# A Review on the Clinical Potential of Lorcaserin in the Treatment of Obesity

**Muhammad Danial bin Daud**

**Correspondence:**
Dr. Muhammad Danial bin Daud
Flat 105 Clifton Court,
Northwick Terrace,
NW8 8JA,
London
Tel: +447809472084
**Email:** dr.dandaud@gmail.com

Received: September 2021; Accepted: September 2021; Published: October 1, 2021.
Citation: Muhammad Danial bin Daud. A Review on the Clinical Potential of Lorcaserin in the Treatment of Obesity. World Family Medicine. 2021; 19(10): 124-128 DOI: 10.5742/MEWFM.2021.94143

## Abstract

Obesity is a chronic disease characterized by excessive fat accumulation and associated with impaired metabolism and cardiovascular disease. The high global prevalence of obesity has resulted in the production of anti-obesity drugs over the last couple of decades, normally to be used in combination with lifestyle modifications such as physical activity and diet. One such medication is lorcaserin, a selective serotonin 5-hydroxytryptamine2C (5-HT2C) receptor agonist approved by the FDA in 2012 as a drug therapy for weight management in conjunction with lifestyle modifications. Importantly, the FDA recently issued a request to withdraw lorcaserin from the market as it may promote certain types of cancers, including pancreatic, colorectal, and lung, but further clinical data is being collected and analyzed to assess its carcinogenic risk. This review will address lorcaserin's therapeutic potential for the treatment of obesity, considering the pre-clinical and clinical trials describing its efficacy in weight loss along with its adverse carcinogenic effects to ultimately determine the likelihood of its reintroduction into the market.

Key words: Lorcaserian, obesity, carcinogenic risk

## Introduction

Recent evidence through systematic analysis demonstrates that cardiovascular diseases such as myocardial infarction or stroke, along with cancer are the leading causes of death worldwide(1). These pathologies are highly associated with the obesity epidemic which plagues the globe today. In particular, obesity or overweight (as determined by body-mass index, BMI) strongly predicts and increases the risk for cardiovascular diseases (2,3). Obesity is also widely associated with at least 13 cancer types, including meningiomas, cancers of the liver and pancreas, and more, which make up 40% of all diagnosed cancers in the United States each year (4,5). Thus, a clear therapeutic need exists for obesity interventions aimed at improving both weight management and mitigating weight regain.
Generally, the current approach to reduce obesity and manage weight gain involves caloric restriction diets and increased physical activity (6). However, clinical studies indicate that without the use of pharmacological intervention in addition to these lifestyle changes, most individuals with obesity lose modest amounts of weight, and many of those who lose significant weight return to their original weight within a few years due to low rates of long-term adherence (7). Due to these weight management issues, many strategies to improve weight management in those who cannot achieve substantial weight loss through lifestyle alterations alone involve the use of anti-obesity medications (7).

Food intake and overall satiety are primarily controlled by central and peripheral hormonal signaling, which impact a variety of signaling pathways throughout the body. As such, modern pharmacology has targeted these pathways, such as increasing energy expenditure, reducing appetite, and decreasing fat and calorie absorption through the inhibition of lipases within the gastrointestinal system, to improve weight management in obese patients (7,8). The efficacy of these medications is mixed. While some of the drugs, such as phentermine, orlistat, and lorcaserin, do improve weight loss in obese individuals, they are associated with serious adverse effects (9).

The clinical potential of lorcaserin as an anti-obesity medication is of particular interest considering it was one of the most prescribed weight-loss drugs until early 2020 when the FDA revealed the drug may increase the risk of cancer and cancer-related mortality (10,11). Lorcaserin was approved by the FDA as a weight-loss medication on June 27th, 2012, but never gained approval from the European Medical Agency (EMA) due to its associated risks with breast cancer, psychiatric disorders, and valvulopathy. Specifically, the drug is a highly selective agonist to serotonin 2C (5-HT2c) receptors in the pro-opiomelanocortin (POMC) neurons of the central nervous system. The stimulation of these neurons results in the release of alpha-melanocortin-stimulating hormone (alpha-MSH) to suppress appetite (12,13).

