Lorcaserin (Belviq)
National Drug Monograph
June 2013
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

- The mean body mass index (BMI kg/m^2) of Veterans as increased every year since 2002. The prevalence of obesity (BMI>30) in 2011 was 39.8%. These findings are reflective of OEF/OIF veterans as well as the veteran population in general.
- Being overweight or obese is associated with a number of chronic conditions including type 2 diabetes, hypertension, sleep apnea, hyperlipidemia and stroke. Weight loss has been shown to improve or reduce the risk for developing weight-related comorbidities.
    - Lorcaserin has an FDA label indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 kg/m^2 or greater (obese) or
    - A BMI of 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome, obstructive sleep apnea, and degenerative joint disease/osteoarthritis.
- The dose of lorcaserin is one 10 mg tablet by mouth twice a day without regard to meals.
- Lorcaserin should be discontinue if 5% weight loss is not achieved by week 12 as it is unlikely that a meaningful weight loss will be achieved and sustained with continued treatment.
- Lorcaserin is contraindicated in pregnancy; FDA Pregnancy Category X
- In two pivotal clinical trials submitted to FDA that excluded patients with diabetes, lorcaserin resulted in a mean percentage of body change in body weight of -5.8 compared to -2.5 with placebo. The proportion of patients losing >5% of body weight with lorcaserin was 47% compared to 23% with placebo. A third trial that only enrolled patients with diabetes found a mean percent change in body weight of -4.5 with lorcaserin and -1.5 with placebo. The proportion of patients losing $\geq$5% of body weight was 38% with lorcaserin and 16% with placebo.
- Significant secondary benefits were seen with lorcaserin compared to placebo in systolic and diastolic blood pressures, weight circumference, glycemic control and lipid profiles. The net change in medications for hypertension, type 2 diabetes, and hyperlipidemia favored lorcaserin.
- Lorcaserin is a serotonin agonist which generates concerns about valvulopathy. After 1 year the risk for valvulopathy did not differ in patients treated with lorcaserin compared to placebo. Common adverse effects include headache, fatigue, dizziness, constipation and dry mouth. Concurrent use of lorcaserin with other drugs affecting serotonin or antidopaminergic drugs may increase the risk of serotonin syndrome or neuroleptic malignant-like syndrome.

Introduction[1-4]

Obesity has never been more prevalent among veterans. The mean body mass index (BMI, kg/m^2) of veterans receiving care from VHA has increased every year since FY2002 through 2011; 28.7 to 29.4. The same pattern is true for the percent of veterans who are obese (BMI $\geq$30) which was 34.7% in 2002 and was 39.8% in 2011. The 2011 prevalence of obesity was 35%-39% in 7 VISNs and $\geq$40% in the remaining 14 VISNs. Among OEF/OIF veterans only one VISN had a prevalence of obesity between 30%-34%. The prevalence of obesity in OEF/OIF veterans was $\geq$40% 10 VISNs. Over 77% of Veterans receiving care from VHA are either overweight (BMI 25-29.9) or obese.

Veterans who are overweight (BMI 25-29.9) or obese are at greater risk for developing hypertension, diabetes, dyslipidemia, cardiovascular disease, stroke, obstructive sleep apnea, and some types of cancers. Overweight and obese women are at increased risk for developing infertility and menstrual irregularities. Clinical trials have demonstrated that weight loss improves blood pressure, cholesterol, glycemic control, and obstructive sleep apnea and reduces incident hypertension and type 2 diabetes. There is no direct evidence from prospective clinical trials demonstrating that weight loss reduces cardiovascular morbidity and mortality. It is well established that mortality begins to increases in a linear fashion starting with a BMI of 25.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating lorcaserin as part of a treatment strategy for weight loss and weight maintenance for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[5-6]

Previously marketed medications for weight loss that have affected serotonin (5-HT) receptors have been withdrawn from the market their association with valvulopathy, possibly pulmonary hypertension, cardiovascular events, and stroke. Drugs such as fenfluramine were nonselective and activated $5\text{-}HT_{2b}$ receptors which are highly expressed in cardiac valvular tissue and not in the central nervous system. Activation of $5\text{-}HT_{2A}$ receptors can induce hallucinations. $5\text{-}HT_{2C}$ receptors are predominantly expressed in the CNS in the choroid plexus, prefrontal cortex, hippocampus, basal ganglia and are associated with control of mood, cognition and appetite.

