

Brand Name: Belviq®

Generic Name: lorcaserin hydrochloride

Manufacturer³: Eisai Inc.

Drug Class^{1,2}: Serotonin 5-HT_{2C} Receptor Agonist

Uses:

Labeled Uses^{1,2,3,4,5}: Adjunctive treatment for obesity in addition to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- $\geq 30 \text{ kg/m}^2$ (obese) **OR**
- $\geq 27 \text{ kg/m}^2$ (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes)

Unlabeled Uses¹: None

Mechanism of Action^{1,3,4,5}:

The exact mechanism of lorcaserin is unknown. However, lorcaserin is believed to decrease food consumption and promote satiety by selectively activating 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons in the hypothalamus. At the recommended daily dose, lorcaserin interacts selectively with 5-HT_{2C} receptors (versus 5-HT_{2A}, 5-HT_{2B}, other 5-HT receptor subtypes, 5-HT receptor transporter, and 5-HT reuptake).

Pharmacokinetics^{1,3,4,5}:

Absorption/Distribution:

T_{max}	1.5 to 2 hours (2.5 hours in elderly patients)
Effect of food	No effect on exposure
Bioavailability	Not yet determined
t_{1/2}	11 hours
Clearance	Not reported
Protein binding	70% to plasma proteins
CNS	Distributes to CSF/CNS

Metabolism: Lorcaserin is extensively metabolized in the liver by multiple enzymatic pathways to lorcaserin sulfamate (M1), N-carbamoyl glucuronide lorcaserin (M5), and sulfate and glucuronide conjugates of oxidative metabolites. Neither CYP 450 enzymes nor glutathione are involved in its metabolism. M1 (inactive) is the major circulating metabolite, but is only a minor metabolite in the urine, accounting for only 3% of the dose. M5 (inactive) is the major metabolite in the urine.

Elimination: Lorcaserin is primarily excreted through the kidneys into urine (92.3%). 2.2% of the dose is excreted in the feces.

Efficacy:

Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med. 2010;363(3):245-56.

Study Design: 2-year, multicenter, randomized, placebo-controlled, double-blind, parallel design study

Description of Study: *Methods:* 3182 patients with a mean BMI of 36.2 were randomized to receive either placebo or lorcaserin 10 mg twice daily for 52 weeks, in addition to a diet and exercise counseling program. At that point, the lorcaserin group was randomized again 2:1 to receive either lorcaserin or placebo. Efficacy was evaluated using the change in body weight at baseline compared to 1 year later. For year 2, efficacy was evaluated based on those who maintained a reduction in baseline body weight of $\geq 5\%$ during year 2. Safety was evaluated by heart rate, PASP, and Beck Depression Inventory II (BDI-II) score.

Outcome Results: At the end of year 1, 47.5% of patients receiving lorcaserin had lost 5% body weight, as compared with 20.3% of patients receiving placebo ($P < 0.001$). Patients in the lorcaserin group lost an average (\pm SE) of $5.81 \pm 0.16\%$ of the baseline body weight versus $2.16 \pm 0.14\%$ in the placebo group ($P < 0.001$). Among patients in the lorcaserin group who had weight loss of 5% or more at year 1, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 than in those who were reassigned to receive placebo (67.9% vs. 50.3%, $P < 0.001$).

Limitations: The study was supported by Arena Pharmaceuticals, the company responsible for the research and development of lorcaserin. Also, several authors and researchers were employers of the company, introducing a potential conflict of interest. The rate of discontinuation at 1 year was nearly 50%, however this was similar to the rates in other large randomized trials of obesity. Analysis included only 63.6% (1015 of 1595) of patients in the lorcaserin group and 56.0% (888 of 1587) of patients in the placebo group. The applicability of safety or efficacy to a broader population is unknown, since patients with a BP above 140/90, a binge-eating disorder, a BMI above 45, and/or diabetes mellitus were excluded. The trial was underpowered to detect the incidence of valvulopathy.

Conclusion: This study showed that lorcaserin combined with behavioral modification was associated with significant weight loss of 5-10% baseline body weight, and improved maintenance of that loss. However, patients who started placebo after 1 year on lorcaserin rapidly regained their body weight, implying the need for chronic lorcaserin to maintain weight loss. Biomarkers that may be predictors of future cardiovascular events, including lipid levels, insulin resistance, levels of inflammatory markers, and blood pressure were

also improved with lorcaserin use, although these cannot be considered significant difference since no statistical tests on these values was performed. Future research may expand the applicability to the population at large by studying populations such as patients with type 2 diabetes mellitus. In addition, future research should also focus on a sufficiently powered study that can detect the true incidence of valvulopathy in patients taking lorcaserin versus placebo.

Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial. J Clin Endocrinol Metab. 2011;96(10):3067-77.

Study Design: 52-week, 97-center, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: *Methods:* 4008 patients, aged 18–65 yr, with a body mass index between 30 and 45 kg/m² or between 27 and 29.9 kg/m² with an obesity-related comorbid condition were randomly assigned 2:1:2 to receive lorcaserin 10 mg twice daily, lorcaserin 10 mg once daily, or placebo along with diet and exercise counseling. Efficacy was evaluated by the proportion of patients achieving $\geq 5\%$ reduction in body weight, mean change in body weight, and proportion of patients achieving at least 10% reduction in body weight at week 52. Safety evaluations included all patients who received at least one dose of study medication, judged by the incidence at week 52 of valvulopathy.

Outcome Results: Significantly more lorcaserin patients (BID and QD) lost at least 5% of baseline body weight (47.2 and 40.2%, respectively) as compared with placebo (25.0%, $P < 0.001$ vs. lorcaserin BID). Least squares mean (95% confidence interval) weight loss with lorcaserin BID and QD was 5.8% (5.5–6.2%) and 4.7% (4.3–5.2%), respectively, compared with 2.8% (2.5–3.2%) with placebo ($P < 0.001$ vs. lorcaserin BID; least squares mean difference, 3.0%). Weight loss of at least 10% was achieved by 22.6 and 17.4% of patients receiving lorcaserin 10 mg BID and QD, respectively, and 9.7% of patients in the placebo group ($P < 0.001$ vs. lorcaserin BID). Headache, nausea, and dizziness were the most common lorcaserin-related adverse events. U.S. Food and Drug Administration-defined echocardiographic valvulopathy occurred in 2.0% of patients on placebo and 2.0% on lorcaserin 10 mg BID.

Limitations: The study was supported by Arena Pharmaceuticals, the company responsible for the research and development of lorcaserin. Also, several authors and researchers were employers of the company, introducing a potential conflict of interest. Several relevant preexisting conditions were excluded (e.g. type 2 diabetes mellitus, recent cardiovascular events). High discontinuation rates were observed in this study, however they were not well accounted for. The current study has insufficient power to detect new FDA-defined valvulopathy. Future analyses will be needed to more fully detect the risk of valvular heart disease among patients taking lorcaserin.

Conclusion: Lorcaserin used for up to 1 year was associated with significant weight loss among obese and overweight adults. This study contributes to the overall understanding of lorcaserin's risk-benefit profile by demonstrating safety and efficacy for both the twice daily and daily dosage regimens. Lorcaserin efficacy appears to be dose dependent. This supports continued evaluation of lorcaserin in more inclusive populations, especially at the more effective twice daily dosage. This study was insufficiently powered to detect the risk of valvulopathy, so future research should increase the sample size studied in order to improve power.

O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring). 2012;20(7):1426-36.

Study Design: 52-week, multicenter, randomized, placebo-controlled, double-blind, parallel study

Description of Study: *Methods:* 604 patients with type 2 diabetes mellitus were randomized 1:1:1 to placebo, lorcaserin 10 mg once daily or lorcaserin 10 mg twice daily, all with diet and exercise counseling. Safety monitoring included serial echocardiograms. Efficacy was evaluated by the proportion of patients achieving $\geq 5\%$ reduction in baseline body weight at the end of 1 year, change in weight, and the proportion of patients achieving $\geq 10\%$ reduction in baseline body weight. Safety was evaluated using laboratory values, vital signs, electrocardiograms and the BDI-II depression score.

Outcome Results: More patients lost $\geq 5\%$ body weight with lorcaserin BID (37.5%; $P < 0.001$) or lorcaserin QD (44.7%; $P < 0.001$) vs. placebo (16.1%). Least square mean (\pm SEM) weight change was $-4.5 \pm 0.35\%$ with lorcaserin BID and $-5.0 \pm 0.5\%$ with lorcaserin QD vs. $-1.5 \pm 0.36\%$ with placebo ($P < 0.001$ for each). HbA1c, fasting glucose both were significantly decreased in the lorcaserin group. However, symptomatic hypoglycemia occurred in 7.4% of patients on lorcaserin BID, 10.5% on lorcaserin QD, and 6.3% on placebo. Common adverse events were headache, back pain, nasopharyngitis, and nausea.

