemic events in patients on sulfonylurea in clinical trial (BLOOM-DM)
    - Has not been studied in patients on insulin yet
- Priapism
    - Has not been proven, but use caution due to the 5-HT_{2c} receptor agonism
- Heart Rate Decreases
    - Use caution in patients with history of bradycardia or heart block greater than first degree
- Laboratory Changes:
    - Hematological Changes: decrease in white blood cell count seen
    - Prolactin Elevation
    - Pulmonary Hypertension: not proven

Allergies/Interactions:

- Drug-Interactions:
    - Other serotonergic neurotransmitter system medications (SSRIs, MAOIs, SNRIs, triptans, TCAs, dextromethorphan, tramadol, etc.);
    - Medications that use CYP2D6 metabolism (lorcaserin is a CYP2D6 inhibitor)
- Food-Drug: None known

Common Adverse Events in Clinical Trials (>5% compared to placebo):

BLOOM and BLOSSOM combined data	Number of patients (%)	
Adverse Events (Non-diabetic patients)	Belviq 10mg BID (N=3195)	Placebo (N=3185)
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Fatigue	229 (7.2)	114 (3.6)
Nausea	264 (8.3)	170 (5.3)
Dry Mouth	169 (5.3)	74 (2.3)
Constipation	186 (5.8)	125 (3.9)

BLOOM-DM data	Number of patients (%)	
Adverse Events (Diabetic patients)	Belviq 10mg BID (N=256)	Placebo (N=252)
Hypoglycemia	75 (29.3)	53 (21)
Headache	37 (14.5)	18 (7.1)
Back pain	30 (11.7)	20 (7.9)
Cough	21 (8.2)	11 (4.4)
Fatigue	19 (7.4)	10 (4.0)

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.

Authors: Chelsea Smith, Pharm.D. Candidate, M. Herink, Pharm.D.