Lorcaserin is a selective agonist of $5\text{-}HT_{2C}$ receptors. Lorcaserin' s selectivity for the $5\text{-}HT_{2C}$ receptor is ~15-times and ~100-times greater than it is for $5\text{-}HT_{2A}$ and $5\text{-}HT_{2B}$ receptors, respectively (Table 1). Lorcaserin's exact mechanism of action to decrease food consumption and promote satiety is unknown. It is hypothesized that it does so by acting as an agonist on $5\text{-}HT_{2C}$ receptors in hypothalamic melanocortin system. Lorcaserin may also have an active role in regulating glucose tolerance and hepatic insulin sensitivity.

Table 1 Lorcaserin's Pharmacokinetic and 5-HT Receptor Binding Profiles

Parameter	Lorcaserin		
Bioavailability	Undetermined		
Tc_{max}	1.5-2.0 hrs		
Protein binding	~70%		
Metabolism CYP effects	Hepatic, multiple pathways resulting in multiple inactive metabolites. Lorcaserin inhibits CYP 2D6-mediated metabolism		
Elimination Half-life	92% excreted in urine as parent drug and metabolites; 2.2% excreted in feces. ~11 hrs		
	Serotonin Receptor Subtype		
	5-HT_{2A}	**5-HT_{2B}**	**5-HT_{2C}**
Potency (EC_{50}, nM)	553	2380	39
Binding affinity (Ki, nM)	92	147	13

FDA Approved Indication(s)

As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of:

- 30 kg/m^2 or greater or
- 27 kg/m^2 or greater in the presence of at least one weight-related comorbid condition, e.g., hypertension, dyslipidemia, type 2 diabetes

Lorcaserin is Schedule IV.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Use as a weight loss agent by individuals with a BMI less than 27, i.e., casual weight loss.

Current VA National Formulary Alternatives

None

Dosage and Administration

- One 10 mg tablet by mouth twice a day without regard to meals.
- Discontinue if 5% weight loss is not achieved by week 12 as it is unlikely that a meaningful weight loss will be achieved and sustained with continued treatment.

Dose in Patients with Renal Impairment

- Dose adjustment is not required in mild renal impairment. Lorcaserin should be used with caution in patients with moderate renal impairment. Use is not recommended in patients with severe renal impairment or end stage renal disease.

Doses in Patients with Hepatic Impairment

- No dose adjustment is required for patients with mild (Child-Pugh score 5-6) to moderate (Child-Pugh score 7-9) hepatic impairment. Lorcaserin has not been studied in patients with severe hepatic impairment and should be used with caution in such patients.

Efficacy

Efficacy Measures[7]

FDA uses two measures to establish the efficacy of weight-loss medications. The first, a mean efficacy criterion, is a statistically significant difference in mean weight loss of at least 5% between active drug and placebo groups. The second, a categorical efficacy criterion, includes the loss of at least 5% of baseline body weight in at least 35% of participants in the active drug group; such weight loss in approximately double the proportion of participants in the active drug group as in the placebo group; and a significant difference between groups.

Summary of efficacy findings

Phase 2 Clinical Trials

Effect on Energy Intake and Expenditure[8]

In a randomized, double-blind, placebo-controlled 56 day trial, 58 adults age 18-65 years (68% women, 63% Caucasian) were studied to measure lorcaserin's (10 mg twice a day) effects on energy intake (EI, calories consumed) and energy expenditure (EE, measured during a 24 hour stay in a respiratory chamber). Eligible subjects with a BMI of 27 – 45 kg/m^2 were confined to a clinical research center for 3 days to obtain baseline EI and EE values. The three day confinement was repeated on days 5-7 and 54-56 following randomization. After their second confinement subjects were discharged with study medication and instructions to follow a standardized diet that targeted a 600 kcal/d deficit and an exercise plan.

After 56 days, subjects receiving lorcaserin lost more weight than those assigned to placebo (3.8 kg vs. 2.2 kg) with the majority of the difference between the groups accounted for in loss of fat free mass (1.3 kg vs. 0.2 kg, $p<.01$). Both treatment arms demonstrated significant reductions in EI (lorcaserin -470 kcal and placebo -205 kcal); the difference in EI between the groups was significant. Larger reductions in EI correlated with larger reductions in body weight. Subjects assigned to lorcaserin reported a significantly greater reduction in prospective food consumption prior to lunch as measured on a visual analog scale. There were no differences between treatment groups in self-reported changes in food cravings, body image, dietary restraint and disinhibition. After adjusting for body composition (body weight) changes in 24 hour EE, sleep EE, resting metabolic rate and metabolic equivalents did not differ between lorcaserin and placebo. Both groups demonstrated a metabolic adaptation consistent with weight loss. Treatment with lorcaserin resulted in significant greater decreases in total and LDL cholesterols (-23.3 mg/ld. and -19.8 mg/ld., respectively) than placebo (-9.8 mg/ld. and -6.3 mg/ld., respectively). No significant differences were found between groups for systolic or diastolic blood pressures, heart rate, HDL cholesterol or triglycerides. The study demonstrated that weight loss by lorcaserin is achieved by reduced EI as opposed to increased EE.