Limitations: The study was not designed to primarily evaluate glycemia. Whether the improvement in glycemic control can be attributed to weight loss is unclear since antihyperglycemic medications could be adjusted after the 12th week of the trial. Lorcaserin was evaluated only in patients whose diabetes was treated with oral agents that included metformin and/or a SFU. Whether these results are generalizable to a broader population is unknown. Discontinuation rate was high, ranging from 22.1% of patients in the lorcaserin QD group to 37.9% in the placebo group.

Conclusion: Lorcaserin was associated with significant weight loss and improvement in glycemic control in obese and overweight patients with type 2 diabetes. It was also associated with significant and clinically meaningful weight reduction, improvements in A1C, and fasting glucose. Efficacy was similar to the BLOSSOM trial, however a dose-related response was not observed in this diabetic population. Safety was similar to non-

diabetic patients from the BLOSSOM trial, with no clear evidence of increased depression or valvulopathy. However, the sample size was insufficient to detect the true incidence of valvulopathy. Because significant improvements in glycemic control were also observed, lorcaserin could represent a clinically useful weight management tool for overweight and obese type 2 diabetic patients in the future. However, future research should identify whether its glycemic benefits and other effects are independent of concomitant medications.

Contraindications^{1,3,4,5}:

Pregnancy: Lorcaserin is a Pregnancy Category X drug for all trimesters. It is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. There are no adequate or well-controlled human studies on the use of lorcaserin during pregnancy. In rats, maternal exposure resulted in lower birth weight of offspring which persisted to adulthood. However, no developmental abnormalities were observed and reproductive performance was unaffected. Patients must be counseled on the potential hazards to the fetus if a patient uses this drug during pregnancy or becomes pregnant while taking this drug.

Precautions^{1,3,4,5}:

Lactation: It is unknown whether lorcaserin is excreted in breast milk. Patients should notify their physician if they are nursing or intend to nurse while on the medication.

Pediatrics Use: Safe and effective use for patients less than 18 years of age has not been established.

Geriatric Use: In lorcaserin clinical trials, 135 patients were 65 years of age or older. This number does not include a sufficient number of geriatric patients to determine variations in response to the drug versus younger patients. Be cautious about use in the elderly since sensitivity cannot be ruled out, and base use on renal function.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: This has been reported during the use of serotonergic drugs, particularly when used in combination. If mental status changes, autonomic instability, gastrointestinal symptoms, hyperthermia, or muscle rigidity appear, discontinue lorcaserin immediately and give supportive symptomatic treatment.

Valvular Heart Disease: Regurgitant cardiac valvular disease has been reported in patients who have taken 5-HT_{2B} receptor agonists, which appear to activate receptors in cardiac interstitial cells. Lorcaserin is selective for 5-HT_{2C} at therapeutic concentrations. Use with caution in patients with CHF and patients with other serotonergic or dopaminergic drug therapy. Evaluate and consider discontinuation of therapy in patients who develop symptoms of valvular heart disease.

Cognitive Impairment: Impairments in attention and memory have been reported, as well as confusion, somnolence, and fatigue. Caution patients about operating hazardous machinery until they are certain lorcaserin does not affect them adversely.

Psychiatric Disorders: Euphoria, hallucinations, and dissociation have been reported at suprathreshold doses. Do not exceed the recommended dose of 10 mg twice daily. Some drugs that target the CNS have been associated with depression or suicidal ideation. Monitor patients for emergence or worsening of depression, suicidal thoughts, or unusual changes in mood or behavior. Discontinue lorcaserin in patients who experience these symptoms.

Potential Risk of Hypoglycemia in Patients with Type 2 Diabetes Mellitus on Antidiabetic Therapy: Weight loss may increase the risk of hypoglycemia in patients with type 2 diabetes mellitus treated with insulin or insulin secretagogues like sulfonylureas. Monitor blood glucose prior to and during treatment with lorcaserin. Consider decreasing non-glucose-dependent anti-diabetic medication doses as necessary.

Priapism: Priapism is a potential effect of 5-HT_{2C} receptor agonism. Men who have an erection lasting greater than 4 hours should immediately discontinue the drug and seek emergency medical attention. Use lorcaserin with caution in men with sickle cell anemia, multiple myeloma, leukemia, deformation of the penis, and those using PDE-5 inhibitors.

