New York Department of Health

Dossier Summary and Response

Topic: Belviq® (lorcaserin HCl) **Date**: March 3, 2016

Dossier Submission

Hodes & Landy, on behalf of Eisai, Inc., submitted a dossier on Belviq® for chronic weight management on November 5, 2015. The dossier was completed in accordance with the Department's instructions and included 17 articles (14 summarized / 8 quality-assessed) for review published between 2000 and 2015. Of the submitted articles, seven were rated by the submitter as having good methodologic quality, and one was rated fair quality. The submitted articles provided information on the efficacy and safety of lorcaserin, a serotonin 2C receptor agonist for weight loss in obese adults and those who are overweight with one or more comorbid conditions.

Dossier Review Process

The Center for Evidence-based Policy (Center) provided a review of the submitted dossier. Submitted articles were independently assessed for inclusion, methodological quality, and reported results. Literature searches of the MEDLINE® (Ovid) database and Center's core sources[1] (a select group of resources considered high quality due to being independent and using systematic methods) were conducted to identify any additional relevant evidence.

Review Results

Evidence Evaluation – Included Studies

The Center staff performed a search to identify any additional articles relevant to the topic. The search methodology is detailed in Appendix A. The search was limited to articles published after 2005. When reviewing the studies either submitted in the dossier or identified by the subsequent search, only comparative studies were considered for evaluation of efficacy. Included studies were limited to English language, systematic reviews (SRs) with or without meta-analyses (MAs), randomized controlled trials (RCTs), or observational studies. Case series were additionally considered to evaluate harms. In addition, only patient important outcomes have relevance for New York Department of Health. The rationale for study inclusion can be found in the New York Department of Health Dossier Methods Guidance (New York

[1] Center core sources searched include Hayes, Inc., Cochrane Library (Wiley Interscience), the United Kingdom National Institute for Health and Care Excellence (NICE), the Blue Cross/Blue Shield Health Technology Assessment (HTA) program, the Veterans Administration Technology Assessment Program (VATAP), *BMJ Clinical Evidence*, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Washington State Health Technology Assessment Program, the United States Preventive Services Task Force (USPSTF), and the Agency for Healthcare Research and Quality (AHRQ).

Department of Health, 2015). Exclusion criteria were selected prior to review of the studies, and study methods were assessed prior to review of outcomes to eliminate bias.

Exclusion criteria included:

- Original research with less than 10 participants
- Less than six months of follow-up for efficacy outcomes (studies included for harms)
- Information from research study published more than once (only the highest quality article was included)

A search of Center core sources identified three SRs in addition to those submitted in the dossier (Chan et al., 2013; Ryan & Braverman-Panza, 2014; Yanovski & Yanovski, 2014). The Medline® search identified 122 studies, of which 11 were identified as potentially relevant and selected for full text review. Six additional studies were selected for final inclusion that were not included in the dossier submission. Appendix B provides the rationale for study inclusion and exclusion based on full text review.

Review of the included dossier materials resulted in exclusion of 10 of the 14 submitted articles based on study design, population, intervention, or treatment under study (see Table 2 for studies descriptions and exclusion criteria). Table 1 includes a complete list of articles included in this report, and associated methodological quality ratings, sample size and findings. Study quality was rated by the Center using the same quality assessment forms as provided by the submitter. Appendix C includes the both raters quality assessment for all included studies.

Evidence Review

This section provides an overview of included studies and a summary of the findings regarding effectiveness, harms and costs related to lorcaserin for weight loss. The quality ratings included in this section refer to the ratings by the Center unless otherwise specified. Table 1 provides greater study detail than included in the summary below.

Included Studies

Seven SRs and/or MAs are included in this review. Five of the SR/MAs were rated as having good methodological quality, and two were rated as having fair methodologic quality. There was substantial overlap in study inclusion across the SRs and MAs, with most reviews drawing upon data from three published Phase III RCTs. Given the study overlap across SRs, the primary RCTs are described in detail below.

Three good quality multicenter Phase III randomized double-blind placebo-controlled trials addressing the efficacy and harms of lorcaserin for obese and overweight individuals with one or more co-morbidities were included: BLOOM (n=3,182) (Smith et al., 2010), BLOSSOM (n=4,008) (Fidler et al., 2011), and BLOOM-DM (n=604) (O'Neil et al., 2012). The BLOOM trial

compared lorcaserin 10 milligrams (mg) twice daily to placebo, while BLOSSOM and BLOOM-DM included three groups: lorcaserin twice daily, lorcaserin daily, and placebo. The BLOOM-DM study was the only RCT that addressed use of lorcaserin in patients with diabetes. Strengths of the three Phase III RCTs include that they were multicenter studies, that randomization was performed by a third party, and they were performed in a double blinded manner. Weaknesses across all studies include a high drop-out rate, strict exclusion criteria which limits generalizability, and lack of long-term follow-up to enable accurate assessment of harms and benefits. In addition, the studies were not adequately powered to detect FDA-defined valvulopathy. All three Phase III RCTs were funded, designed, and performed by the makers of Belviq®. In addition, a fair quality Phase I RCT (n=469) comparing lorcaserin to placebo over a 12-week period (Smith et al., 2009) and a fair quality RCT (n=35) assessing the abuse potential of lorcaserin in polydrug users were included for assessment of harms only (Shram et al., 2011). Table 1 provides further description of the methods, outcomes, and limitations of each study.

Effectiveness

The outcomes summarized below were selected by Eisai, Inc., and include weight loss, waist circumference, body mass index (BMI), glycemic parameters, and cardiovascular risk factors. Weight loss can be measured in many ways, with varying degrees of relevance to cardiac risk. Weight loss of at least five percent has been associated with improvements in cardiovascular risk factors and diabetes, and therefore is a clinically significant measure (Wing et al., 2011). Body mass index, measured in kilograms per meter squared (kg/m^2), is commonly used in weight loss studies, however, it is a poor measure of adiposity. Therefore, it is a less reliable measure of clinically meaningful weight loss (Rothman, 2008). A cut-point for waist circumference has not been identified. In general, increasing waist circumference, as a measure of abdominal obesity, is associated with increased cardiovascular risk (Jensen et al., 2013).

Outcome #1: Weight Loss

In three phase III RCTs, 37.5 to 47.5% of participants taking lorcaserin twice daily lost at least five percent of their baseline body weight compared to placebo (16.1 to 25.0%) at the end of one year. Similarly, the proportion of those who lost at least 10% of their baseline body weight was higher in the lorcaserin groups (16.3 to 22.6%) compared to those in the placebo arms (4.4 to 9.7%). The change in baseline body weight averaged 4.7 to 5.8 kilograms (kg) across studies for those taking lorcaserin compared to 1.6 to 2.9 kg in the placebo groups. The BLOSSOM RCT demonstrated a dose response, with those in lorcaserin twice daily group losing more weight than the lorcaserin once daily group. A dose response was not demonstrated in the BLOOM-DM RCT. In each RCT, the differences between lorcaserin and placebo were statistically significant, and p-values are list in Table 1 (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010).

A good quality meta-analysis of the three Phase III RCTs described above determined that the average weight loss was 3.23 kg (95% confidence interval [CI], -3.57 to -2.70 kg) over one year (Chan et al., 2013). However, data from the Smith and colleagues (2010) RCT was heterogeneous[2]. When this RCT was removed, the heterogeneity score was reduced to zero, and mean weight loss was reduced to 2.93 kg (95% CI, -3.3 kg to -2.51 kg) across the remaining two studies (Chan et al., 2013).

Outcome #2: Waist Circumference

There was a statistically significant reduction in waist circumference seen in all three Phase III RCTs for participants taking lorcaserin twice (-5.5 to -6.8 centimeters [cm]) or once (-5.0 to -5.8 cm) daily compared to placebo (-3.3 to -4.1 cm) at the end of one year. A dose response was observed for this measure in both the Fidler (2011) and O'Neil (2012) RCTs (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010). A good quality meta-analysis of the three RCTs determined average reduction in waste circumference was -2.51 cm (95% CI, -3.04 to -1.99 cm) (Chan et al., 2013).

A second good quality meta-analysis included the three Phase III RCTs and a Phase I RCT by Smith and colleagues (2009). This meta-analysis reported a near-significant reduction in waist circumference at three (-2.29 cm; 95% CI, -7.23 to 2.67) and 12 months (-2.45 cm; 95%CI, -4.99 to 0.08). In a mixed-treatment comparison meta-analysis, Chilton and colleagues determined there was no significant difference in waist circumference reduction between lorcaserin and orlistat (2014).

Outcome #3: Body Mass Index

There was a statistically significant reduction in BMI across all three RCTs in the lorcaserin twice (-1.6 to -2.09 kg/m^2) and once (-1.7 kg/m^2) daily groups compared to placebo (-0.6 to 1.0 kg/m^2) at the completion of one year. Table 1 includes p-values reported in each RCT (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010). In a meta-analysis of the three Phase III RCTs, Chan and colleagues (2013) determined the average reduction in BMI was -1.16 kg/m^2 (95% CI, -1.34 to -0.98). There was heterogeneity in this estimate that was eliminated when the Smith and colleagues (2010) RCT was removed from the analysis, without significantly changing the estimate of BMI reduction (-1.07 kg/m^2; 95% CI, -1.21 to -0.93).