Dose Finding[9]

A 12-week double-blind, placebo-controlled, randomized, parallel-arm study compared placebo, lorcaserin 10 mg/d, 15 mg/d and 10 mg twice a day in 469 healthy obese (BMI 30-45) patients. After 2-weeks, a dose-dependent weight loss was demonstrated across the lorcaserin groups. At the end of the trial patients in the lorcaserin 10 mg/d, 15 mg/d and 10 mg twice a day groups had lost an average of 1.7, 2.2, and 3.1 kg, respectively, compared to a 0.2 kg loss in the placebo group ($p<.001$). This same relationship was found in the proportion of patients losing $\geq$5% of their body weight over the course of the study: 12.8% lorcaserin 10 mg/d, 19.5% lorcaserin 15 mg/d, and 31.2% lorcaserin 10 mg twice a day. Dose-related decreases in BMI (0.7, 1.0, and 1.3) and waist circumference (2.7, 3.7 and 4.4 cm) occurred in the lorcaserin groups. The changes were significant with the two higher doses of lorcaserin. The placebo group experienced small decreases in BMI, 0.1kg/m^2, and waist circumference, 2.1 cm. Small, but significant, changes in total cholesterol (decrease) and HDL cholesterol (increase) were found with lorcaserin 15 mg/d and 10 mg twice a day.

Phase 3 Clinical Trials

Behavioral Modification and Lorcaserin for Overweigh and Obesity Management (BLOOM)[10]

The BLOOM trial was a double-blind, placebo-controlled, randomized, 2-year study designed to evaluate the safety and efficacy of lorcaserin (10 mg twice a day) as part of a weight loss and maintenance strategy. Lifestyle modifications for all participants included moderate exercise for 30 minutes daily and a diet that was 600kcal/day below their individual estimated daily energy requirement. The study's primary endpoints for Year 1were the percentage of subjects who lost 5% and10% of their baseline body weight. The primary endpoint after 2 years was the proportion of patients who achieved at least a 5% weight loss after the first year and maintained this reduction during the second year. Secondary outcome measures included changes from baseline in lipids, glycemic control, blood pressure, physical measures, inflammatory markers of cardiovascular risk and IWQOL-LITE score (Impact of Weight on Quality of Life-Lite questionnaire, 0-100, with higher scores indicating a better quality of life). Subjects were eligible for enrollment if they were 18-65 years and had a BMI 30-45 or 27-45 with at least one comorbid condition (hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea). Exclusion criteria included diabetes mellitus, systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg, moderate or more severe aortic regurgitation (valvulopathy as defined by FDA), depression or psychiatric disorder in the past 2 years. Subjects were randomized 1:1 lorcaserin to placebo for the first year. Prior to the start of Year 2, subjects assigned to lorcaserin were re-randomized to lorcaserin or placebo (2:1) and those originally assigned to placebo continued placebo. The noninferiority study's power was based on the proportion of subjects in whom FDA-defined valvulopathy had developed by week 52. The study's final statistical power was 60% (instead of 80%) to rule out the relative risk of 1.5 of valvulopathy in the lorcaserin arm because the observed rate of FDA-defined valvulopathy in the placebo arm was 2.3% per year instead of 5% per year observed in a Phase 2 study.

A total of 3182 subjects were randomized with 55.4% completing Year 1 in the lorcaserin group compared to 45.1% assigned to placebo. The study groups were composed of 83% women, with ~67% Caucasian and 19% African American, mean age was 44 years, BMI 36 and weight 100kg. Subjects assigned to lorcaserin experienced greater weight loss in all three primary outcome measures (Table 2). Patients switched from lorcaserin to placebo for Year 2 gained enough weight for the groups mean body weight to be comparable to the group who received placebo for both years; a difference of ~2 kg greater than those receiving lorcaserin.