Heart Rate Decreases: Due to small decreases in heart rate observed in clinical trials, use caution in patients with bradycardia or history of heart block greater than first degree.

Hematological Changes: Consider periodic monitoring of CBC during treatment with lorcaserin due to small risk of decreases in white or red blood cell count.

Prolactin Elevation: Lorcaserin moderately elevates prolactin levels. Measure prolactin when symptoms and signs of prolactin excess are suspected (e.g. galactorrhea, gynecomastia).

Pulmonary Hypertension: Other centrally-acting weight loss agents that act on the serotonin system have been associated with pulmonary hypertension. The clinical trial experience is inadequate to determine if lorcaserin also increases the risk of pulmonary hypertension due to its low incidence, so use caution.

Adverse Effects³:

Occurring in $\geq 2\%$ of patients and more commonly than with placebo in patients without diabetes mellitus:

Gastrointestinal Disorders:

- Nausea (8.3%)
- Diarrhea (6.5%)
- Constipation (5.8%)
- Dry mouth (5.3%)
- Vomiting (3.8%)

General Disorders and Administration Site Conditions:

Fatigue (7.2%)

Infections and Infestations:

Upper respiratory tract infection (13.7%)

Nasopharyngitis (13.0%)

Urinary tract infection (6.5%)

Musculoskeletal and Connective Tissue Disorders:

Back pain (6.3%)

Musculoskeletal pain (2.0%)

Nervous System Disorders:

Headache (16.8%)

Dizziness (8.5%)

Respiratory, Thoracic and Mediastinal Disorders:

Cough (4.3%)

Oropharyngeal pain (3.5%)

Sinus congestion (2.9%)

Skin and Subcutaneous Tissue Disorders:

Rash (2.1%)

Occurring in $\geq 2\%$ of patients and more commonly than with placebo in patients without diabetes mellitus:

Gastrointestinal Disorders:

Nausea (9.4%)

Toothache (2.7%)

General Disorders and Administration Site Conditions:

Fatigue (7.4%)

Peripheral edema (4.7%)

Immune System Disorders:

Seasonal allergy (3.1%)

Infections and Infestations:

Nasopharyngitis (11.3%)

Urinary tract infection (9.0%)

Gastroenteritis (3.1%)

Metabolism and Nutrition Disorders:

Hypoglycemia (29.3%)

Worsening of diabetes mellitus (2.7%)

Decreased appetite (2.3%)

Musculoskeletal and Connective Tissue Disorders:

Back pain (11.7%)

Muscle spasms (4.7%)

Nervous System Disorders:

Headache (14.5%)

Dizziness (7.0%)

Psychiatric Disorders:

Anxiety (3.5%)

Insomnia (3.5%)

Stress (2.7%)

Depression (2.3%)

Respiratory, Thoracic and Mediastinal Disorders:

Cough (8.2%)

Vascular Disorders:

Hypertension (5.1%)

Other:

Serotonin-associated:

SSRIs, SNRIs, bupropion, tricyclic antidepressants, and MAOIs were excluded from the lorcaserin trials, however there were still two patients who reported symptoms consistent with serotonergic excess (chills, tremor, confusion, disorientation). Association between lorcaserin and serotonin syndrome cannot be ruled out.

Hypoglycemia in patients with type 2 diabetes:

Hypoglycemia requiring the assistance of another person was reported in 4 (1.6%) patients treated with lorcaserin, however all 4 were also using a sulfonylurea at the same time. BG \leq 65 mg/dL occurred in 19 (7.4%)

Cognitive impairment:

Occurred in 2.3% of lorcaserin patients (e.g. difficulty with concentration, difficulty with memory, confusion)

Psychiatric disorders:

Lorcaserin-treated patients were hospitalized due to psychiatric disorders more frequently (2.2%) than those treated with placebo (1.1%)

Euphoria

Incidence increased with high doses of 40 mg and 60 mg (0.17%)

Depression and suicidality

Depression/mood problems occurred in 2.6%; suicidal ideation occurred in 0.6%; 1.3% of patients discontinued drug due to depression, mood, or suicidal events

Laboratory abnormalities:

Lymphocyte and neutrophil counts (*< lower limit of normal*)

12.2% and 5.6% of lorcaserin patients, respectively

Hemoglobin (*< lower limit of normal*)

10.4% of patients taking lorcaserin

Prolactin (*> upper limit of normal*)

Elevations $>$ the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, occurred in 6.7%, 1.7%, and 0.1% of lorcaserin-treated patients

Eye disorders:

Patients on lorcaserin reported an eye disorder more than patients on placebo in clinical trials of patients without diabetes (4.5%) and with type 2 diabetes (6.3%).