Outcome #4: Glycemic Parameters

The BLOOM-DM trial included 604 patients with type II diabetes and a glycated hemoglobin (HbA1c) of 7.0 to 10.0%. Glycemic parameters were statistically significantly improved at one year among those taking lorcaserin twice or once daily compared to placebo. Fifty percent of patients taking lorcaserin twice daily and 52% of patients taking lorcaserin once daily achieved a

[2] Variability that is not due to sampling error

HbA1c of less than or equal to 7% at one year, compared to 26% of patients in the placebo group (p<0.001) (O'Neil et al., 2012). Those in the lorcaserin groups also had greater reductions in markers of insulin resistance, including fasting insulin and homeostatic model assessment-insulin resistance. However, these differences were not statistically significant. Those taking lorcaserin were slightly more likely to reduce use of antidiabetic medications (17.1% lorcaserin twice daily, 23.4% lorcaserin once daily, and 11.7% placebo; differences not statistically significant) and less likely to have antidiabetic medication dose increases (13.5% lorcaserin twice daily, 11.7% lorcaserin once daily, and 22.2% placebo; p=0.011).

Outcome #5: Cardiac Risk Factors

The three Phase III RCTs evaluated the effect of lorcaserin on total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride levels. The three trials also measured systolic and diastolic blood pressure and inflammatory markers such as high-sensitivity C reactive protein, fibrinogen, and apolipoproteins A1 and B. For the purposes of this report, emphasis is placed on lipids and blood pressure measure measurements. While inflammatory markers can predict cardiovascular disease risk, they are also associated with other cardiovascular disease risk factors, such as elevated glucose, LDL cholesterol, and waist circumference (Ebrahimi et al., 2016). Because it is unclear whether inflammation drives or is a product of the cardiovascular disease process, markers of inflammation are not emphasized here (Koenig, 2013).

In the BLOOM RCT (Smith et al., 2010), there was a statistically but not clinically significant decrease in total cholesterol at the end of one year comparing lorcaserin twice daily to placebo groups (-0.90% ± 0.33% change vs. 0.57% ±0.34%, p<0.001). There was no significant difference in HDL cholesterol, and both groups had increased LDL cholesterol levels, although the percent increase was statistically significantly lower in the lorcaserin twice daily group (2.87% ± 0.56%) compared to placebo (4.03% ± 0.58%, p=0.05). Triglycerides decreased by approximately six percent in the lorcaserin twice daily group, and by less than one percent in the placebo group (p<0.001).

In the BLOSSOM RCT (2011), there were no significant differences in total or LDL cholesterol levels between groups at the end of one year. However, there was a statistically significant increase in the HDL levels for the lorcaserin twice daily group (3.7 mg/dl ± 15.4[3]) and once daily group (3.5 mg/dl ± 15.4) compared to placebo (1.3 mg/dl ± 15.3) (lorcaserin twice daily vs. placebo: p<0.001; lorcaserin once daily vs. placebo: p<0.01). Triglyceride levels in both lorcaserin groups also significantly decreased (lorcaserin twice daily: -4.3 ± 36.9 mg/dl, lorcaserin once daily: -5.5 mg/dl ± 36.9, placebo: -0.9 mg/dl ± 36.9; lorcaserin twice vs. placebo: p=0.02, lorcaserin once daily vs. placebo: p<0.01) (Fidler et al., 2011). With the exception of

[3] Standard deviation

HDL levels among those taking lorcaserin twice daily (5.2% ± 1.0% change) compared to placebo (1.6 ± 1.0% change, p=0.005) in the BLOOM-DM RCT, there were no statistically significant differences in cholesterol levels (including total cholesterol, LDL, HDL, and triglycerides). There was a reduction in triglyceride levels for the lorcaserin twice daily group (-10.7% ± 2.4% change) compared to placebo (-4.8% ± 2.5% change, p=0.054) (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010). In a meta-analysis of the three Phase III RCTs, Chan and colleagues (2013) determined that there was a statistically significant small reduction in total cholesterol (-1.06%; 95% CI, -1.07 to -0.42%), LDL cholesterol (-1.29%; 95% CI, -2.32 to -0.25%), and triglycerides (-4.70%; 95% CI, -6.53 to -2.87%) for participants receiving lorcaserin compared to placebo, and there was a trend toward a slight increase in HDL cholesterol (1.82%; 95% CI, -0.05 to 3.70%).

Systolic and diastolic blood pressure decreased slightly at the end of one year in those taking lorcaserin twice daily compared to placebo in the BLOOM RCT. At the end of one year, systolic blood pressure decreased by -1.4 ± 0.3 mm Hg in the lorcaserin twice daily group compared to -0.8 ± 0.3 mm Hg in the placebo group (p=0.04). Diastolic blood pressure decreased by -1.1 ± 0.2 mm Hg in the lorcaserin group compared to -0.6 ± 0.2 mm Hg in the placebo group (p=0.01). There were no significant differences in systolic or diastolic blood pressures at the end of one year in BLOSSOM or BLOOM-DM RCTs (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010). When the data from these three RCTs were included in a meta-analysis (Chan et al., 2013), there was a statistically significant reduction in systolic (-0.61 mm Hg (95% CI, -1.16 to -0.07)) and diastolic blood pressure -0.49 mg Hg (95% CI, -0.88 to -0.11) at the end of one year. This difference was very small and unlikely to have clinical importance.

Table 1. *Evidence Review – Included References*

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Systematic Reviews					
Weissman et al. (2013) Design Meta-analysis of echocardiogram data Included Study Designs RCTs	Good	Good	k = 3 N = 6,897 (5,249 completed echo-cardiograms)	FDA-defined valvulopathy after 52 weeks that was not present at baseline: Lorcaserin group: 2.20% Placebo group: 1.88% RR: 1.18 (95% CI, 0.8 to 1.73) Decreases in weight were associated with increased risk of valvulopathy	Included studies Fidler et al. (2011), O'Neil et al. (2012), Smith et al. (2010)
Chan et al. (2013) Design Meta-analysis and SR Included Study Designs RCTs	*Not included*	Good	k=6 N= 7,789 in meta-analysis	Primary Outcomes *Mean reduction in weight (kg)*: -3.23 kg (95% CI, -3.75 to -2.70) *Mean reduction in BMI (kg/m^2)*: -1.16 (95% CI, -1.34 to -0.98) Excluding Smith et al. (2010) reduced heterogeneity, but did not significantly reduce effect measures Secondary Outcomes *Waist circumference (cm)*: -2.51 (95% CI, -3.04 to -1.99) *Systolic blood pressure (mm Hg)*: -0.61 (95% CI, -1.16 to -0.07) Harms Headache (RR 1.68; 95% CI, 1.48 to 1.90)	Included studies Fidler et al. (2011), Martin et al. (2011), O'Neil et al. (2012), Smith et al. (2009), Smith et al. (2010) Included in meta-analysis Fidler et al. (2011), O'Neil et al. (2012), Smith et al. (2010) Primary outcome measurements

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				Nausea (RR 1.51; 95% CI, 1.26 to 1.90) Dizziness (RR 1.97; 95% CI, 1.45 to 2.66) Fatigue (RR 1.99; 95% CI, 1.61 to 2.46) Urinary tract infection (RR 1.25; 95% CI, 1.04 to 1.50) Constipation (RR 1.48; 95% CI, 1.19 to 1.85) Dry mouth (RR 2.29; 95% CI, 1.75 to 3.00)	included only ITT data. Secondary measures included ITT data when available, but also used per protocol data if necessary.
Smith et al. (2014) Design Meta-analysis Included Study Designs RCTs	*Not included*	Good	k=3 N=6,897	Outcome A weight loss of ≥ 5% at week 12 was a strong predictor of sustained weight loss at 1 year in both the diabetic and non-diabetic populations taking lorcaserin or placebo Harms Those who responded at 12 weeks experienced harms in same proportion as the entire population	Included Studies Fidler et al. (2011), O'Neil et al. (2012), Smith et al. (2010)
CADTH, 2014; Ryan and Braverman-Panza (2014) Design SR Included Study Designs RCTs	*Not included*	Good	k=1 relevant to lorcaserin n=604	Conclusion A significantly greater proportion of patients who received pharmaceutical intervention combined with diet and exercise counseling achieved weight loss than those receiving diet and exercise counseling alone. A higher proportion of obese patients with DM II who achieved ≥ 5% reduction in baseline body weight achieved significantly improved glycemic control and a decrease in antidiabetic medications compared to those who did not.	Included Studies O'Neil et al. (2012)

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Yanovski and Yanovski (2014) Design SR Included Study Designs RCTs	*Not included*	Fair	k=4 relevant to lorcaserin N=7,794	Outcomes Lorcaserin results on average a 3% decrease in initial weight at one year. The proportion of patients achieving clinically meaningful (≥ 5%) weight loss ranges from 37 to 47%. While lorcaserin produces improvements in cardiovascular and metabolic risk factors, it has not been shown to reduce cardiovascular morbidity or mortality. Harms Adverse effects include headache, nausea, and fatigue, and dizziness. Pulmonary hypertension and incidence of valvulopathy were numerically higher in RCTs, and the meta-analysis by Weissman (2013) was not included. Conclusion Lorcaserin leads to greater weight loss and increased likelihood of achieving clinically meaningful weight loss at one year compared to placebo. Clinicians can reduce unnecessary harms by discontinuing therapy in those who do not respond with ≥ 5% weight loss at 12 weeks.	Included Studies Fidler et al. (2011), O'Neil et al. (2012), Smith et al. (2010), Chan et al. (2013) Study quality was not taken into account Investigators only searched one database
Chilton et al. (2014) Design Meta-analysis and Mixed-treatment comparison meta-analysis	*Not included*	Good	k=4 relevant to lorcaserin N=7,794	Outcome (Waist Circumference) Greater waist circumference reduction than placebo at 3 months (-2.29 cm; 95% CI, -7.23 to 2.67 cm) and 12 months (-2.45 cm; 95%CI, -4.99 to 0.08 cm)	Included Studies Fidler et al. (2011), O'Neil et al. (2012), Smith et al. (2009), Smith et al. (2010)