Table 2. Weight loss by treatment group: BLOOM

Outcome, ITT-LOCF	**Placebo (n=1499)**	**Lorcaserin (n=1538)**	**p-value**
Year 1			
≥5% body weight loss	20.3%	47.5%	<0.001
≥10% body weight loss	7.7%	22.6%	<0.001
Mean weight loss, kg	-2.2 +/- 0.1	-5.8 +/- 0.2	<0.001
	Placebo Year 2-only (n=275)	**Lorcaserin Yrs 1+2 (n=564)**	
Year 2, Maintain 5% loss	50.3%	67.9%	<0.001

Among the secondary outcome measures, after one year subjects receiving lorcaserin demonstrated nearly twice the reduction in waste circumference than placebo (-6.8 vs. -3.9 cm) and greater than a 2-fold decrease in change in BMI (-2.09 vs. -0.78), p<0.001 for both comparisons. Changes in SBP (-1.4 vs. -0.8 mmHg) and DBP (-1.1 vs. -0.6 mmHg) were significant. Total cholesterol declined 0.9% in the lorcaserin group and increased 0.57% in the placebo group, p<.001. LDL cholesterol increased in both groups, 2.87% vs. 4.03%, significantly more in the placebo group. Triglycerides declined in both groups, -6.15% vs. -0.14%, p<0.001. Significant improvements (p≤0.001) favoring lorcaserin were noted in fasting glucose (-0.8 vs. 1.1 mg/dL), fasting insulin (-3.33 uU/mL vs. -1.28 uU/mL), homeostasis model assessment of insulin resistance (HOMA-IR, -0.41 vs. -0.17) and glycated hemoglobin (-0.04% vs. 0.03%). Significant improvements in high-sensitivity C-reactive protein and fibrinogen also favored lorcaserin. The change in IWQOL-LITE® score favored lorcaserin (12.4 vs. 10.7, p<0.001).

BLOOM- DM[11]

The BLOOM-DM trial was designed to assess lorcaserin's efficacy and safety as a weight loss agent in patients with type 2 diabetes. Secondary outcome measures focused on lorcaserin's effect on glycemic control. The 1-year, randomized, double-blind, placebo-controlled study's primary and secondary endpoints were identical to those of the BLOOM trial. Enrollment criteria included type 2 diabetes being treated with metformin and/or a sulfonylurea, an HbA_{1c} of 7-10%, age 18- 65 years old with a BMI of 27-45, and were able to participate in an exercise program of moderate intensity. Subjects could not be taking insulin, nor could they have a history of cardiac valve disease or pulmonary arterial hypertension, myocardial infarction or stroke with 6 months, or unstable angina. Randomization was 1:1:1 to placebo, lorcaserin 10 mg daily or 10 mg twice a day. Lifestyle modifications for all participants included moderate exercise for 30 minutes daily and a diet that was 600kcal/day below their individual estimated daily energy requirement.

A total of 604 subjects enrolled, 54% women, with a mean age of ~53 years. The percentage of subjects that were Caucasian ranged from 65.9% placebo, 58.6% lorcaserin 10 mg twice day, and 51.6% lorcaserin 10 mg daily. This distribution was 17.9%, 21.5%, and 27.4%, respectively, for African Americans. The mean weights ranged from 103 kg to 106 kg, and BMI averaged 36. Mean baseline glycemic measures were an HbA_{1c} of 8.1% (with ~82% $\leq$9%) and a fasting glucose of 155-165 mg/dL. At least 91% of subjects in each group were taking metformin, 50% a sulfonylurea, and 41% both.

Both doses of lorcaserin resulted in significantly greater weight loss in all three primary outcome measures compared to placebo, $p<0.001$ for all comparisons (Table 3).

Table 3 Weight Loss by Treatment Group – BLOOM-DM

Outcome, MITT-LOCF	**Placebo (n=248)**	**Lorcaserin 20 mg (n=251)**	**Lorcaserin 10 mg (n=95)**
$\geq$5% body weight loss	16.1%	37.5%	44.7%
$\geq$ 10% body weight loss	4.4%	16.3%	18.1%
Mean weight loss, % of baseline	1.5	4.5	5.0

Changes from baseline in glycemic measures are shown in Table 4. The results demonstrate both lorcaserin treatment arms improved significantly compared to placebo in fasting glucose, HbA_{1c}, and in the proportion of subjects achieving a HbA_{1c} $\leq$7% or $\leq$6.5% at 1-year. Insulin resistance (HOMA-IR) was significantly improved with the lorcaserin 20 mg/day. The same measures (excluding an HbA1c $\leq$6.5and HOMA-IR data not provided) improved significantly among subjects whose baseline HbA_{1c} was <9%. Among subjects whose baseline HbA1c was $\geq$9%, only the change in fasting glucose between lorcaserin 20 mg/day and placebo was significant. Comparisons to lorcaserin 10 mg/day were limited by the small cell size. BMI, waist and hip circumference, and heart rate were significantly reduced in both lorcaserin groups compared to placebo. HDL cholesterol increased with lorcaserin 20 mg/day. Changes in SBP, DBP, and triglycerides were not significant. Only subjects taking lorcaserin 10 mg/day reported a significant improvement in IWQOL-Lite score.

