Single- and Multiple-dose Pharmacokinetics of a Lorcaserin Extended-release Tablet

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ABSTRACT

Purpose: Lorcaserin is a serotonin 2C receptor agonist indicated for chronic weight management as an adjunct to diet and exercise. The initial approved formulation is a 10-mg, immediate-release (IR) tablet for administration BID. These studies investigated the single- and multiple-dose pharmacokinetic properties of a new, recently US Food and Drug Administration–approved, extended-release, 20-mg once-daily formulation.

Methods: We performed 2 separate 2-period, 2-sequence crossover studies in 36 healthy adults: a study comparing the IR formulation to the extended-release formulation under fasting conditions and a study comparing the extended-release formulation under fed and fasted conditions.

Findings: Compared with lorcaserin IR, the T_{max} after a single dose of lorcaserin extended-release was greater (median, 12 vs 3 hours), and the C_{max} was 26% lower (38.8 vs 52.3 ng/mL). AUC data were bioequivalent for the 2 formulations in both single- and multiple-dose regimens, confirming no formulation effect on lorcaserin bioavailability. In fasted and fed conditions, T_{max} after a single dose was identical (median, 12 hours), but C_{max} was approximately 45% higher in the fed state (mean, 38.5 ng/mL fasted vs 56.1 ng/mL fed). However, at steady state, C_{max} and AUC were determined to be bioequivalent between the fasted and fed states, indicating no clinically relevant food effect on the pharmacokinetic properties of lorcaserin extended-release. The safety profile was consistent between the 2 formulations.

Implications: Overall, the results indicate that lorcaserin extended-release is a suitable once-daily alternative to the approved IR BID formulation. (*Clin Ther*. 2016;38:2227–2238) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: extended-release, lorcaserin, obesity, overweight, pharmacokinetic properties.

INTRODUCTION

Obesity (body mass index [BMI] ≥ 30 kg/m^2) and overweight (BMI ≥ 25 and < 30 kg/m^2) have become highly prevalent conditions in the United States, with the most recent estimates indicating that $> 69\%$ of American adults are affected.[1] Both obesity and overweight are associated with increased risk of numerous comorbidities, including cardiovascular disease, hypertension, orthopedic disability, type 2 diabetes mellitus (T2DM), and certain cancers.[2,3] As a chronic disease, obesity requires a long-term model of care, which has traditionally included lifestyle interventions, such as diet and exercise.[4] However, for most patients, these lifestyle changes are often limited in their ability to sustain clinically relevant weight loss.[4,5] For this underserved population, adjunctive pharmacotherapy may provide a useful weight loss option.[4,5]

Lorcaserin has been approved in multiple countries as a 10-mg tablet for BID dosing and is indicated for long-term weight management in adults with obesity or overweight in the presence of ≥ 1 weight-related comorbidity as an adjunct to a reduced-calorie diet and increased physical activity.[6,7] Lorcaserin is a highly selective serotonin (5-HT) 2C receptor agonist that has approximately 14-fold and 61-fold greater potency at the 5-HT_{2C} receptor than at 5-HT_{2A} and 5-HT_{2B} receptors, respectively.[8] Activation of 5-HT_{2A}

Accepted for publication August 31, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.08.016
0149-2918/$ - see front matter

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and 5-HT_{2B} receptors can be associated with disturbances in perception and cardiac valvulopathy, respectively.[9] Although the exact mechanism of action is unknown, it is thought that lorcaserin promotes satiety, and thereby decreases food consumption, through the selective activation of 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons within the hypothalamus.[10,11]

The safety and efficacy of lorcaserin were found in 3 Phase III studies: Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM), Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) in patients without T2DM, and Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus (BLOOM-DM) in patients with T2DM.[12–14] These studies indicate that patients receiving lorcaserin as an adjunct to a prescribed diet and exercise program had significantly greater weight loss after 52 weeks than those receiving diet and exercise counseling only (−5.8% vs −2.5%, $P < 0.001$ for patients without T2DM[15]; −4.5% vs −1.5%, $P < 0.001$ for patients with T2DM[14]). Furthermore, more than twice as many patients receiving lorcaserin compared with placebo achieved weight losses of ≥5% (47.1% vs 22.6%, $P < 0.001$ for patients without T2DM[15]; 37.5% vs 16.1%, $P < 0.001$ for patients with T2DM[14]) and ≥10% (22.4% vs 8.7%, $P < 0.001$ for patients without T2DM[15]; 16.3% vs 4.4%, $P < 0.001$ for patients with T2DM[14]).

Lorcaserin is highly soluble and highly permeable, meeting the criteria for Biopharmaceutics Classification System Class 1. Lorcaserin is rapidly absorbed after oral dosing (T_{max}, 1.5–2 hours)[8] and has a plasma $t_{½}$ of approximately 11 hours. Lorcaserin is metabolized in the liver by multiple human cytochrome P450 enzymes and flavin-containing monooxygenase 1.[8] Lorcaserin sulfamate (M1) is the major circulating metabolite, and the N-carbamoyl glucuronide of lorcaserin (M5) is the major excreted metabolite. Multiple sulfotransferases and uridine 5'-diphospho-glucuronosyltransferases are responsible for the formation of M1 and M5, respectively. These metabolites are not pharmacologically active.[8] Lorcaserin can be administered without regard to food.

Patients with chronic diseases are likely to become less adherent to their medication schedules over time.[16] Studies have found that decreasing the frequency of dose administration is associated with higher adherence rates in a variety of patient groups being treated for different illnesses.[16,17] For orally administered medications, modified-release formulations, in particular, increase patient adherence for a number of chronic conditions.[18–20] Importantly, in long-term Phase III clinical studies, population pharmacokinetic/pharmacodynamic modeling revealed a highly significant and predictive association between probability of weight loss and lorcaserin AUC after twice-daily administration of an immediate-release (IR) formulation. On the basis of this association, an extended-release formulation that achieves bioequivalence to the IR formulation with respect to AUC would be expected to achieve equivalent efficacy. In addition, the finding that lorcaserin C_{max} values are no greater after multiple dosing of an extended-release formulation than the IR formulation would support a conclusion that the safety database developed for the IR formulation is relevant to the extended-release formulation. The extended-release formulation of lorcaserin was recently approved by the US Food and Drug Administration.

Overall, the aim of pharmacokinetic/pharmacodynamic-based bridging from the lorcaserin Phase III program is to reveal the following: (1) an equivalent extent of absorption of the extended-release compared with the IR formulation based on AUC and (2) that C_{max} is not higher for the extended-release compared with the IR formulation. In a previous Phase I study (data on file, APD356-031), the pharmacokinetic properties of 3 prototype 20-mg lorcaserin extended-release formulations (designated slow, medium, and fast release based on in vitro dissolution profiles) were evaluated. For all extended-release formulations, tablet dissolution was delayed by functional excipients to modify lorcaserin release. The study found that AUC, C_{min}, and C_{max} of each 20-mg lorcaserin extended-release prototype were within target levels compared with a single dose of the approved 10-mg IR formulation. AUC of the 20-mg lorcaserin extended-release formulation was approximately twice that of the 10-mg IR formulation. Of the 3 prototype extended-release formulations, the designated slow-release prototype had the optimal characteristics (lowest C_{max}, highest C_{min}, best preservation of AUC) and was selected for further development.

We present the results of a study designed to determine bioequivalence with respect to AUC of

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