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Included Study Designs RCTs				In the mixed-treatment comparison meta-analysis, there was not a significant difference between lorcaserin and orlistat in reducing waist circumference Harms No significant difference in the proportion of withdrawals due to adverse events between lorcaserin and placebo	
Kelly, Tungol, and Wesolowicz (2013) Design SR Included Study Designs RCTs	*Not included*	Fair	k=3 N=6,897	Outcome (Weight Loss) A statistically significant higher proportion of individuals lost ≥ 5% of body weight among those taking lorcaserin compared to placebo. There was also a higher mean weight loss when compared with placebo Harms Safety concerns include cardiac valvulopathy and increased risk of psychiatric, cognitive, and serotonergic adverse effects	Included Studies Fidler et al. (2011), O'Neil et al. (2012), Smith et al. (2010)
Randomized Controlled Trials					
Smith et al. (2009) Population Adults (18-65 yrs) with BMI 30-45, all chronic conditions other than stable HTN or dyslipidemia excluded Study length	*Not included*	Fair	n= 469	Harms No significant changes in pulmonary artery pressure, mitral, or aortic valve regurgitation Common adverse events: headache 26.7% lorcaserin bid, 17.8% placebo; nausea 11.2% lorcaserin bid, 3.4% placebo; dizziness 7.8% lorcaserin bid, 0 placebo (sig. NR) No severe adverse events attributed to study drug	Phase I industry study Effectiveness outcomes not included because duration < 6 m

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
14 weeks Intervention Placebo or lorcaserin 10 mg qd or lorcaserin 15 mg qd or lorcaserin 10 mg bid plus usual habits Analysis Harms were recorded for anyone who took one dose of drug					
BLOOM Smith et al. (2010) Population Adults (18-65 yrs) with BMI 30-45 or 27-45 with 1 co-morbid condition[4], diabetics were excluded Study length	Good	Good	n =3,182	Primary Outcomes (weight loss, 1 year follow-up) *Loss of ≥5% of baseline body weight*: lorcaserin (47.5%) vs. placebo (20.5%) (p<0.001) *Change in weight*: lorcaserin (-5.8 ±0.2[5] kg) vs. placebo (-2.8 ±0.2 kg) (p<0.001) *Loss of ≥10% of baseline body*: lorcaserin (22.6%) vs. placebo (7.7%) (p<0.001) Secondary outcomes (1 year follow-up) *Change in waist circumference*: lorcaserin (-6.8 ±0.2 cm) vs placebo (-3.9 ±0.2 cm) (p<0.001)	Completion rate at one year 50.3%. 72.6% of those who completed Year 1 completed Year 2 ITT analysis performed using LOCF for missing data. It is unclear how this would impact results

[4] Co-morbid conditions include hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, and sleep apnea
[5] Values for Smith et al. (2010) RCT are reported as mean ± standard error

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
2 years Intervention Placebo or lorcaserin 10 mg bid plus diet and exercise counseling Analysis ITT/LOCF				*Change in systolic blood pressure*: lorcaserin (-1.4±0.3 mm Hg) vs. placebo (-0.8±0.3mm Hg) (p<0.001) *Change in HbA1c (%):* lorcaserin (-0.04±0.01) vs placebo (0.03±0.01) (p<0.001) Safety end points and harms *Heart rate (bpm)*: lorcaserin (-2.0 ± 0.3), placebo (-1.6 ± 0.4); p=0.05 *PASP (mm Hg)*: lorcaserin (-0.92 ± 0.23), placebo (-0.23 ± 0.23); NS *BDI-II score*: lorcaserin (-1.1 ± 0.1), placebo (-0.9 ±0.1); NS *Headache*: lorcaserin (18%), placebo (11%); sig. NR *Upper Respiratory Tract Infection*: lorcaserin (14.5%), placebo (11.9%); sig. NR *Dizziness*: lorcaserin (8.2%), placebo (3.8%); sig. NR *Nausea*: lorcaserin (7.5%), placebo (5.4%); sig. NR	Extensive exclusion criteria limits generalizability Not sufficiently powered to detect increased valvulopathy Industry-funded study
BLOSSOM Fidler et al. (2011) Population Adults (18-65 yrs) with BMI 30-45 or 27-45 with 1 co-morbid	Good	Good	n = 4,008	Primary Outcome (weight loss) *Loss of ≥5% of baseline body weight*: lorcaserin bid (47.2%), lorcaserin qd (40.2%), placebo (25.0%); p<0.001 between each treatment group and placebo, p<0.01 for lorcaserin bid vs. qd *Change in weight*: lorcaserin bid (-5.8 ± 6.4[7] kg), lorcaserin qd (-4.7 ± 6.4 kg), placebo (-2.9 ± 6.3 kg);	Completion rate 55.5% MITT analysis means that those who had at least dose of study drug and one post-

[7] Values for Fidler et al. (2011) RCT are reported as mean (standard deviation)

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
condition[6], diabetics were excluded Study length 1 year Intervention Placebo or lorcaserin 10 mg bid or lorcaserin qd plus diet and exercise counseling Analysis MITT/LOCF				p<0.001 between each treatment group and placebo, p<0.01 for lorcaserin bid vs. qd *Loss of ≥10% of baseline body*: lorcaserin bid (22.6%), lorcaserin qd (17.4%), placebo (9.7%); p<0.001 between each treatment group and placebo, p<0.01 for lorcaserin bid vs. qd Secondary Outcomes *Waist circumference*: lorcaserin bid (-6.3 ± 8.3), lorcaserin qd (-5.8 ± 8.2), placebo (-4.1 ± 8.0); p<0.001 for treatment groups compared to placebo *Systolic blood pressure (mm Hg)*: lorcaserin bid (-1.9 ± 10.7), lorcaserin qd (-1.4 ± 10.8), placebo (-1.2 ± 11.0); p<0.001 for lorcaserin bid vs. placebo, NS for lorcaserin qd vs. placebo *HbA1c (%):* lorcaserin bid (-0.19 ± 0.3), lorcaserin qd (-0.17 ± 0.3), placebo (-0.14 ± 0.3); NS *% change in total body fat*[8]: lorcaserin bid (-9.9 ± 3.1), lorcaserin qd (-6.1 ± 3.1), placebo (-4.6 ± 3.1); p<0.01 lorcaserin bid vs. placebo, NS for lorcaserin qd vs. placebo	baseline weight were included Missing data handled by LOCF. It is unclear how this would impact results. Extensive exclusion criteria limits generalizability Not sufficiently powered to detect increased valvulopathy Industry-funded study

[6] Co-morbid conditions include hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, and sleep apnea
[8] Performed on a subset of patients (n=189)

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				Safety End Point and Harms *PASP*: lorcaserin bid (0.04 ± 5.6), lorcaserin qd (-0.2 ± 5.5), placebo (-0.4 ± 5.5); p=0.01 lorcaserin bid vs. placebo, NS lorcaserin qd vs. placebo *BDI-II score*: NR *Headache*: lorcaserin bid and qd (15.6%), placebo (9.2%) ; sig. NR *Upper respiratory tract infection*: lorcaserin bid (12.7%), lorcaserin qd (14.6%), placebo (12.6%); sig. NR *Nausea*: lorcaserin bid (9.1%), lorcaserin qd (7.6%), placebo (5.3%), sig. NR *Dizziness*: lorcaserin bid (8.7%), lorcaserin qd (6.2%), placebo (3.9%); sig. NR *Fatigue*: lorcaserin bid (8.4%), lorcaserin qd (6.6%), placebo (4.1%); sig. NR	
BLOOM-DM O'Neil et al. (2012) Population Diabetic adults aged 18-65 with BMI 27-45 and HbA1c of 7.0-10.0%	Good	Good	n = 604	Primary Outcome (weight loss) *Loss of ≥5% of baseline body weight*: lorcaserin bid (37.5%), lorcaserin qd (44.7%), placebo (16.1%); p<0.001 between each treatment group and placebo *Change in weight*: lorcaserin bid (-4.7 ± 0.4[9] kg), lorcaserin qd (-5.0 ± 0.6 kg), placebo (-1.6 ± 0.4 kg); p<0.001 between each treatment group and placebo	Completion rate: 66.4% MITT analysis means that those who had at least dose one post-baseline weight were included

[9] Results from O'Neil et al. (2012) RCT reported as mean ± standard error

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
Study length 1 year Intervention Placebo or lorcaserin 10 mg bid or lorcaserin qd plus diet and exercise counseling Analysis MITT/LOCF				*Loss of ≥10% of baseline body*: lorcaserin bid (16.3%), lorcaserin qd (18.1%), placebo (4.4%); p<0.001 between each treatment group and placebo Secondary Outcomes *Waist circumference (cm)*: lorcaserin bid (-5.5 ± 0.5), lorcaserin qd (-5.0 ± 0.8), placebo (-3.3 ± 0.5); p=0.001 lorcaserin bid vs. placebo, p=0.053 lorcaserin qd vs. placebo *Systolic blood pressure (mm Hg)*: lorcaserin bid (-0.8 ± 0.8), lorcaserin qd (0.56 ± 1.3), placebo (-0.9±0.9); NS *HbA1c (%):* lorcaserin bid (-0.9 ± 0.06), lorcaserin qd (-1.0 ± 0.09), placebo (-0.4 ± 0.06); p=0.08 lorcaserin bid vs. placebo, p=0.03 lorcaserin qd vs. placebo Safety End Points and Harms *Heart rate (bpm)*: lorcaserin bid (-2.0 ± 0.6), placebo (-0.4 ± 0.6); p=0.03, 0.012 for lorcaserin bid and qd compared to placebo, respectively *PASP*: NR *BDI-II score*: lorcaserin bid (-0.1 ± 0.3), lorcaserin qd (-2.9 ± 0.9), placebo (-0.3 ± 0.3), NS *Headache*: lorcaserin bid (14.5%), lorcaserin qd (16.8%), placebo (7.1%); sig. NR *Nasopharyngitis*: lorcaserin bid (11.3%), lorcaserin qd (22.3%), placebo (9.9%); sig. NR	Missing data handled by LOCF, it is unclear how this would impact results Extensive exclusion criteria limits generalizability Did not show a dose response Not sufficiently powered to detect increased valvulopathy Industry-funded study HbA1c percent reduction is a marker for DM control, but unclear if long-term diabetic complications are impacted