Table 4 Mean Change from Baseline in Glycemic Measures and Stratified by Baseline HgA_{1c}

Outcome, MITT-LOCF	**Placebo (*n=group)**	**Lorcaserin 20 mg (*n=group)**	**Lorcaserin 10 mg (*n=group)**
Fasting glucose, mg/dL			
• All	-11.9 (248)	-27.4 (251)	-28.4 (93)
• HbA_{1c} < 9%	-8.0 (204)	-22.9 (205)	-23.9 (80)
• HbA_{1c} $\geq$ 9%	-32.2 (44)	-50.5 (46)	-51.5 (14)
HbA_{1c}, %			
• All	-0.4	-0.9	-1.0
• HbA_{1c} < 9%	-0.3	-0.8	-0.9
• HbA_{1c} $\geq$ 9%	-1.3	-1.7	-1.6
% HbA_{1c}, $\leq$7%			
• All	26.3	50.4	52.2
• HbA_{1c} < 9%	28.9	54.9	56.4
• HbA_{1c} $\geq$ 9%	13.2	31.1	28.6

% HbA_{1c}, ≤6.5% , All	8.6	23.9	28.3

*Group n's are for the stratified groups All, HbA_{1c} <9% or >9% by treatment arm.

Behavioral Modification and Lorcaserin Second Study for Obese Management (BLOSSOM)[12]
The BLOSSOM study evaluated the safety and efficacy of lorcaserin 10 mg twice a day and 10 mg once a day as part of a weight loss strategy that included nutritional and exercise programs over 52 weeks. BLOOSM used a randomized, double-blind, placebo-controlled, parallel group design. Men and women ages 18-65 years with a BMI of 30-45 or 27-29.9 plus at least one weight-related comorbidity (e.g., hypertension, impaired glucose tolerance, hyperlipidemia) and the ability to exercise at a moderate intensity were eligible to enroll. Exclusion criteria included diabetes, uncontrolled hypertension, triglycerides ≥500 mg/dL or the use of an SSRI within the past year. There were no exclusion criteria based on echocardiograph findings. Randomization to lorcaserin 20 mg/d, 10 mg/d or placebo was 2:1:2. All subjects were instructed to decrease their daily caloric intake to 600 kcal below their estimated energy requirements and to exercise for 30 minutes each day. The study's primary outcomes were changes in weight, and percent of subjects who lost ≥5% and ≥10% of their body weight. Secondary outcomes consisted of changes in lipids, blood pressure, body composition and quality of life. Because of concern for potential serotinergic-induced valvulopathy, the incidence of new valvulopathy at week 52 was the primary echocardiographic endpoint as defined by FDA as a mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation. Echocardiograms were performed at randomization, weeks 24 and 52, and at study discontinuation.

A total of 4008 persons were randomized, 79.8% were women, the mean age was 43.8 years, and subjects were primarily Caucasian (67%) and African-American (20%). Subjects assigned to either dose of lorcaserin achieved significantly greater weight loss on 3 primary outcome measures than placebo, p<.001 all comparisons (Table 5). A significant difference between lorcaserin 10 mg and lorcaserin 20 mg was also found favoring the 20 mg dose, p<.01 all comparisons.

Table 5 BLOSSOM Results: Primary and Select Secondary Outcomes

Outcome, MITT-LOCF	**Placebo, n=1541**	**Lorcaserin 20 mg/d n=1561**	**Lorcaserin 10 mg/d n=771**
Baseline body wgt, kg	100.8	100.3	100.1
Mean Δ body wgt, kg	-2.9	-5.8	-4.7
Mean Δ body wgt, %	-2.8	-5.8	-4.7
% >5% weight loss	25.0	47.2	40.2
% >10% weight loss	9.7	22.6	17.4
Baseline BMI, kg/m^2	36.0	36.1	35.9
Δ BMI	-1.0	-2.1	-1.7
Baseline waist circum., cm	110.2	108.9	108.5
Δ waist circum., cm	-4.1	-6.3	-5.8
Baseline HDL-C, mg/dL	51.3	51.5	51.8
%Δ	1.3	3.7	3.5
Baseline IWQOL-LITE/100	75.3	74.7	75.3
Δ IWQOL-LITE	10.0	11.8	11.3

