

Lorcaserin: a selective serotonin receptor (5-HT_{2C}) agonist for the treatment of obesity

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ABSTRACT

Lorcaserin is a selective serotonin receptor (5-HT_{2C}) agonist that recently received the U.S. Food and Drug Administration (FDA) approval for chronic weight management. The efficacy of this drug in reducing body weight and improving metabolic parameters of obese patients has been demonstrated in three phase-3 clinical trials. The available evidence indicates that this drug does not show heart valve abnormalities, and the treatment improves the risk factors for type 2 diabetes and cardiovascular diseases. However, the drug's manufacturer will be required to conduct postmarketing studies, including a long-term cardiovascular outcomes trial to assess the effect of Lorcaserin on the risk for major adverse cardiac events such as heart attack and stroke.

Keywords: Anti-obesity drug, Sibutramine, Orlistat, 5-hydroxytryptamine receptor agonist

INTRODUCTION

The U.S. Food and Drug Administration (FDA) approved Lorcaserin hydrochloride (Belviq) on 27th June 2012, for chronic weight management. Lorcaserin is approved for use in adults with a body mass index (BMI) of 30 or greater, or adults with a BMI of 27 or greater and who have at least one weight-related condition such as high blood pressure, type 2 diabetes, or high cholesterol. Lorcaserin (Belviq) is developed by Arena Pharmaceuticals GmbH of Zofingen, Switzerland.

There are several drugs available for the treatment of obesity for short-term usage (e.g. Diethylpropion, Phentermine, Benzphetamine, and Phendimetrazine). Orlistat is approved by the US FDA for long-term maintenance of weight loss.¹ Orlistat blocks caloric absorption of the ingested fat by inhibiting gastric and pancreatic lipases in the gut lumen.² The inactivated enzymes cannot hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides, which may have a positive effect on weight control. Orlistat can reduce the absorption of fat-soluble vitamins. Thus, vitamin supplementation is recommended.² Orlistat has efficacy to reduce weight up to 8%-10%.³ However, there are no long-term efficacy or safety data available for using Orlistat beyond 2 years and patients often regain weight upon discontinuation of the medication. Sibutramine was approved for the long-term treatment of obesity by the US FDA in November 1997

and in October 2010, following the findings of a comprehensive study examining the potential cardiovascular risks, Abbott Laboratories, the manufacturers of sibutramine, withdrew sibutramine from the US, Australia, and other countries.⁴ Lorcaserin is a centrally acting drug approved for long-term maintenance of weight loss.

MECHANISM OF ACTION

Lorcaserin is believed to decrease food consumption and promote satiety by selectively activating 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons located in the hypothalamus.⁵ Lorcaserin at the recommended daily dose selectivity interacts with 5-HT_{2C} receptors as compared to 5-HT_{2A} and 5-HT_{2B} receptors, other 5-HT receptor subtypes, the 5-HT receptor transporter, and 5-HT reuptake sites.

CLINICAL TRIALS

The efficacy and safety of Lorcaserin for chronic weight management were evaluated in three phase-3 randomized, double-blind, placebo-controlled trials with durations ranging from 52 to 104 weeks. Two trials in adults without type 2 diabetes mellitus (BLOOM; Behavioral modification and Lorcaserin for Overweight and Obesity Management and BLOSSOM; Behavioral modification and Lorcaserin Second Study for Obesity Management) and one study in adults with type 2 diabetes mellitus

(BLOOM-DM; Behavioral modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus) evaluated the effect of Lorcaserin 10 mg twice daily. The primary efficacy parameter in these studies was weight loss at 1 year, which was assessed by percent of patients achieving greater than or equal to 5% weight loss, percent of patients achieving greater than or equal to 10% weight loss, and mean weight change.

BLOOM was a 2-year study that enrolled 3182 patients who were obese (BMI 30-45 kg/m²), or who were overweight (BMI 27-29.9 kg/m²) and had at least one weight-related comorbid condition such as hypertension or dyslipidemia.⁶ In Year 2, placebo patients were continued on placebo and Lorcaserin patients were re-randomized in a 2:1 ratio to continue Lorcaserin or to switch to placebo. The mean age was 44 (range 18-65); 83.5% were women. Mean baseline body weight was 100.0 kg and mean BMI was 36.2 kg/m². At 1 year, 47.5% of patients in the Lorcaserin group and 20.3% in the placebo group had lost 5% or more of their body weight, corresponding to an average loss of 5.8+/-0.2 kg with Lorcaserin and 2.2+/-0.1 kg with placebo during year 1. Among the patients who received Lorcaserin during year 1 and who had lost 5% or more of their baseline weight at 1 year, the loss was maintained in more patients who continued to receive Lorcaserin during year 2 (67.9%) than in patients who received placebo during year 2 (50.3%).