Citation, Study Details	Dossier QA	Center QA	# of Studies (k) / Study Size (n)	Study Summary and Findings	Comments
				Dizziness: lorcaserin bid (7.0%), lorcaserin qd (11.6%), placebo (6.3%); sig. NR *Nausea*: lorcaserin bid (9.4%), lorcaserin qd (8.4%), placebo (7.9%); sig. NR	
Shram et al. (2011) <u>Population</u> Recreational polydrug users <u>Study length</u> 24 hr after dose administration <u>Intervention</u> Placebo or lorcaserin (20 mg, 40 mg, 60 mg), zolipidem (15 mg, 30 mg) and ketamine (100 mg) in single doses <u>Analysis</u> Cross-over	*Not included*	Fair	n=35	<u>Harms</u> Common adverse events included headache, nausea, abdominal discomfort, dizziness. Proportion of patient experiencing averse events increased with supratherapeutic doses (40 mg and 60mg). Negative effect measures were not significantly different than placebo for those taking lorcaserin qd.	Completion rate: 83% Cross-over trial in which participants were given one dose of study drug and asked to assess symptoms in a 24 hour period after administration. There was a seven day washout period between doses

Abbreviations: BDI-II = Beck Depression Inventory II score; bid = twice daily; BMI = body mass index (kg/m_2); bpm = beats per minute; CI = confidence interval; cm = centimeter; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; HTN = hypertension; hr = hour; (M)ITT/LOCF = (modified) intention to treat/ last observation carried forward; m = month; mg = milligram; NR = not reported; NS = not significant; PASP = pulmonary arterial systolic pressure; qd = once daily; RCT = randomized controlled trial; RR = relative risk; SR = systematic review

Harms

Common Adverse Reactions

The most common adverse reactions reported in RCTs are summarized in Table 1 and include headache, upper respiratory tract infections, dizziness, nausea, and fatigue (Fidler et al., 2011; O'Neil et al., 2012; Shram et al., 2011; Smith et al., 2009; Smith et al., 2010). The BLOOM RCT reported adverse events over the two year follow-up period. The other Phase III RCTs (Fidler et al., 2011 and O'Neil et al., 2012) reported adverse events over one year. A good quality meta-analysis of the three Phase III RCTs revealed that there was a significantly increased relative risk of headache, nausea, dizziness, fatigue, urinary tract infection, constipation, and dry mouth for those taking lorcaserin compared to placebo (Chan et al., 2013).

In the BLOSSOM RCT, more discontinuations were attributed to adverse events for those taking lorcaserin twice (8.6%) or lorcaserin once (6.3%) daily than placebo (4.3%). Serious adverse events occurred slightly more often in patients taking lorcaserin than placebo without a single harm contributing to the difference (Fidler et al., 2010). Six serious adverse events were considered to be related to the study drug. Three occurred in the placebo group (syncope, ventricular tachycardia, and anaphylactic reaction), and three occurred in the lorcaserin twice daily group (syncope, moderate depression, and acute anxiety attack) (Fidler et al., 2010). In the BLOOM-DM RCT, serious adverse events occurred at similar frequencies across groups (lorcaserin twice daily: 6.3%, lorcaserin once daily: 8.4%, placebo: 6.7%; statistical significance not reported) (O'Neil et al., 2012). There were similar rates of discontinuation for adverse events between lorcaserin (7.1%) and placebo (6.7%) groups in the BLOOM RCT. However, more patients in the lorcaserin group than the placebo group withdrew because of headache (2.0% vs. 0.8%) or dizziness (0.8% vs. 0.1%; statistical significance not reported) (Smith et al., 2010).

Harm #1: Harms in Pregnancy

The use of lorcaserin in pregnancy was not tested by the studies identified. Intentional weight loss in pregnancy is generally contradicted due to increased nutritional needs in pregnancy.

Harm #2: Serotonin Syndrome

None reported in included studies, however, patients taking medications serotonergic drugs other than lorcaserin were excluded from participation. The theoretical risk is reported in the Belviq ® package insert.

Harm #3: Valvular Heart Disease

The three Phase III RCTs were not powered to detect FDA-defined valvulopathy. A meta-analysis that combined the data from all three RCTs addressed this question, and found that the incidence of FDA-defined valvulopathy was slightly higher among those taking lorcaserin,

although the relative risk (RR) was not statistically significant (RR 1.18; 95% CI, 0.8 to 1.73) (Weissman et al., 2013).

Harm #4: Cognitive Impairment

Fatigue was reported as occurring more frequently in those taking lorcaserin than placebo in all three Phase III RCTs. Additionally, according to the package insert:

> In clinical trials of at least one year in duration, impairments in attention and memory were reported adverse reactions associated with 1.9% of patients treated with BELVIQ and 0.5% of patients treated with placebo, and led to discontinuation in 0.3% and 0.1% of these patients, respectively. Other reported adverse reactions associated with BELVIQ in clinical trials included confusion, somnolence, and fatigue.

Harm #5: Risk of Hypoglycemia in Patients with Type II Diabetes on Anti-Diabetic Therapy

In the BLOOM-DM RCT, hypoglycemic episodes were more common in the group of patients taking lorcaserin twice (7.4%) or once (10.5%) daily than placebo (6.3%) (statistical significance not reported). No patient reported an episode of severe hypoglycemia that resulted in confusion, loss of consciousness, or treatment with intravenous medications. The incidence of reported hypoglycemic episodes was higher among those taking sulfonylureas than metformin for treatment of diabetes, across all treatment groups (O'Neil et al., 2012).

Harm #6: Psychiatric Disorders

Beck Depression Inventory II scores decreased slightly in all groups in all three Phase III RCTs. Rates of suicidal thoughts did not differ in the BLOOM RCT. Rates of depression, depressed mood and suicidal ideation did not differ in the BLOSSOM RCT. In the BLOOM-DM RCT, a larger proportion of those taking lorcaserin once daily reported depression as an adverse event compared to lorcaserin twice daily or placebo (5.3%, 2.3%, and 2.0%, respectively; statistical significance not reported) (Fidler et al., 2011; O'Neil et al., 2012; Smith et al., 2010).

Harm #7: Priapism

No events of priapism were reported in the RCTs. The theoretical risk is reported in the Belviq ® package insert.

Harm #8: Heart Rate Decreases

Two RCTs reported statistically significant decreases in mean heart rate among those taking lorcaserin compared to placebo. The difference in mean heart rate in the BLOOM was small and unlikely to be clinically meaningful (lorcaserin twice daily: -2.0 ± 0.3 beats per minute (bpm), placebo: -1.6 ± 0.4 bpm; p=0.05) (Smith et al., 2010). However, the difference in the BLOOM-DM RCT had a reduction that may be clinically meaningful compared to placebo in those taking lorcaserin twice or once daily (lorcaserin twice daily: -2.0 ± 0.06 bpm, lorcaserin once daily: -2.9 ± 0.9 bpm, placebo: -0.4 ± 0.06 bpm; lorcaserin twice daily vs. placebo: p=0.03, lorcaserin once

daily vs. placebo: p=0.01) (O'Neil et al., 2012). The BLOSSOM RCT found mean decreases in heart rate that were not statistically significantly different between groups (Fider et al., 2011).

Harm #9: Hematologic Changes

There were no reported changes in hematologic changes in the three Phase III RCTs. However, in the lorcaserin package insert, an increased risk of hematologic changes is described:

> In clinical trials of at least one year in duration, adverse reactions of decreases in white blood cell count (including leukopenia, lymphopenia, neutropenia, and decreased white cell count) were reported in 0.4% of patients treated with BELVIQ as compared to 0.2% of patients treated with placebo. Adverse reactions of decreases in red blood cell count (including anemia and decreases in hemoglobin and hematocrit) were reported by 1.3% of patients treated with BELVIQ as compared to 1.2% treated with placebo.

Harm #10: Prolactin Elevation

There were no reported changes in prolactin levels in the three Phase III RCTs. However, the lorcaserin package insert states:

> Lorcaserin moderately elevates prolactin levels. In a subset of placebo controlled clinical trials of at least one year in duration, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, measured both before and 2 hours after dosing, occurred in 6.7%, 1.7%, and 0.1% of BELVIQ treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively.

Harm #11: Pulmonary Hypertension

Pulmonary artery systolic pressure (PASP) did not change significantly between groups in the BLOOM RCT (Smith et al., 2010). While statistically significant changes in PASP between lorcaserin twice daily and placebo group was demonstrated in the BLOSSOM RCT, the difference was not clinically meaningful (+0.4 ± 5.6 vs. -0.4 ± 5.5 mm Hg, p=0.01). No statistically significant difference in PASP was found in comparing lorcaserin once daily to placebo groups in the BLOSSOM RCT (Fidler et al., 2011).