The discovery of selective 5-HT2c agonists resulted in numerous pre-clinical and clinical trials on various drugs over the past two decades, and one showing the most promise as an anti-obesity drug was the serotonin releaser/reuptake inhibitor known as (dex)fenfluramine. (Dex)fenfluramine reduced appetite and helped obese individuals lose weight (14,15). However, the drug (along with other 5-HT2c agonists) was associated with various cardiovascular disease-related side effects, prompting its withdrawal from clinical use in the early 2000s (16). Despite the negative findings, testing of different selective 5-HT2c receptor agonists persisted throughout the early 2000, and lorcaserin was eventually discovered by Arena Pharmaceuticals.

Together with lifestyle modifications, lorcaserin is the only 5-HT2c receptor agonist that has been approved as an anti-obesity drug by the FDA. It has also been approved in Mexico, Taiwan, Israel, South Korea, while larger markets such as the EU and Japan have approved it for clinical use. Concerning lorcaserin's recent withdrawal from the market, this review will discuss its clinical potential, including its efficacy and adverse effects in recent clinical trials, along with the likelihood of it being reintroduced into the market as an anti-obesity medication.

## *In vivo* and pre-clinical pharmacology

Initial investigations on lorcaserin administration to rodents found the drug reduced alcohol intake and locomotor activity,(17,18) and similar observations were observed with other 5-HT2c receptor agonists as well (19). Rodent motor activity was also affected when higher doses of lorcaserin were administered, indicating lower-dose lorcaserin administration may reduce exploratory drive in addition to impaired motor performance (20).

Increased brain serotonin levels and the activation of 5-HT receptors can trigger certain behaviors from rodents including yawning or penile grooming (YPG), a behavior specific to activation of the 5-HT2c receptor (21). In rats subcutaneously administered 0.3-10mg/kg lorcaserin, YPD was significantly induced at even the lowest dose (18). Additionally, when these animals were treated with SB-242084, a selective 5-HT2c receptor antagonist, along with 10mg lorcaserin, they exhibited a wet dog shake (WDS) behavior commonly associated with specific activation of the 5-HT2a receptor, suggesting lorcaserin may have off-target effects at higher doses (18,19).

*In vivo* investigations on the administration of lorcaserin in rodents on food intake, satiety, obesity, and type 2 diabetes have been described at length. Specifically, lorcaserin treatment reduces sugar consumption and promotes satiety in a dose-dependent manner at doses between 0.1-3.0mg/kg body weight (22). Further research has discovered these effects persist in obese, aged (12-14 month-old) mice as well, and that the appetite-reducing effects are specific to POMC activation (23). Interestingly, studies show lorcaserin administration and subsequent

activation of the 5-HT2c receptors of dopaminergic neurons inhibits binge-like eating behavior in mice as well (24).

Feeding studies that investigate the effects of lorcaserin treatment in diet-induced obesity (DIO) rodent models indicate the drug is effective at reducing body and fat mass in the acute term, but long-term investigations have less successful results. Two studies observed the effects of high oral-dose lorcaserin treatment (9-36mg/kg,(25) 4.5-18mg/kg(26)) on weight gain and body composition in rat (DIO) models, and identified dose-dependent reductions in body weight gain over 28-days, with the highest dose resulting in a 12% decrease. Despite the reduction in body weight observed over the 28 days, lorcaserin's ability to reduce food intake over the period was less effective. In particular, lorcaserin significantly reduced food intake during the first 2 days of oral administration, but this effect constantly diminished after a week (25,26). Moreover, once lorcaserin treatment was stopped, daily food intake increased and body weight levels rose to values similar to pre-lorcaserin administration levels (26). Additional 28-day lorcaserin investigations on DIO rats have been conducted as well, specifically on low-dose (1-2mg/kg subcutaneous) administration (27). The study found the 2mg/kg lorcaserin administration resulted in 5% less weight gained compared to control mice, and the disparity was due to reductions in fat mass relative to lean mass. The authors also showed that similar to previous studies, lorcaserin induced a robust reduction in food intake during the first few days of administration, but the effect wore off after the first week.

