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EDITORIAL

Lorcaserin approval in the United States: Paving the way?☆

Autorización de lorcaserina en los Estados Unidos: ¿preparando el terreno?

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For over a decade, the world of obesity pharmaceuticals has been stagnant, with most medications that have been studied for use in the management of obesity being rejected or withdrawn due to an unacceptable side effect profile.¹ Since the withdrawal of sibutramine in 2010 due to concerns regarding an increased risk of cardiovascular events, the only available medical therapy is orlistat, which provides very modest weight loss, and is poorly tolerated by many patients due to the gastrointestinal side effect profile.

On June 27, 2012, lorcaserin was approved by the American FDA for chronic weight management in addition to a reduced calorie diet and exercise, in adults with a BMI ≥ 30 kg/m², or a BMI ≥ 27 kg/m² with at least one weight related condition such as type 2 diabetes, hypertension, or dyslipidemia. This brings to an end a 13-year era without any approval of newer agents for obesity management, an area where pharmaceutical treatment options are desperately needed.

Lorcaserin is an agonist of the 5-hydroxytryptamine (5-HT, or serotonin) receptor 5-HT_{2C}.² It works selectively on the central 5-HT_{2C} receptors, with a functional selectivity of approximately 15 and 100 times over that for 5-HT_{2A} and 5-HT_{2B}, respectively. The suppression of appetite is predominantly mediated by 5-HT_{2C} as well as 5HT_{1B} receptors. Previously available nonselective serotonergic agents

for obesity management such as fenfluramine caused pulmonary arterial hypertension and valvulopathy via an effect on the 5-HT_{2B} receptors, which is expressed on pulmonary artery smooth muscle cells and cardiac valvular interstitial cells. Receptor pharmacology studies strongly suggest that lorcaserin will not activate the 5-HT_{2B} receptor at therapeutic doses,³ and appropriately powered risk ratio analyses ruled out a 1.5 fold or greater incidence of valvulopathy with lorcaserin treatment for up to 2 years.

Clinical trial evidence demonstrates that lorcaserin results in about 4 kg of placebo subtracted weight loss over a 1 year period, and that there is some sustained weight loss benefit after 2 years of treatment.⁴ Thus, the weight loss seen with lorcaserin is slightly more than currently available orlistat, which provides 2–3 kg of weight loss. Mechanistic studies suggest that lorcaserin results in weight loss via an influence on appetite control, which in turn reduces total energy intake, and not via alterations in energy expenditure or substrate oxidation.⁵

In type 2 diabetics, lorcaserin has been shown to improve glycemic control in addition to facilitating weight loss, and has modest benefits on lipid profile and blood pressure as well. In a recent trial in type 2 diabetics, weight loss was 4.5% with lorcaserin twice daily and 5.0% with lorcaserin once daily, versus 1.5% with placebo. HbA_{1c} decreased by 0.9 with lorcaserin twice daily, 1.0 with lorcaserin once daily, and 0.4 ± 0.06 with placebo.⁶ Symptomatic hypoglycemia occurred in 7.4% of patients on lorcaserin twice daily, 10.5% on lorcaserin once daily, and 6.3% on placebo.

A prudent point in the practical use of lorcaserin is to discontinue the medication in patients who have failed to lose 5% or more of body weight after 12 weeks on the

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medication, as these individuals are unlikely to achieve clinically meaningful weight loss with continued treatment. It is increasingly appreciated that the genetic basis for the development of obesity is highly variable between individuals, and as such, the clinical response to one weight loss agent can also be highly variable from one individual to the next. This speaks to the need for a diversity of agents with heterogeneous mechanisms to help manage obesity, such that therapy can be individualized and optimized.

Lorcaserin is generally well tolerated. The most common effects observed include upper respiratory tract infection, headaches, dizziness, and nausea; discontinuation rates in clinical trials were similar to placebo. In diabetics, the most common side effects include hypoglycemia, headache, back pain, cough, and fatigue. As lorcaserin has the potential to bind 5HT_{2A} receptors, and because 5HT_{2A} agonism has been associated with perceptual disturbances, lorcaserin has been evaluated in this regard and was found to have low abuse potential. It is important to note that lorcaserin has not been shown to have an adverse effect on heart rate or blood pressure, which has been a concern with other previously considered (and subsequently rejected/withdrawn) agents.

In the United States, lorcaserin now presents an option to facilitate moderate weight loss in a patient with obesity, and is a welcome addition to an area where therapeutic agents are sparse. Having said that, the weight loss induced by lorcaserin is not as impressive as the weight loss seen with other agents that are currently being evaluated for potential use as weight loss agents. Perhaps the biggest accomplishment

of lorcaserin is its acceptance by the FDA as a viable option for obesity management, after thirteen years of repeated drug rejection in this area. Lorcaserin's approval by the FDA may represent a shift in mentality towards an increasing acceptance of the need for more medications with an acceptable benefit to risk profile in this therapeutic area, hopefully paving the way for agents that have even greater efficacy to gain approval in the years to come.

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