Ongoing Clinical Trials

The Center staff searched Clinicaltrials.gov for any registered trials of the use of lorcaserin for weight loss. The following trials are currently underway or have been recently completed:

A Single Dose Pharmacokinetic Study of Lorcaserin Hydrochloride in Obese Pediatric Subjects 6 to 11 Years of Age
Sponsor: Eisai Inc
Phase: Phase 1
Study Completion: May 2015

Lorcaserin for Weight Loss Management in Patients on Antipsychotics: A Pilot Study
Sponsor: Southern California Institute for Research and Education
Phase: Phase 4
Primary Completion: July 2015

Lower Level Laser Treatment (LLLT) and Lorcaserin for Weight Management
Sponsor: Mayo Clinic
Phase: Phase 3
Study Completion: December 2015

Lorcaserin for Preventing Weight Gain among Smokers
Sponsor: Mayo Clinic
Phase: Phase 1 / Phase 2
Study Completion: December 2015

A Study of APD356 (Lorcaserin) in Health Japanese Adult Subjects
Sponsor: Eisai Inc
Phase: Phase 1
Study Completion: January 2016

Lifestyle Modification and Lorcaserin for Weight Loss Maintenance
Sponsor: University of Pennsylvania, Eisai Inc
Phase: not stated
Primary Completion: April 2018

A Study to Evaluate the Effect of Long-term Treatment with Belviq (Lorcaserin HCl) on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects with Cardiovascular Disease or Multiple Cardiovascular Risk Factors
Sponsor: Eisai Inc, Thrombolysis in Myocardial Infarction (TIMI) Academic Research Organization
Phase: Phase 4
Primary Completion: June 2018

Addressing Post Cessation Weight Gain
Sponsor: Mayo Clinic
Phase: Phase 2 / Phase 3
Primary Completion: August 2020

Excluded Studies

Table 2 provides exclusion criteria for submitted articles that were not included in this evaluation.

Table 2. *Submitted References – Reason for Exclusion*

Citation	Exclusion Criteria
Apovian et al. (2015)	Design: Guideline
Garvey et al. (2014)	Design: Guideline
Jensen et al. (2014)	Design: Guideline
National Institutes of Health (2000)	Design: Guideline
Seger J.C. et al. (2013)	Design: Guideline
Vargas, Sanchez, Shanahan, Anderson, and Arena Pharmaceuticals (2012)	Design: Poster
F. Wang et al. (2006)	Methods: No intervention of interest
Z. Wang, Li, Powers, and et al. (2013)	Design: Abstract
Z. Wang, Li, Knoth, and et al. (2015)	Design: Abstract
Weiner et al. (2013)	Methods: No intervention of interest

Overall Strength of Body of Evidence by Outcome

Table 3 presents the submitter's assessment of the strength of evidence for the submitted outcomes, as well as the assessment of the Center and rationale for this assessment. Evidence that is graded high means that further evidence in unlikely to change our confidence in the estimate of the effect. Moderate strength of evidence means that further evidence is likely to change our confidence in the estimate of the effect and may change the estimate. Low strength of evidence means that further research is very likely to impact our confidence in the estimate of the effect and is likely to change the estimate of effect. Very low strength means that the estimate of the effect is very uncertain (Grade Working Group, 2004).

The Center uses the approach developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for assessing the strength of evidence to enhance consistency in rating bodies of scientific literature. Randomized controlled trials are initially categorized as having high strength of evidence and observational studies are categorized as having low strength of evidence. The strength of evidence rating can be downgraded based on limitations related to the risk of bias in studies (also referred to as study quality), inconsistency of results, uncertainty of directness of measurement or population, imprecise or sparse data, and high probability of reporting bias. The rating can be increased if

there is evidence of a strong association[10,11], or a dose-response gradient. The grade is also increased is all plausible confounders would have reduced the effect (GRADE Working Group, 2004).

Table 4. *Outcomes – Strength of Evidence*

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	Center	
Weight loss	High	Moderate	Good quality RCTs consistently report a statistically significant reduction in weight loss compared to placebo, however, investigations have not been performed outside of a controlled trial setting, heightening concern for reporting bias and generalizability to use in real-world populations and settings. Outcomes are not yet reported beyond a year.
Change in waist circumference	High	Moderate	Good quality RCTs consistently report a statistically significant reduction in waist circumference compared to placebo, however, investigations have not been performed outside of a controlled trial setting, heightening concern for reporting bias and limited generalizability. Outcomes are not yet reported beyond a year.
Body mass analysis	High	Low	Good quality RCTs consistently report a statistically significant reduction in BMI compared to placebo, however, investigations have not been performed outside of a controlled trial setting, heightening concern for reporting bias and limited generalizability. The correlation between BMI and adiposity is uncertain.
Change in Glycemic parameters	High	Moderate	One good quality RCT demonstrated a significantly higher proportion of patients met their HbA1c goal in the lorcaserin group compared to placebo, however, investigations have not been performed outside of a controlled trial setting, heightening concern for reporting

[10] Significant relative risk of >2 or less than <0.5 with no plausible confounders in two or more observational studies

[11] Significant relative risk of >5 or less than <0.2 based on direct evidence with no major threats to validity

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	Center	
			bias and limited generalizability. Outcomes have not been reported beyond one year.
Change in Cardiac Risk Factors	High	Moderate	Statistically significant and small improvements in lipids, blood pressure, and other markers of cardiac risk are demonstrated in good quality RCTs, however investigations have not been performed outside of a controlled trial setting, heightening concern for reporting bias and limited generalizability. Outcomes have not been reported beyond one year.
Harms			
Pregnancy contraindication	*None*	*None*	Pregnant women were excluded from RCTs.
Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions	Included in Package Insert	*None*	No events were reported in the RCTs that excluded participants taking other serotonergic medications. This is a rare event that is unlikely to be detected in the clinical trial setting. Lorcaserin is a serotonergic medication, and therefore a theoretic risk is present for this syndrome.
Valvular heart disease	Included in Package Insert	Moderate	At the end of one year, the rate of FDA-defined valvulopathy was slightly higher among those taking lorcaserin.
Cognitive impairment	Included in Package Insert	Moderate	Good quality RCTs reported increased fatigue and impairments in attention and memory. Long-term data in a more generalizable population would impact estimate.
Psychiatric disorders	Included in Package Insert	Low	Randomized controlled trials report inconsistent results. Additionally, investigations outside of the trial setting, which set strict criteria around psychiatric comorbidities would impact estimate.
Risk of Hypoglycemia for Patients with Diabetes Mellitus Type 2 on Anti-glycemic therapy	[Not reported]	Moderate	In a good quality RCT, hypoglycemic episodes were more common among those with diabetes taking lorcaserin than placebo. Long-term data in a more generalizable population would impact estimate.

Outcome	Strength of Evidence Assessment		Rationale
	Submitter	Center	
Priapism	Included in Package Insert	*None*	No events of priapism were reported in RCTs, however, the risk is included in the FDA package insert.
Decreased heart rate	Included in Package Insert	Low	Two of the three good quality Phase III RCTs reported statistically significant reductions in heart rate for those taking lorcaserin compared to placebo, while one did not detect a difference in heart rate. Long-term data in a more generalizable population would impact estimate.
Hematologic changes	Included in Package Insert	Moderate	Hematologic changes were reported more commonly in those taking lorcaserin than placebo in the Phase III RCTs. Long-term data in a more generalizable population would impact estimate.
Elevated prolactin	Included in Package Insert	Moderate	Prolactin levels were more likely to be elevated in those taking lorcaserin than placebo in RCTs likely to have reporting bias. Long-term data in a more generalizable population would impact estimate.
Pulmonary hypertension	Included in Package Insert	Very Low	Inconsistent outcomes and relatively sparse data for this rare disease reported across RCTs which are likely to have reporting bias.

Section 6: "The service must be cost-effective or cost neutral outside the investigational setting"
The dossier submission did not include any published cost analyses. The Center's search identified one poor quality cost-utility analysis that was funded by Vivus, Inc., and is likely to be biased in favor of Qysmia®. This cost-utility analysis determined that Weight Watchers® and Qysmia® had the most favorable average cost-effectiveness ratios compared to Jenny Craig®, orlistat, and lorcaserin. There was no detailed explanation of the variables used to inform the model. Furthermore, costs and outcomes were not discounted and the sensitivity analysis was not robust. The findings were mainly based on the finding the Qymsia® produces greater weight loss than lorcaserin or orlistat at the end of 12 months. The estimated cost per kilogram of weight loss for lorcaserin was $545 (Finkelstein & Kruger, 2014).

Table 5. *Evidence Review – Economic Studies*

Study Citation	Dossier QA	Center QA	Study Size (n)	Findings	Limitations / Comments
Finkelstein and Kruger (2014)	Not included	Poor	n = unclear	Average cost per kilogram weight loss: Lorcaserin: $545 Orlistat: $546 Vtrim: $213 Qysmia®: $203 Jenny Craig®: $424 Weight Watchers®: $155 Lorcaserin and Orlistat were not as effective and more costly than Qysmia	Unclear what studies informed cost-analysis. No discounting included. Sensitivity analysis not robust. Funded by Vivus, Inc. (makers of Qysmia®)

Section 7: Other payer coverage of the service

Center staff searched for policies on the coverage of lorcaserin for weigh loss from Aetna, Anthem, Cigna, and UnitedHealthCare and the Centers for Medicare and Medicaid Services (CMS). Across the national private payers reviewed, Aetna and Anthem Blue Cross Blue Shield (BCBS) include lorcaserin as part of broader weight reduction medication policies. UnitedHealthCare manages lorcaserin through OptumRx (specific coverage criteria not identified), and no coverage policies on lorcaserin from Cigna or CMS were identified.

