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A Review on Lorcaserin – A Selective 5-HT Serotonin Receptor Agonist in Obesity Management

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ABSTRACT

Lorcaserin is a novel anti-obesity agent. The study retrospect's the pharmacokinetic effects, mode of action, adverse drug reactions and various uses of Lorcaserin. Lorcaserin is pro-opiomelanocortin neurons stimulator present in the nucleus of hypothalamus resulting in a peak melacortin-4 receptor activity, which results in satiety and decreased food intake. Though some side effects were reported, the potential benefits of Lorcaserin outweigh the risks. Serum drug monitoring is not required. Lorcaserin is a 5HT2C receptor agonist whose property may also be studied to treat anxiety, Alzheimer's disease, depression and parkinsonism. Literature review was conducted to identify relevant studies. The study reviewed the pharmacokinetics, pharmacodynamics and clinical trials proposed so far on lorcaserin.

Key Words: Lorcaserin, 5-HT agonist, Anti-obesity

INTRODUCTION

Physical interventions such as exercise, diet and surgery, behavioural therapies, and pharmacological treatments are the approaches taken for the management of weight reduction in obese individuals. This may be done alone or in combination for greater efficiency.

Administration of anti-obesity drugs may lead to a reduction in the absorption of nutrients and appetite. It may also results in an increased satiety and energy expenditure. The better results were achieved with the pharmacotherapy for weight loss of about 2 to 7.9kg when compared to that treated with placebo.

5-HT is a monoamine neurotransmitter is mostly seen in the central serotogenic neurons and enterochromaffin cells with a broad spectrum of behavioural and physiological function. Hence, 5-HT receptor is considered as an anti-obesity drug target.

There is a wide range of 5-HT_{2c} receptor modulating drugs having the ability to deal with a variety of conditions by changing the central serotogenic function. Such conditions are addiction, depression, anxiety, Alzheimer's disease, parkinson's disease and obesity[1].

For the treatment of obesity only limited numbers of drugs are in use. In 1999, Orlistathas got approval by the Food and Drug Administration (FDA). Later in June 2012, a new drug Lorcaserin was approved and promoted for prescription by FDA. But In October 2012, it was rejected initially due to some cancer signal detection in animal studies. Finally, from further research such as BLOOM and BLOSSOM the drug was approved in the same year[2].

Lorcaserinis chemically [1R]-8-chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzapine and acts as a selective 5-hydroxy tryptamine (5-HT, serotonin)$_{2c}$ receptor agonist which is developed particularly to aim human appetite expression. Lorcaserin, a selective serotonin ($5HT_{2c}$) receptor agonist is capable of suppressing appetite and food intake. Induction of this receptor gives rise to a number of reactions that finally stimulates the release of 2-melanocortin stimulating hormone, which acts on melanocortin-4-receptors to control appetite.[3]

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Table 1: Drug profile[4-8]

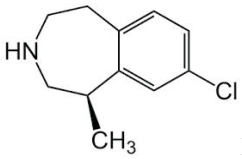
Brand name	Belviq
Generic name	Lorcaserin hydrochloride
Drug class	Serotonin $5HT_{2c}$ receptor agonist
Structure	 Molecular formula: $C_{11}H_{14}NCl$
IUPAC name	(1R)-8-Chloro-2,3,4,5-tetrahydro-1-methyl-1H-3-benzazepine
Mechanism of action	Lorcaserin is pro-opiomelanocortin neurons stimulator present in the nucleus of hypothalamus resulting in a peak melacortin-4 receptor activity. This leads to satiety and decreased food intake. Comparatively, Lorcaserin has a greater affinity towards 5-HT_{2C} receptor than other 5-HT subtypes under recommended doses.
Absorption	For oral administration, Lorcaserin has a better absorption from gastro-intestinal tract and its peak plasma concentration (t_{max}) after a dose was found within 1.5 to 2 hours. The availability of the drug in systemic circulationhas not been determined exactlyand no significance effect was found on peak concentration (C_{max}). A study was conducted to describe the impact of food on absorption of lorcaserin which was performed on 12 adult volunteers(6 men and 6 women) administered by single 10mg dose after eating high fat meal and during fasting. Results show an increase by 9% and 5% for C_{max}area under the curve (AUC). This explains that there is no significant difference was found inpatient's drug administration after food intake.
Distribution	The drug bounds of about 70% to plasma proteinsand has good distribution in human central nervous system and cerebrospinal fluid.
Metabolism	Metabolism of lorcaserin to lorcaserin sulfamate (M1), N-carbamoyl glucuronide lorcaserin (M5) and sulfate and glucuronide conjugates of oxidative metabolites was achieved by multiple enzymes pathway since it is independent to single enzymatic cycle. The major circulating metabolite is M1 (inactive) but it accounts only for about minimum of 3% administered dose in urine and another inactive form of metabolite M5 was found to be have maximum metabolism in urine.
Excretion	About 92 % was eliminated primarly in urine and rarely through feces (2.2%).
Dose	An oral dose of 10mg is recommended to give twice a day with or without food. In patients with renal failure, dose adjustment is not necessary. And use of lorcaserin is not recommended in patients with severe renal failure.
Dosage form	BELVIQ – Each tablet contain 10mg of Lorcaserin Hydrochloride Hemihydrates. BELVIQ XR – Each tablet contain 20mg of Lorcaserin Hydrochloride anhydrous extended release.
Adverse effects	The most common effects include vasodilator effects such as hypertension, headache, and dizziness. Various adverse effects listed alphabetically by body system and by decreasing frequency within body system are; Body as a whole: pain Gastro-intestinal system: Nausea, Vomiting, Diarrhea, Constipation. Respiratory system: Cough, sinus congestion. Reproductive system: Urinary tract infection. Post marketing adverse effects such as rashes and back pain are also reported.
Drug interactions	Combination of lorcaserin with other serotonergic agents results in serotonin syndrome and neuroleptic malignant syndrome (NMS)-like reaction. Medications such as serotonin nor-epinephrine reuptake inhibitor (SNRIs), Selective serotonin reuptake inhibitor (SSRIs), tricyclic antidepressants, Monoamine oxidase inhibitors, Antipsychotic agents, Dopamine agonists are to be avoided.
Contraindications	Contraindication can be seen with concomitant of potent CYP3A4 inhibitor (e.g. Ketoconazole) and CYP2D6 inhibitor (e.g. Quinidine).