Of the secondary outcome measures only changes in BMI, waist circumference, HDL-C, and quality of life were significantly different for both doses of lorcaserin compared to placebo (Table 5). The change in BMI was only significant different between the two doses of lorcaserin; favoring the higher dose. Systolic and diastolic blood pressures were reduces by a mean of ~1-2 mm Hg and heart rate declined ~1-2 bpm in each of the three treatment arms. The proportion of subjects who were able to decrease their net use of medications to treat (2.6% vs. 1.4%) or avoid increases in mediations to treat dyslipidemia (4% vs. 5%) favored lorcaserin 10 mg twice a day compared with placebo. More patients assigned to lorcaserin 10 mg twice a day were able to reduce their antihypertensive medications than those assigned to placebo, 4.0% vs. 3.1%, respectively.

Adverse Events (Safety Data)

Deaths and Other Serious Adverse Events[5, 10-12]

Two deaths were reported in the three major clinical trials, both in patients assigned to placebo, one due to a motor vehicle accident and the other attributed to an asthma exacerbation. Valvulopathy aside, 3patients experienced adverse events deemed serious that could be attributed lorcaserin: syncope, major depression, and acute anxiety attack.

Common Adverse Events[5]

Table 6. Adverse Reactions Reported by ≥2% of Lorcaserin Patients and More Commonly than with Placebo in Patients without Diabetes

	Number of patients (%)	
Adverse Reaction	**Lorcaserin 10 mg Twice a Day N=3195**	**Placebo N=3185**
Gastrointestinal Disorders		
Nausea	264 (8.3)	170 (5.3)
Diarrhea	207 (6.5)	179 (5.6)
Constipation	186 (5.8)	125 (3.9)
Dry mouth	169 (5.3)	74 (2.3)
Vomiting	122 (3.8)	83 (2.6)
General Disorders And Administration Site Conditions		
Fatigue	229 (7.2)	114 (3.6)
Infections And Infestations		
Upper respiratory tract infection	439 (13.7)	391 (12.3)
Nasopharyngitis	414 (13.0)	381 (12.0)
Urinary tract infection	207 (6.5)	171 (5.4)
Musculoskeletal And Connective Tissue Disorders		
Back pain	201 (6.3)	178 (5.6)
Musculoskeletal pain	65 (2.0)	43 (1.4)
Nervous System Disorders		
Headache	537 (16.8)	321 (10.1)
Dizziness	270 (8.5)	122 (3.8)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	136 (4.3)	109 (3.4)
Oropharyngeal pain	111 (3.5)	80 (2.5)
Sinus congestion	93 (2.9)	78 (2.4)
Skin And Subcutaneous Tissue Disorders		
Rash	67 (2.1)	58 (1.8)

Other Adverse Events[5]

Valvulopathy

The incidence of FDA defined valulopathy (a mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation) in 7794 patients in three prospective clinical trials of a 1 year or longer is shown in Table 7. At 1 year, 2.4% of patients assigned to lorcaserin and 2% assigned to placebo developed valvular regurgitation. After 2-years of exposure to lorcaserin (BLOSSOM) the rate of valvulopathy was 2.6% and 2.7% in the placebo arm.

Table 7. Incidence and Relative Risk of FDA-defined Valvulopathy at 1 Year

	BLOOM		**BLOSSOM**		**BLOOM-DM**	
	Lorcaserin n=1278	**Placebo n=1191**	**Lorcaserin n=1208**	**Placebo n=1153**	**Lorcaserin n=210**	**Placebo n=209**
Valvulopathy, n (%)	34 (2.7)	28 (2.4)	24 (2.0)	23 (2.0)	6 (2.9)	1 (0.5)
Rel. Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled Rel. Risk	1.16 (0.81, 1.67)					

Abuse Potential and Dependence[5]

In a human abuse potential study in recreational drug abusers, supratherapeutic oral doses of lorcaserin (40 and 60 mg) produced up to two- to six-fold increases on measures of "High", "Good Drug Effects", "Hallucinations" and "Sedation" compared to placebo. These responses were similar to those produced by oral administration of the positive control drugs, zolpidem (15 and 30 mg) and ketamine (100 mg).

Overall, in short-term studies with healthy individuals, the rate of euphoria following oral administration of lorcaserin was 16% following 40 mg (n = 11 of 70) and 19% following 60 mg (n = 6 of 31). However, in clinical studies with obese patients with durations of 4 weeks to 2 years, the incidence of euphoria and hallucinations following oral doses of lorcaserin up to 40 mg was low (< 1.0%).