BLOSSOM was a 1-year study that enrolled 4008 patients who were obese (BMI 30-45 kg/m²) or were overweight (BMI 27-29.9 kg/m²) with at least one comorbid condition such as hypertension or dyslipidemia.⁷ The mean age was 44 (range 18-65); 80% were women. Mean baseline body weight was 100.2 kg and mean BMI was 35.9 kg/m². Significantly more patients treated with Lorcaserin 10 mg BID and QD lost at least 5% of baseline body weight (47.2 and 40.2%, respectively) as compared with placebo (25.0%). 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.

BLOOM-DM was a 1-year study that enrolled 604 adult patients with BMI greater than or equal to 27 kg/m² and inadequately controlled type 2 diabetes (HbA1c range 7-10%) being treated with metformin and/or a sulfonylurea.⁸ Mean age was 53 (range 21-65); 54% were women. Mean BMI was 36 kg/m² and mean HbA1c was 8.1%. More patients lost ≥5% body weight with Lorcaserin BID (37.5%) or Lorcaserin QD (44.7%) vs. placebo (16.1%). HbA1c decreased 0.9 ± 0.06 with Lorcaserin BID, 1.0 ± 0.09 with Lorcaserin QD, and 0.4 ± 0.06 with placebo (P < 0.001 for each); fasting glucose decreased 27.4 ± 2.5 mg/dl, -28.4 ± 3.8 mg/dl, and 11.9 ± 2.5 mg/dl, respectively.

ADVERSE EFFECTS

In clinical trials of at least one year in duration, 8.6% of patients treated with Lorcaserin prematurely discontinued treatment due to adverse reactions, compared with 6.7% of placebo-treated patients. The most common adverse reactions leading to discontinuation more often among Lorcaserin treated patients than placebo were headache (1.3% vs. 0.8%), depression (0.9% vs. 0.5%) and dizziness (0.7% vs. 0.2%).⁹

The most common adverse reactions for non-diabetic patients (greater than 5% and more commonly than placebo) treated with Lorcaserin compared to placebo were headache, dizziness, fatigue, nausea, dry mouth, and constipation.⁹ The most common adverse reactions for diabetic patients were hypoglycemia, headache, back pain, cough, and fatigue.⁹

Treatment with Lorcaserin may cause serious side effects, including serotonin syndrome, particularly when taken with certain medicines that increase serotonin levels or activate serotonin receptors. These include, but are not limited to, drugs commonly used to treat depression and migraine. Lorcaserin may also cause disturbances in attention or memory.

Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in patients who took serotonergic drugs with 5-HT_{2B} receptor agonist activity.⁹ The etiology of the regurgitant valvular disease is thought to be activation of 5-HT_{2B} receptors on cardiac interstitial cells. At therapeutic concentrations, Lorcaserin is selective for 5-HT_{2C} receptors as compared to 5-HT_{2B} receptors. Heart valve function was assessed by echocardiography in nearly 8,000 patients in the Lorcaserin development program. There was no statistically significant difference in the development of FDA-defined valve abnormalities between Lorcaserin and placebo-treated patients.⁹ Because preliminary data suggest that the number of 5-HT_{2B} receptors may be increased in patients with congestive heart failure, Lorcaserin should be used with caution in patients with this condition. Lorcaserin has not been studied in patients with serious valvular heart disease. The drug's manufacturer will be required to conduct postmarketing studies, including a long-term cardiovascular outcomes trial to assess the effect of Lorcaserin on the risk for major adverse cardiac events such as heart attack and stroke.

PLACE IN THERAPY

Pharmacological interventions in addition to lifestyle changes (diet and physical activity) and in some cases behavioural modifications are used to promote weight loss. Recently the U.S. FDA has approved two drugs for chronic weight management as an addition to a reduced-calorie diet and exercise, Belviq (Lorcaserin) and Qsymia (phentermine and topiramate extended-release). Qsymia is a combination of two FDA-approved drugs, phentermine and topiramate, in an extended-release formulation.

Qsymia has received the US FDA approval on 17th July 2012. Phentermine is indicated for short-term weight loss in overweight or obese adults who are exercising and eating a reduced calorie diet. Topiramate is indicated to treat certain types of seizures in people who have epilepsy and to prevent migraine headaches. Before Belviq and Qsymia, the only prescription drug approved for long-term treatment of obesity was Orlistat. In 1997, Fenfluramine and Dexfenfluramine were removed from the market because of concerns about damage to heart valves.³ In 2010, Sibutramine was also removed because of concerns about an increased risk of heart attacks and strokes.⁴ Orlistat treatment is associated with troublesome side effects such as diarrhoea, flatulence, bloating, abdominal pain, and dyspepsia which may not be acceptable to some patients on long-term treatment.³ So, now two alternative prescription drugs are available in the USA market for chronic weight management. However, the manufacturers of both Belviq and Qsymia will be required to perform long-term trials to examine the effect of these drugs on the risk for heart attacks and strokes.

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