Table 2: Clinical Research - An Overview:

Author	Year	Research work
Steven R. Smith et al[9]	March 2009	Clinical evaluation of lorcaserin was carried to determine safety and efficacy profile for a time period of 12 weeks. Lorcaserin had progressive weight loss effect. Side effects include nausea, dizziness and transient headache.
Steven R. Smith et al[10]	July 15th , 2010	Multi centre, placebo controlled trial of lorcaserin was conducted. Results showed noteworthy weight loss.
Hurren et al[11]	January 11th , 2011	Two phase 3 clinical studies were carried out on lorcaserin. Results indicated lorcaserin had significant weight loss effects and common side effects include nausea, vomiting and cardiovalvulopathy.
Jun Goo Kang et al[12]	February, 2012	Two year BLOOM and BLOSSOM study were conducted on lorcaserin. Test results showed substantial weight loss effects of lorcaserin. The side effects were dry mouth, vomiting, dizziness and fatigue.
Patrick M O'Neil et al[13]	July, 2012	A BLOOM-DM study was conducted to test the efficacy and safety of lorcaserin for weight loss in patients diagnosed with type 2 diabetes mellitus Common side effects were headache, nausea, back pain and nasopharyngitis.
E.W. Chan et al[14]	May, 2013	A systemic review and meta-analysis of randomized controlled trials (RCTS) of lorcaserin was conducted. Clinical studies with longer study duration were needed to inform the long term efficacy and safety of lorcaserin.
Joshua W. Fleming et al[15]	June, 2013	Six prospective Phase 3 trials were reviewed. Appetite suppression and enhanced satiety was reported with Phentermine/topiramate combination. It was concluded that Lorcaserin showed moderate efficacy when compared to Phentermine/topiramatein obese patients with modified lifestyle. In view of the above the new anti-obesity drugs need clinical details in long term perspectives of CVS to evident the safety and its use in therapy.
Neil J. Weisman etal[16]	July 16th, 2013	Data on Echocardiographic and weight change of 5249 obese patients was integrated in phase 3 clinical trials. Results concluded that both lorcaserin and placebo showed same rate of echocardiographic valvulopathy.
Amal A. Bajrai et al[17]	November 14th, 2015	Amount of lorcaserin in plasma and brain tissue samples were determined using UPLC-MS-MS rapid assay methods.

CONCLUSION

Lorcaserin is a novel anti-obesity agent. Since, it is a $5HT_{2C}$ receptor agonist it may have potential in treating depression, anxiety, Alzheimer's disease and Parkinsonism. The advantages of lorcaserin are high rate of renal excretion and minimal drug interaction. The common adverse drug reactions are nausea, dizziness, headache, vomiting, and cardiovalvulopathy. The attempt on review of Lorcaserin will pave the way for budding researchers to explore and fill the gaps in analytical methodology which are not so far reported and also useful for physicians and other health professionals to challenge their research on Lorcaserin.

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