Subcutaneous lorcaserin administration (2mg/kg body weight) to rats also lowered blood cholesterol and glucose levels in a glucose tolerance test (GTT), indicating it may improve lipid profiles and glucose homeostasis as well (27) Similar results have also been observed in mice in a dose-dependent manner, where ¬lorcaserin treatment significantly improved glucose control during a GTT, an effect that was completely diminished in POMC knockout mice. (28). Using insulin tolerance tests (ITT) and hyperinsulinemic/euglycemic clamps, the researchers also displayed lorcaserin treatment improves insulin sensitivity, suppresses hepatic glucose production, and enhances peripheral glucose disposal as well, providing further evidence of the drugs beneficial impact on glucose homeostasis and diabetic symptoms (28).

## Pharmacokinetics

Research has identified a single, 10mg/kg oral dose of lorcaserin in male, Sprague-Dawley rats resulted in rapid drug absorption from the gastrointestinal tract into the systemic circulation with a maximum mean drug concentration at 15 minutes (0.760 ug/mL), and maximal exposure in the brain at 1 hour after treatment. Together, these results demonstrate lorcaserin is rapidly absorbed, has high oral bioavailability, and a moderate half-life (25,26). Further studies investigating the pharmacokinetic properties of lorcaserin have been described as well. Specifically, lorcaserin levels measured in the plasma and cerebrospinal fluid (CSF) after 0.3-6mg/kg subcutaneous injection in Sprague-Dawley rats were directly proportional to the dose injected (29). Additionally, Arena Pharmaceuticals also measured sex-specific differences in lorcaserin treatment in rats and found plasma drug levels were higher in females compared to males (30). Similar pharmacokinetics were also observed in reports on the cynomolgus monkey, where maximal absorption of lorcaserin was observed less than 3.5 hours after administration, along with high oral bioavailability in a dose-dependent manner (30).

Despite the inhibitory activity lorcaserin displays on human cytochrome P2D6, the potential for drug-drug interactions is low since numerous CYP enzymes are involved in the drug's metabolism (12). Evidence also indicates lorcaserin increases the expression of certain CYP enzymes, suggesting that long-term exposure to the drug may increase its metabolism. Furthermore, lorcaserin displays moderate protein-binding capabilities around 60-76%, and the major elimination route of the drug and its metabolites (primarily N-carbomoyl glucuronide lorcaserin) is through the urine. (12).

## Lorcaserin clinical trials

The initial submission of lorcaserin for FDA approval in 2009 was denied, as treatment of the drug to rats was associated with the increased risk of developing several types of cancers compared to placebo-treated rats (9). However, the drug was eventually approved by the FDA in 2012, and this approval was primarily due to a few studies from 2010-2011: the behavioral modification and lorcaserin for overweight and obesity management (BLOOM) study, behavioral modification and lorcaserin for overweight and obesity management in patients of diabetes mellitus type 2 (BLOOM DM) study, and the BLOSSOM investigation, which was a 1-year non-randomized clinical trial analyzing lorcaserin's effectiveness at improving weight loss in obese or overweight adults.

The BLOOM trial was a double-blind, placebo-controlled clinical trial measuring the effects of lorcaserin in weight management. 3,182 obese or overweight individuals were randomly chosen to receive 10mg of lorcaserin twice a day for 1 year. Notably, these patients also received diet and exercise counseling. After 52 weeks, patients in the lorcaserin group were reassigned either to continue receiving the medication or to switch to placebo (31). After 1 year, 47.5% of lorcaserin-treated individuals lost 5% or more of their body weight compared to 20.3% in the placebo group. The increase in body weight lost in the lorcaserin group persisted when comparing it with placebo-treated patients after 2 years as well. Finally, of the over 3000 patients observed, no serious effects (specifically, cardiac valvulopathy, which was previously reported) were attributed to lorcaserin administration, and the most frequently described side effects were headache, dizziness, and nausea (31). Results from the BLOOM study provided the initial clinical framework for lorcaserin's use as a promising weight loss medication together with lifestyle modifications.