Aetna and Anthem BCBS specify detailed criteria for individuals who may be eligible for weight reduction medication. Both payers require that individuals must undergo a minimum six month trial of a weight loss regimen including a reduced calorie diet and exercise program, and have a BMI of greater or equal to 30 kg/m^2. Aetna additionally requires behavioral therapy as part of the weight loss regimen, and allows coverage for individuals with a BMI of greater than or equal to 27 kg/m^2 with one of the following risk factors:

a) Coronary heart disease
b) Dyslipidemia (HDL < 35 mg/dL, LDL ≥ 160 mg/dL, or triglycerides > 400 mg/dL)
c) Hypertension
d) Obstructive sleep apnea
e) Type II diabetes mellitus

In addition, Anthem BCBS will approve weight loss medications for up to 12 weeks and stipulates that individuals may not be receiving two concurrent medications for weight loss. Anthem BCBS may approve an additional 12 weeks of weight loss medication for individuals with a BMI of greater than or equal to 25 kg/m^2 who have achieved or maintained an initial five

percent weight loss or greater, and continue to participate in reduced calorie diet and exercise program.

Summary

Lorcaserin has demonstrated efficacy in reducing weight by an average of 3.2 kg in 12 months compared to placebo when combined with exercise and nutrition counseling at the end of one year in a controlled trial setting. A clinically significant reduction of at least five percent weight loss was demonstrated in 37.5 to 47.5% of participants taking lorcaserin twice daily. Patients with diabetes taking lorcaserin had a greater reduction in HbA1c and were more likely to achieve goal HbA1c levels. Across the included RCTs, there were statistically significant reductions in lipids, blood pressure, and other cardiac markers that were unlikely to be clinically meaningful. Patient-important outcomes such as quality of life, morbidity, and mortality were not reported. Reported harms of lorcaserin were mostly mild. The harms estimates are likely to change outside of the clinical trial setting in which there were extensive exclusion criteria. Further research in a more general population with longer-term follow-up is needed to better understand the benefits and harms of lorcaserin for weight loss. Additionally, studies directly comparing lorcaserin to other weight loss programs and medications are needed to understand the effectiveness and harms of lorcaserin compared to other weight loss methods.

The coverage of lorcaserin is incorporated into broader payer coverage policies of weight loss medications. Aetna and Anthem BCBS require prior trials of weight loss regimens and a BMI of greater than or equal to 30 kg/m^2, with Aetna having additional criteria for individuals with a BMI of greater than or equal to 27 kg/m^2. No policies from CMS, UnitedHealthCare, or Cigna were identified.

Appendix A. Search Strategy

MEDLINE® Search
Database: Ovid MEDLINE(R) <1946 to January Week 4 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 04, 2016>

1 belviq.mp

2 lorcaserin.mp

3 lorqess.mp

4 (APD adj2 "365").mp

5 1 or 2 or 3 or 4

6 exp Obesity/

7 exp Weight Loss/

8 6 or 7

9 5 and 8

10 limit 9 to english language

11 limit 10 to yr="2006 -Current"

The search terms, “belviq,” “lorcaserin,” and “APD 365” were used in the remaining core source searches, which included: Hayes, Inc., the National Institute for Health and Care Excellence (NICE), Cochrane Library, PubMed Health, the Blue Cross/Blue Shield Health Technology Assessment (HTA) program, the Veterans Administration Technology Assessment Program (VATAP), *BMJ Clinical Evidence*, the Washington State Health Technology Assessment Program, the Agency for Healthcare Research and Quality (AHRQ), and Tufts Cost-Effectiveness Analysis Registry. Systematic reviews that were performed in the last ten years were included. Archived government reports were not included.

Appendix B. MEDLINE Results

Table 1. *MEDLINE Articles Selected for Full Text Review*

Citation	Included?	Comments/Rationale
Aronne et al. (2014)	No	Design: Narrative review
Boland, Harris, and Harris (2015)	No	Population: Pediatric
Chilton et al. (2014)	Yes	Systematic review
Finkelstein and Kruger (2014)	Yes	Cost analysis
Fleming, McClendon, and Riche (2013)	No	Design: Narrative review
Kelly et al. (2013)	Yes	Systematic review
Martin et al. (2011)	No	Outcomes: Follow-up period only 56 days, harms not reported
Nigro, Luon, and Baker (2013)	No	Design: Narrative review
Smith et al. (2009)	Yes	Phase I RCT with 12 week follow-up, included for harms only
Smith et al. (2014)	Yes	Meta-analysis
Shram et al. (2011)	Yes	RCT

Appendix C. Quality Assessment Forms

Table 1a. *Systematic Reviews Quality Assessment*

Risk of Bias Assessment Criteria	CADTH (2014)		Chan (2013)		Chilton (2014)	
	Submitter	Center	Submitter	Center	Submitter	Center
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes
1.2 An adequate description of the methodology used is included, and the methods used are appropriate to the question.		Yes		Yes		Yes
1.3 The literature search is sufficiently rigorous to identify all the relevant studies.		Yes		Yes		Yes
1.4 The criteria used to select articles for inclusion is appropriate.		Yes		Yes		Yes
1.5 Study quality is assessed and taken into account.		Yes		Yes		Yes
1.6 There are enough similarities between the studies selected to make combining them reasonable.		Yes		Yes		Yes Yes, for the lorcaserin studies. A mixed treatment meta-analysis was used to compare lorcaserin to orlistat
1.7 There is a conflict of interest statement.		Yes		Yes		Yes
1.8 There is a description of the source(s) of funding.		Yes		No		Yes
2.1 How well was the study done to minimize bias?		**Good**		**Good**		**Good**
2.2 Are the results of this study directly applicable to the patient group targeted by this key question?		Yes		Yes		Yes
2.3 Comments		---		---		---

Table 1b. *Systematic Reviews Quality Assessment*

Risk of Bias Assessment Criteria	Kelly (2013)		Yanovski (2014)	
	Submitter	Center	Submitter	Center
1.1 The study addresses an appropriate and clearly focused question.	*Not included in dossier submission*	Yes	*Not included in dossier submission*	Yes
1.2 An adequate description of the methodology used is included, and the methods used are appropriate to the question.		Yes		Yes
1.3 The literature search is sufficiently rigorous to identify all the relevant studies.		No		No Only searched PubMed
1.4 The criteria used to select articles for inclusion is appropriate.		Yes		Yes
1.5 Study quality is assessed and taken into account.		No		No
1.6 There are enough similarities between the studies selected to make combining them reasonable.		Yes		Yes
1.7 There is a conflict of interest statement.		Yes		Yes
1.8 There is a description of the source(s) of funding.		Yes		Yes
2.1 How well was the study done to minimize bias?		**Fair**		**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this key question?		Yes		Yes
2.3 Comments		---		---

Table 2a. *Randomized Controlled Trials Quality Assessment*

Risk of Bias Assessment Criteria	Fidler (2011)		O'Neil (2012)		Smith (2009)	
	Submitter	Center	Submitter	Center	Submitter	Center
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	Yes	Yes Random sequence generation by 3rd party	Yes	Yes	*Not included in dossier submission*	Unclear
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	Yes	Yes	Yes	Yes		Unclear
1.3 The intervention and control groups are similar at the start of the trial (The only difference between groups is the treatment under investigation).	Yes	Yes	Yes	Yes		Yes
1.4 Investigators, participants, and clinicians were kept "blind" about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.	Yes	Yes	Yes	Yes		Yes
1.5 The intervention and control groups received the same care apart from the interventions studied.	Yes	Yes	Yes	Yes		Yes
1.6 The study had an appropriate length of follow-up.	Yes	Yes	Yes	Yes		Yes
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up.)	Yes	Yes	Yes	Yes		Yes
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did not complete the interventions?	% drop out: 43% Belviq BID vs 48% placebo % did not complete intervention: 43% Belviq vs 48% placebo	55.5%	% drop out: 34% Belviq BID vs 38% placebo % did not complete intervention: 34% Belviq vs 38% placebo	66.4%		25% of placebo patients, 26% of lorcaserin 10 qid, 31% of lorcaserin 15 mg qd, and 34% of lorcaserin bid participants. More in lorcaserin 15 mg qd discontinued due to adverse events.
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (intention to treat analysis).	Yes	Yes	Yes	Yes MITT/LOCF, only those with at least one post baseline		Yes However, primary outcome was weight loss in those who completed the study

Risk of Bias Assessment Criteria	Fidler (2011)		O'Neil (2012)		Smith (2009)	
	Submitter	Center	Submitter	Center	Submitter	Center
				weight measurement were inlcuded		
1.10 All relevant outcomes are measured in a standard, valid, and reliable way.	Yes	Yes	Yes	Yes		Yes
1.11 The study reported on only surrogate outcomes. (If so, comment on the strength of evidence associated the surrogate with the important clinical outcome for this topic).	Yes Weight loss measures were used as surrogates of overall health. Weight loss of ≥ 5% in pts with obesity is associated with improvements in cardiovascular risk factors. This is supported by a strong body of evidence.	No	Yes Weight loss measures were used as surrogates of overall health. Weight loss of ≥ 5% in pts with obesity is associated with improvements in cardiovascular risk factors. This is supported by a strong body of evidence.	No		No
1.12 The study uses a composite outcome as the primary outcome. If so, comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	Yes This study utilized three co-primary endpoints. When assessing a service for weight management the probability of achieving clinically significant weight loss (5% and 10%) and the weight loss itself must be measured.	No	Yes This study utilized three co-primary endpoints. When assessing a service for weight management the probability of achieving clinically significant weight loss (5% and 10%) and the weight loss itself must be measured.	No		No
1.13 Competing interests of members have been recorded and addressed.	Yes	Yes	Yes	Yes		Yes
1.14 View of the funding body have not influenced the content of the study.	Yes	No	Yes	No		No
2.1 How well was the study done to minimize bias?	**Good**	**Good**	**Good**	**Good**		**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?	Yes	Yes	Yes	Yes		Yes