Drug Interactions^{1,3,4,5}:

Use with other agents that affect serotonin pathways

Monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, dextromethorphan, tricyclic antidepressants, bupropion, lithium, tramadol, tryptophan, triptans, and St. John's wort

Inhibitor of CYP2D6

Lorcaserin is an inhibitor of CYP2D6 and as a result may cause increased exposure to drugs metabolized by this enzyme if used in conjunction.

Dosing/Administration^{1,3,4,5}:

Adult Dosing

10 mg PO twice daily with or without food. Do not exceed recommended dose. Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, discontinue lorcaserin, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.

Pediatrics

Safety and efficacy not established.

Elderly

Maximum daily dosage: 20 mg/day by mouth.

Renal impairment

CrCl > 50 ml/min: No dose adjustment required.

CrCl 30—50 ml/min: Use with caution in moderate renal impairment.

CrCl < 30 ml/min: Not recommended in severe renal impairment or end stage renal disease.

Hepatic impairment

No dose adjustment is required for mild to moderate hepatic impairment (Child-Pugh score 5-9). Use of lorcaserin should be avoided in patients with severe hepatic impairment

Use in special circumstances:

Overdosage³: No experience with overdose is available. In clinical studies that used doses higher than recommended, the most frequent adverse reactions associated with lorcaserin were headache, nausea, abdominal discomfort, and dizziness. Single 40 mg and 60 mg doses of lorcaserin caused euphoria, altered mood, and hallucination in some subjects. Treatment of overdose should consist of lorcaserin discontinuation and general supportive measures in the management of overdose. Lorcaserin is not eliminated by hemodialysis.

Abuse³: In a human abuse potential study in recreational drug abusers, supratherapeutic doses of lorcaserin (40 mg and 60 mg) caused 2-6 fold increases on measures of “High,” “Good Drug Effects,” “Hallucinations” and “Sedation” compared to placebo, similar to that of zolpidem, and about one-third of that seen with ketamine. The duration of euphoria following lorcaserin administration persisted longer (> 9 hours) than that following zolpidem (1.5 hours) or ketamine (2.5 hours) administration. Short-term studies indicate a higher risk of euphoria (16%-19%) with lorcaserin than long-term studies (<1.0%).

Dependence³: No data evaluate the capacity of lorcaserin to induce physical dependence via withdrawal symptoms. However, hallucinations, euphoria, and positive subjective responses are concerning that doses higher than recommended could cause physical dependence.

Conclusion:

Lorcaserin is an effective adjunct to diet and exercise for the treatment of weight loss in overweight and obese patients with and without type 2 diabetes mellitus. While weight seems to be rapidly regained when the medication is discontinued, weight loss can be maintained for at least 2 years while taking lorcaserin according to current data. More studies need to be done to evaluate its safety when used long-term. In addition, the potential adverse effects of lorcaserin, including increased risk of valvulopathy, hypoglycemia, depression, serotonin syndrome, and abuse have yet to be fully understood. Future research should be sufficiently powered to detect the incidence of these adverse events, especially concerning valvulopathy. More studies need to be conducted to evaluate whether or not its effect on glycemic control is independent of antihyperglycemic medications, and which antihyperglycemic medications it is most effective with in combination. When used daily for 1 to 2 years in clinical trials, lorcaserin was associated with modest weight loss (5% to 6% of body weight). Weight loss of 5% was achieved and maintained in approximately half of the patients treated with lorcaserin. These results were replicated in the BLOOM trial which proved the superiority of the twice daily dosage, as well as the BLOOM-DM trial which demonstrated the efficacy of lorcaserin in patients with type 2 diabetes mellitus. However, the BLOOM-DM trial failed to demonstrate the dose-response profile observed in BLOSSOM and BLOOM. With the current knowledge about its tolerability, minimal drug interactions, and effectiveness, lorcaserin appears to be a clinically useful agent for the adjunctive treatment of obesity. However, the choice must be individualized based on a risk-benefit profile for each patient, and future research will help to clarify some safety concerns that have not yet been adequately answered.

Recommended References:

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8. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring)*. 2012;20(7):1426-36.

Prepared by: Jordan P. McPherson, Doctor of Pharmacy Candidate