The BLOOM-DM investigation evaluated the efficacy and safety of lorcaserin for weight loss in type 2 diabetic patients. Similar to the BLOOM trial, BLOOM-DM consisted of a 1-year randomized, placebo-controlled trial with over 600 patients 3(2).Patients (mean age of 52.7) were administered either placebo, 10mg of lorcaserin daily or 10mg lorcaserin twice/day. After the 1-year treatment period, more patients from the lorcaserin-treated groups lost at least 5% body weight compared to the placebo group (32). Furthermore, lorcaserin improved glycemic control in patients with type 2 diabetes, as demonstrated by the greater decrease in HbA(1c) levels in the lorcaserin-treated patients compared to placebo (32). Reports of adverse events were consistent with previous clinical trials as well and consisted of headaches, back pain, and nausea.

The BLOSSOM trial was a one-year randomized, placebo-controlled, double-blind clinical trial that included over 4,000 obese or overweight patients between 18-65 years old. The treatment groups were the same as in the BLOOM-DM trials (placebo, 10mg lorcaserin once/day, or 10mg lorcaserin twice/day) (33). Similar to previous observations, 47.2% of individuals given lorcaserin twice daily for a year lost at least 5% of their initial body weight compared to only 25.0% of patients given the placebo (33). Importantly, the group given lorcaserin once per day showed significant improvements in body weight loss compared to placebo as well (40.2% of patients). Along with the BLOOM and BLOOM-DM trials, the BLOSSOM study also reported adverse effects of headache, nausea, and dizziness, but no associations with valvulopathy as measured by echocardiography.

Together, these three trials led to FDA approval of lorcaserin as an anti-obesity medication. However, upon the FDA's review of the safety of lorcaserin, it has since been removed from the market. This review was announced after further analysis of the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) clinical trial data indicated patients receiving lorcaserin were diagnosed with cancer more often compared to patients given the placebo (34). The CAMELLIA-TIMI 61 clinical trial was a randomized, double-blind, placebo-controlled trial of over 12,000 overweight or obese patients with a history of cardiovascular disease, and the major goal of the study was to evaluate any associations between lorcaserin and cardiovascular disease. Individuals were treated with 10mg of lorcaserin twice per day or given placebo, and the primary safety analysis indicated no differences between the groups concerning risk for cardiovascular events (34). However, upon further observation the trial displayed that 7.7% of lorcaserin-treated patients were diagnosed with cancer compared to only 7.1% in the placebo group. Furthermore, cancer-associated mortality rates were higher in the lorcaserin group as well, as 0.9% of the patients died from cancer compared to 0.6% of individuals given the placebo (34). Importantly, the cancer-causing effects were only observed with longer duration lorcaserin use (between 180-900 days), as there were no differences in cancer risk after 180 days of use when compared with the placebo group. The study concluded that risk for developing specific types of cancers may be associated with lorcaserin use as well, including pancreatic, colorectal, and lung cancers (10).

## Concluding remarks

The CAMELLA-TIMI 61 data indicates lorcaserin increases cancer development after long-term use, but finds no such association in the short term (namely, 180 days). These data suggest lorcaserin has some potential as an acute medication to help manage food intake and body weight in obese or overweight individuals struggling to lose weight. The risk for developing cancer and cancer-related mortality rates should not be ignored, nor should the adverse psychological effects, dizziness, and nausea commonly associated with lorcaserin use. Currently, the FDA has approved five drugs for weight management in obese/overweight individuals, including orlistat (Xenical, Alli), phentermine-topiramate (Qsymia), naltrexone-bupropion (Contrave), liraglutide (Saxenda), and semaglutide (Wegovy). However, reports have described adverse (and some serious) side effects associated with most of these medications as well, such as cancer, mental disorders, and cardiovascular events. Thus, while the past decade has seen a substantial increase in weight-loss research and medications to combat the obesity epidemic, there is still much more work to be done.

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