There are no data from well-conducted animal or human studies that evaluate whether lorcaserin can induce physical dependence, as evidenced by a withdrawal syndrome. However, the ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at supratherapeutic doses suggests that lorcaserin may produce psychic dependence.

Tolerability[10-12]

Data on drug-related adverse events resulting in study discontinuation from the BLOOM, BLOOM- DM , and BLOSSOM trials (Table 8).

Table 8 Frequency of Drug-related Study Discontinuation in Clinical Trials

Study	Placebo	Lorcaserin 10 mg twice a day	Lorcaserin 10 mg daily
BLOOM	6.7%	7.1%	---
BLOOM-DM	4.3%	8.6%	6.3%
BLOSSOM	4.6%	7.2%	6.2%

Contraindications[5]

Pregnancy – FDA Category X. Contraindicated because weight loss is not beneficial during pregnancy and may result in fetal harm.

Warnings and Precautions[5]

- *Serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions* are theoretically possible since lorcaserin is a serotonergic drug. Concomitant use with a serotonergic or antidopaminergic drug or an MAOI has not been studied. Extreme caution is advised if lorcaserin is combined with these types of drugs.
- *Valvular heart disease,* regurgitant, primarily affecting the mitral and/or aortic valves has been reported with other agonists of 5-HT_{2B} receptors. Lorcaserin has demonstrated selectivity for 5-HT_{2C} receptors (See Pharmacology and Adverse Events). Lorcaserin has not been studied in patients with congestive heart failure and should be used with caution. Combining lorcaserin with other serotonergic and dopaminergic drugs that are potent 5-HT_{2B} agonists and are known to increase the risk for cardiac valvulopathy (e.g., cabergoline).
- *Cognitive impairment* in the form of impaired attention and memory, confusion, somnolence and fatigue has been reported. Patients should be cautioned when operating machinery and driving until they are know who lorcaserin affects them.
- *Psychiatric disorder* reactions including euphoria, hallucinations and dissociation were observed following supratherapeutic doses of lorcaserin. Patients should be monitored for signs of the emergence or worsening of depression including suicidal thoughts or behavior.

- *Potential risk of hypoglycemia in patients with type 2 diabetes on antidiabetic therapy***.** Hypoglycemia was been reported following weight loss in type 2 diabetic patients taking lorcaserin. Adjustment in a patient's diabetes medication may be needed to avoid hypoglycemia.
- *Priapism* is a potential effect of 5-HT2C receptor agonists. Use with caution in patients who have conditions that predispose them to priapism or patients taking a PDE type 5 inhibitor.
- *Heart rate decrease* was noted to be greater in patients treated with lorcaserin than placebo in clinical trials. Use with caution in patients with bradycardia or a history of heart block greater than first degree.
- *Hematological changes* including decrease in red and white blood cells were reported in clinical trials.
- *Prolactin elevation* – lorcaserin moderately elevates prolactin concentrations. Patients who develop signs or symptoms of excess prolactin should have their prolactin concentrations measured.
- *Pulmonary hypertension* has been associated with other centrally-acting weight loss serotonergic drugs. Due to the low incidence of this disease, the clinical trial experience with lorcaserin is deemed inadequate to determine whether exposure increases the risk for pulmonary hypertension.

Special Populations[5]

Pregnancy
FDA Category X. See Contraindications.

Nursing Mothers
It is not known if lorcaserin is excreted in human milk. It is advised that women not take lorcaserin while nursing or discontinue the drug if they choose to nurse.

Geriatrics
The upper age limit in clinical trials of lorcaserin was 65 years. According to the manufacturer 2.5% (135) of patients the clinical trials were 65 years of age and older. Therefore there is insufficient information on lorcaserin's safety or efficacy in persons older than 65 years of age. Although a dose adjustment is not required for mild renal impairment, lorcaserin should be used with caution in persons with moderate renal impairment which is common in geriatric patients.

Renal or Hepatic Impairment – See Dosage and Administration

Postmarketing Safety Experience
Six postmarketing studies were mandated as part of lorcaserin's approval. These studies are not completed and summarized below.