Risk of Bias Assessment Criteria	Fidler (2011)		O'Neil (2012)		Smith (2009)	
	Submitter	Center	Submitter	Center	Submitter	Center
2.3 Comments	This was a phase 3 registrational study for Belviq	Large drop-out rate and unclear how MITT analysis will impact results. Arena pharmaceutical designed and funded research.	This was a phase 3 registrational study for Belviq	Industry funded, extensive exclusion criteria, unclear how MITT/LOCF will impact results, some markers such as HbA1c results are surrogate, unclear if Belviq® makes a difference in long term diabetic complications		Randomization, allocation, and concealment methods are not clearly stated. Industry study, strict exclusion criteria, follow-up too short for appreciable efficacy outcomes

Table 2b. *Randomized Controlled Trials Quality Assessment*

Risk of Bias Assessment Criteria	Smith (2010)		Smith (2014)		Weissman (2013)	
	Submitter	Center	Submitter	Center	Submitter	Center
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	Yes	Yes Random number sequence generation by 3rd party	*Not include in dossier submission*	Yes	*Not included in dossier submission*	Yes
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.	Yes	Yes		Yes		Yes
1.3 The intervention and control groups are similar at the start of the trial (The only difference between groups is the treatment under investigation).	Yes	Yes		Yes		Yes
1.4 Investigators, participants, and clinicians were kept "blind" about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have Yes occurred.	Yes	Yes		Yes		Yes

Risk of Bias Assessment Criteria	Smith (2010)		Smith (2014)		Weissman (2013)	
	Submitter	Center	Submitter	Center	Submitter	Center
1.5 The intervention and control groups received the same care apart from the interventions studied.	Yes	Yes		Yes		Yes
1.6 The study had an appropriate length of follow-up.	Yes	Yes		Yes		Yes
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up.)	Yes	Yes		Yes		Yes
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did not complete the interventions?	% drop out: 45% Belviq BID vs 55% placebo % did not complete intervention: 45% Belviq vs 55% placebo	55.4% of treatment group and 45.1% of placebo group completed a year, 72.6% of patients who completed year 1 also completed year 2		50 to 64%		51%
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (intention to treat analysis).	Yes	Yes Last observation carried forward was used for missing values. This assumes patient did not gain weight		No MITT/LOCF		Yes
1.10 All relevant outcomes are measured in a standard, valid, and reliable way.	Yes	Yes		Yes		Yes
1.11 The study reported on only surrogate outcomes. (If so, comment on the strength of evidence associated the surrogate with the important clinical outcome for this topic).	Yes Weight loss measures were used as surrogates of overall health. Weight loss of ≥ 5% in pts with obesity is associated with improvements in cardiovascular risk factors. This is supported by a strong body of evidence.	No		No		No
1.12 The study uses a composite outcome as the primary outcome. If so, comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.	Yes This study utilized three co-primary endpoints. When assessing a service for weight management	No		No		No

Risk of Bias Assessment Criteria	Smith (2010)		Smith (2014)		Weissman (2013)	
	Submitter	Center	Submitter	Center	Submitter	Center
	the probability of achieving clinically significant weight loss (5% and 10%) and the weight loss itself must be measured.					
1.13 Competing interests of members have been recorded and addressed.	Yes	Yes		Yes		Yes
1.14 View of the funding body have not influenced the content of the study.	Yes	Unclear Arena pharmaceuticals involved in all aspects of research, bias towards improvement likely present		Yes		No
2.1 How well was the study done to minimize bias?	**Good**	**Good**		**Good**		**Good**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?	Yes	Yes		Yes		Yes
2.3 Comments	This was a phase 3 registrational study for Belviq	May be biased towards showing a benefit in using the LOCF approach to handling missing data, dropout rate was high		Industry-funded study, meta-analysis of 3 Phase III RCTs (answers for this form based on methods of RCTs)		Funded by Arena pharmaceuticals, some investigators were employees and stock holders of Arena pharmaceuticals

Table 3. *Crossover Study Quality Assessment*

Risk of Bias Assessment Criteria	Shram (2011)	
	Submitter	Center
1.1 An appropriate method of randomization was used to allocate participants to intervention groups.	*Not included in dossier submission*	Unclear
1.2 An adequate concealment method was used such that investigators, clinicians, and participants could not influence enrolment or intervention allocation.		Yes
1.3 The intervention and control groups are similar at the start of the trial (The only difference between groups is the treatment under investigation).		Unclear
1.4 Investigators, participants, and clinicians were kept "blind" about treatment allocation and other important confounding/prognostic factors. If the answer is no, describe any bias that might have occurred.		Yes
1.5 The intervention and control groups received the same care apart from the interventions studied.		Yes
1.6 The study had an appropriate length of follow-up.		Yes
1.7 All groups were followed up for an equal length of time (or the analysis was adjusted to allow for differences in length of follow-up.)		Yes
1.8 What percentage of the individuals or clusters recruited into each group of the study dropped out before the study was completed? What percentage did not complete the interventions?		83%
1.9 All the subjects were analyzed in the groups to which they were randomly allocated (intention to treat analysis).		Yes
1.10 All relevant outcomes are measured in a standard, valid, and reliable way.		Yes
1.11 The study reported on only surrogate outcomes. (If so, comment on the strength of evidence associated the surrogate with the important clinical outcome for this topic).		No
1.12 The study uses a composite outcome as the primary outcome. If so, comment on the appropriateness of the composite and whether any single outcome strongly influenced the composite.		No
1.13 Competing interests of members have been recorded and addressed.		Yes
1.14 View of the funding body have not influenced the content of the study.		No
2.1 How well was the study done to minimize bias?		**Fair**
2.2 Are the results of this study directly applicable to the patient group targeted by this topic?		Yes
2.3 Comments		Funded by Arena pharmaceuticals, and two investigators are employees of arena pharmaceutical, small sample size (n=35)

Table 4. *Economic Study Quality Appraisal*

Risk of Bias Assessment Criteria	Finkelstein & Kruger (2014)	
	Submitter	Center
1.1 The results of this study are directly applicable to the patient group targeted by this key question.	*Not included in dossier submission*	Yes
1.2 The healthcare system in which the study was conducted is sufficiently similar to the system of interest in the topic key question(s).		Yes
2.1 The research question is well described.		Yes
2.2 The economic importance of the research question is stated.		Yes
2.3 The perspective(s) of the analysis are clearly stated and justified (e.g. healthcare system, society, provider institution, professional organization, patient group).		Yes
2.4 The form of economic evaluation is stated and justified in relation to the questions addressed.		Yes
2.5 Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies). *or* Details of the design and results of effectiveness study are given (if based on a single study).		No
2.6 Estimates of effectiveness are used appropriately.		n/a
2.7 Methods to value health states and other benefits are stated.		Yes
2.8 Outcomes are used appropriately.		Yes
2.9 The primary outcome measure for the economic evaluation is clearly stated.		Yes
2.10 Details of the subjects from whom valuations were obtained are given.		No
2.11 Competing alternatives are clearly described.		No
2.12 All important and relevant costs for each alternative are identified.		Unclear
2.13 Methods for the estimation of quantities and unit costs are described.		Yes
2.14 Quantities of resource use are reported separately from their unit costs.		Yes
2.15 Productivity changes (if included) are reported separately.		Yes
2.16 The choice of model used and the key parameters on which it is based are justified.		Yes
2.17 All costs are measured appropriately in physical units.		Yes
2.18 Costs are valued appropriately.		Yes
2.19 Outcomes are valued appropriately.		Yes
2.20 The time horizon is sufficiently long enough to reflect all important differences in costs and outcomes.		Yes
2.21 The discount rate(s) is stated.		No
2.22 An explanation is given if costs and benefits are not discounted.		No
2.23 The choice of discount rate(s) is justified.		n/a

Risk of Bias Assessment Criteria	Finkelstein & Kruger (2014)	
	Submitter	Center
2.24 All future costs and outcomes are discounted appropriately.		No
2.25 Details of currency of price adjustments for inflation or currency conversion are given.		No
2.26 Incremental analysis is reported or it can be calculated from the data.		Yes
2.27 Details of the statistical tests and confidence intervals are given for stochastic data.		No
2.28 Major outcomes are presented in a disaggregated as well as aggregated form.		No
2.29 Conclusions follow from the data reported.		Yes
2.30 Conclusions are accompanied by the appropriate caveats.		Yes
3.1 The approach to sensitivity analysis is given.		Yes
3.2 All important and relevant costs for each alternative are identified.		No
3.3 An incremental analysis of costs and outcomes of alternatives is performed.		Yes
3.4 The choice of variables for sensitivity analysis is justified.		No
3.5 All important variables, whose values are uncertain, are appropriately subjected to sensitivity analysis.		No
3.6 The ranges over which the variables are varied are justified.		Yes
4.1 Competing interests of members have been recorded and addressed.		Yes
4.2 Views of funding body have not influenced the content of the study.		No
5.1 How well was the study done to minimize bias?		**Poor**
5.2 If coded as fair or poor, what is the likely direction in which bias might affect the study results?		---
5.3 Other reviewer comments:		Likely to be biased in favor of Qysmia, which has a greater weight loss impact. Funded by Visus, Inc., the makers of Qysmia.

References

Apovian, C. M., Aronne, L. J., Bessesen, D. H., McDonnell, M. E., Murad, M. H., Pagotto, U., . . . Still, C. D. (2015). Pharmacological management of obesity: An endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism, 100*(2), 342-362. doi:10.1210/jc.2014-3415

Aronne, L., Shanahan, W., Fain, R., Glicklich, A., Soliman, W., Li, Y., & Smith, S. (2014). Safety and efficacy of lorcaserin: A combined analysis of the BLOOM and BLOSSOM trials. *Postgraduate Medicine, 126*(6), 7-18. doi:10.3810/pgm.2014.10.2817

Boland, C. L., Harris, J. B., & Harris, K. B. (2015). Pharmacological management of obesity in pediatric patients. *Annals of Pharmacotherapy, 49*(2), 220-232. doi:10.1177/1060028014557859

Canadian Agency for Drugs and Technologies in Health (CADTH). (2014). *Obesity interventions delivered in primary care for patients with diabetes: A review of clinical effectiveness*. Ottowa: CADTH. Retrieved from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0070673/pdf/PubMedHealth_PMH0070673.pdf.