1. A clinical pharmacology study to assess pharmacokinetic parameters related to a lorcaserin dose of 10 mg in pediatric patients ages 12 to 17 years.
2. A clinical pharmacology study to assess pharmacokinetic parameters related to a lorcaserin dose of 10 mg in pediatric patients ages 7 to 11 years.
3. A 52-week, randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of lorcaserin for the treatment of obesity in pediatric patients ages 12 to 17 years.
4. A 52-week, randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of lorcaserin for the treatment of obesity in pediatric patients ages 7 to 11 years.
5. A juvenile animal study with lorcaserin to assess effects on learning, memory, motor development, physical development and sexual maturation, mating and fertility.
6. A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with lorcaserin on the incidence of major adverse cardiovascular events (non-fatal myocardial

infarction, non-fatal stroke, and cardiovascular death) in obese and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors.

Sentinel Events
None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name *Lorcaserin*: *Loratidine, Lotensin, lorazepam, loperamide*
LA/SA for trade name *Belviq*: None identified

Drug Interactions[5]

Drug-Drug Interactions

- Use of SSRIs and SNRIs was excluded in clinical trials because of theoretical risk for serotonin syndrome.
- There are no studies on the safety or efficacy of combining lorcaserin with other weight loss drugs such as phentermine, topiramate or orlistat.
- Use with caution with drugs that are CYP 2D6 substrates whose exposure can be increased.

Drug-Lab Interactions
None
Acquisition Costs

Refer to VA pricing sources for updated information.

Conclusions
Given the prevalence of overweight and obesity as well as weight-associated conditions among Veterans, the availability of a medication that decreases appetite is a potentially valuable component of a comprehensive approach to weight loss and maintenance. In clinical trials, the lorcaserin demonstrated its efficacy as part of a weight loss and management strategy.

Compared to placebo, the absolute amount of weight lost, the proportion of patients who lost $\geq$5% and $\geq$10% of their baseline body weight, and reductions in waist circumference were significantly greater with the lorcaserin compared to placebo. Additional benefits related to weight-loss were reported in patients treated with the lorcaserin included reductions in blood pressure, improved glycemic control and positive effects on the lipid profile. The net change in medications used to treat these conditions was also realized.

Lorcaserin is a FDA Pregnancy Category X. Lorcaserin is a serotonin agonist which generates concerns about valvulopathy that lead to the withdrawal of fenfluramine. After 1 year the risk for valvulopathy did not differ in patients treated with lorcaserin compared to placebo. Common adverse effects include headache, fatigue, dizziness, constipation and dry mouth. Concurrent use of lorcaserin with other drugs affecting serotonin or antidopaminergic drugs may increase the risk of serotonin syndrome or neuroleptic malignant-like syndrome.

The clinical trials with lorcaserin were not conducted in patients reflective of Veterans. Trial participants were primarily women and less 65 years of age. Thus, it cannot be stated with certainty that the weight loss, other benefits, and the safety profile reported in clinical trials will be realized in the patients cared for by VHA. As outlined in the VA/DoD Clinical Practice Guideline for Screening and Management of

Overweight and Obesity, and VA MOVE!®, weight loss medications are to be introduced after, and with the continuation of, behavioral interventions to improve diet, reduce daily caloric intake, and increase physical activity.

References

1. VHA Corporate Data Warehouse (CDW-2013). Courtesy of Ken Jones, PhD.
2. Department of Veterans Affairs and Department of Defense Clinical Practice Guidelines for Screening and Management of Overweight and Obesity, 2006. Available at: http://www.healthquality.va.gov/. Accessed November 20, 2012.
3. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
4. Gonzalez AB, Hartge P, Cerhan JR, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med 2010;363:2211-9.
5. BELVIQ (lorcaserin hydrochloride) package insert. June 2012.
6. Thomsen WJ, Grottick AJ, Menzaghi, et al. Lorcaserin, a novel selective human 5-hydroxytryptamine$_{2C}$ agonist: in vitro and in vivo pharmacologic characterization. JPET 2008;325:577-587.
7. Guidance for industry: developing products for weight management (draft). Silver Spring, MD: Food and Drug Administration 2007 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071612.pdf. Accessed November 19, 2012.
8. Corby MK, Redman LM, Zhang J, et al. Lorcaserin, a 5-HT$_{2C}$ receptor agonist, reduces body weight by decreasing energy intake without influencing energy expenditure. J Clin Endocrinol Metab 2011;96:837-45.
9. Smith SR, Prosser WA, Donahue DJ, et al. Lorcaserin (APD356), a selective 5-HT$_{2C}$ agonist, reduces body weight in obese men and women. Obesity 2008;17:494-503.
10. Smith SR, Weissman NJ, Anderson CM, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010;363:245-56.
11. 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 2012;20:1426-36.
12. 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;96:3067-77.

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