Chan, E. W., He, Y., Chui, C. S., Wong, A. Y., Lau, W. C., & Wong, I. C. (2013). Efficacy and safety of lorcaserin in obese adults: A meta-analysis of 1-year randomized controlled trials (RCTs) and narrative review on short-term RCTs. *Obesity Reviews, 14*(5), 383-392. doi:10.1111/obr.12015

Chilton, M., Dunkley, A., Carter, P., Davies, M. J., Khunti, K., & Gray, L. J. (2014). The effect of antiobesity drugs on waist circumference: a mixed treatment comparison. *Diabetes, Obesity & Metabolsim, 16*(3), 237-247. doi:10.1111/dom.12198

Ebrahimi, M., Heidari-Bakavoli, A. R., Shoeibi, S., Mirhafez, S. R., Moohebati, M., Esmaily, H., . . . Ghayour-Mobarhan, M. (2016). Association of Serum hs-CRP Levels With the Presence of Obesity, Diabetes Mellitus, and Other Cardiovascular Risk Factors. *Journal of Clinical Laboratory Analysis*. doi:10.1002/jcla.21920

Fidler, M. C., Sanchez, M., Raether, B., Weissman, N. J., Smith, S. R., Shanahan, W. R., & Anderson, C. M. (2011). A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: The BLOSSOM trial. *Journal of Clinical Endocrinology and Metabolism, 96*(10), 3067-3077. doi:10.1210/jc.2011-1256

Finkelstein, E. A., & Kruger, E. (2014). Meta- and cost-effectiveness analysis of commercial weight loss strategies. *Obesity, 22*(9), 1942-1951. doi:10.1002/oby.20824

Fleming, J. W., McClendon, K. S., & Riche, D. M. (2013). New obesity agents: lorcaserin and phentermine/topiramate. *Annals of Pharmacotherapy, 47*(7-8), 1007-1016. doi:10.1345/aph.1R779

Garvey, W. T., Garber, A. J., Mechanick, J. I., Bray, G. A., Dagogo-Jack, S., Einhorn, D., . . . On Behalf Of The Aace Obesity Scientific, C. (2014). American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the 2014 advanced framework for a new diagnosis of obesity as a chronic disease. *Endocrine Practice, 20*(9), 977-989. doi:10.4158/ep14280.ps

GRADE Working Group. (2004). Grading quality of evidence and strength of recommendations. *British Medical Journal, 328*, 1-8.

Jensen, M. D., Ryan, D. H., Apovian, C. M., Ard, J. D., Comuzzie, A. G., Donato, K. A., . . . Tomaselli, G. F. (2014). 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Journal of the American College of Cardiology, 63*(25), 2985-3023. http://dx.doi.org/10.1016/j.jacc.2013.11.004

Kelly, E. M., Tungol, A. A., & Wesolowicz, L. A. (2013). Formulary management of 2 new agents: lorcaserin and phentermine/topiramate for weight loss. *Journal of Managed Care Pharmacy, 19*(8), 642-654.

Koenig, W. (2013). High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. *International Journnal of Cardiology, 168*(6), 5126-5134. doi:10.1016/j.ijcard.2013.07.113

Martin, C. K., Redman, L. M., Zhang, J., Sanchez, M., Anderson, C. M., Smith, S. R., & Ravussin, E. (2011). Lorcaserin, a 5-HT(2C) receptor agonist, reduces body weight by decreasing energy intake without influencing energy expenditure. *Journal of Clinical Endocrinology Metabolism, 96*(3), 837-845. doi:10.1210/jc.2010-1848

National Institutes of Health (NIH), National Heart, Lung, and Blood Institute, . (2000). *The practical guide: Identification, evaluation and treatment of overweight and obesity in adults.* Bethesda, MD: NIH.

New York Department of Health (NY DOH). (2015). *Dossier methods guidance*. Albany, NH: NY DOH. Retrieved from http://www.health.ny.gov/health_care/medicaid/redesign/docs/dossier_methods_guidance.pdf

Nigro, S. C., Luon, D., & Baker, W. L. (2013). Lorcaserin: Aa novel serotonin 2C agonist for the treatment of obesity. *Current Medical Research Opinion, 29*(7), 839-848. doi:10.1185/03007995.2013.794776

O'Neil, P. M., Smith, S. R., Weissman, N. J., Fidler, M. C., Sanchez, M., Zhang, J., . . . Shanahan, W. R. (2012). Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: The BLOOM-DM study. *Obesity, 20*(7), 1426-1436. doi:10.1038/oby.2012.66

Rothman, K. J. (2008). BMI-related errors in the measurement of obesity. *International Journal of Obesity, 32*(S3), S56-S59. Retrieved from http://dx.doi.org/10.1038/ijo.2008.87

Ryan, D. H., & Braverman-Panza, J. (2014). Obesity in women. *Journal of Family Practice, 63*(2 Suppl), S15-20.

Seger J.C., Horn, D. B., Westman, E. C., Lindquist, R., Scinta, W., Richardson, L. A., . . . Bays, H. E. (2013). *American Society of Bariatric Physicians obesity algorithm: Adult adiposity evaluation and treatment*. Retrieved from http://media.clinicaladvisor.com/documents/55/obesityalgorithm_13552.pdf

Shram, M. J., Schoedel, K. A., Bartlett, C., Shazer, R. L., Anderson, C. M., & Sellers, E. M. (2011). Evaluation of the abuse potential of lorcaserin, a serotonin 2C (5-HT2C) receptor agonist, in recreational polydrug users. *Clinical Pharmacology Therapy, 89*(5), 683-692. doi:10.1038/clpt.2011.20

Smith, S. R., O'Neil, P. M., Astrup, A., Finer, N., Sanchez-Kam, M., Fraher, K., . . . Shanahan, W. R. (2014). Early weight loss while on lorcaserin, diet and exercise as a predictor of week 52 weight-loss outcomes. *Obesity, 22*(10), 2137-2146. doi:10.1002/oby.20841

Smith, S. R., Prosser, W. A., Donahue, D. J., Morgan, M. E., Anderson, C. M., & Shanahan, W. R. (2009). Lorcaserin (APD356), a selective 5-HT(2C) agonist, reduces body weight in obese men and women. *Obesity, 17*(3), 494-503. doi:10.1038/oby.2008.537

Smith, S. R., Weissman, N. J., Anderson, C. M., Sanchez, M., Chuang, E., Stubbe, S., . . . Shanahan, W. R. (2010). Multicenter, placebo-controlled trial of lorcaserin for weight management. *New England Journal of Medicine, 363*(3), 245-256. doi:10.1056/NEJMoa0909809

Vargas, E., Sanchez, M., Shanahan, W. R., Anderson, C. M., & Arena Pharmaceuticals, I. (2012). *Effect of lorcaserin on the use of concomitant medications for dyslipidemia, hypertension, and diabetes during phase 3 clinical trials assessing weight loss*. San Diego, CA: Arena Pharmaceuticals.

Wang, F., McDonald, T., Bender, J., Reffitt, B., Miller, A., & Edington, D. W. (2006). Association of healthcare costs with per unit body mass index increase. *Journal of Occupational and Environmental Medicine, 48*(7), 668-674. doi:10.1097/01.jom.0000225045.77734.f4

Wang, Z., Li, X., Knoth, R., & et al. (2015). *Cost implication of using lorcaserin in weight management prior to bariatric surgery.* Paper presented at the ISPOR, Philadelphia, PA.

Wang, Z., Li, X., Powers, A., & et al. (2013). *Health-related quality of life in overweight and obese patients treated with lorcaserin.* Paper presented at the Obesity Week, Atlanta, GA.

Weiner, J. P., Goodwin, S. M., Chang, H. Y., Bolen, S. D., Richards, T. M., Johns, R. A., . . . Clark, J. M. (2013). Impact of bariatric surgery on health care costs of obese persons: A 6-year follow-up of surgical and comparison cohorts using health plan data. *Journal of the*

American Medical Association, Surgery, 148(6), 555-562. doi:10.1001/jamasurg.2013.1504

Weissman, N. J., Sanchez, M., Koch, G. G., Smith, S. R., Shanahan, W. R., & Anderson, C. M. (2013). Echocardiographic assessment of cardiac valvular regurgitation with lorcaserin from analysis of 3 phase 3 clinical trials. *Circulation, Cardiovasc Imaging, 6*(4), 560-567. doi:10.1161/circimaging.112.000128

Wing, R. R., Lang, W., Wadden, T. A., Safford, M., Knowler, W. C., Bertoni, A. G., . . . Group, t. L. A. R. (2011). Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care, 34*(7), 1481-1486. doi:10.2337/dc10-2415

Yanovski, S. Z., & Yanovski, J. A. (2014). Long-term drug treatment for obesity: A systematic and clinical review. *Journal of the American Medical Association, 311*(1), 74-86. doi:http://dx.doi.org/10.1001/jama.2013.281361

About the Center for Evidence-based Policy

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring diverse and relevant perspectives are considered, and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon. Further information about the Center is available at www.ohsu.edu/policycenter.

Suggested citation: Pensa, M., Thielke, A., & King, V. (2016). *Belviq (lorcaserin HCl) – dossier review.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University.

Conflict of Interest Disclosures: No authors have conflicts of interest to disclose. All authors have completed and submitted the Oregon Health & Science University form for Disclosure of Potential Conflicts of Interest, and none were reported.

Funding/Support: This research was funded by the Center for Evidence-based Policy's Medicaid Evidence-based Decisions project at Oregon Health & Science University.