Drug Monograph Assignment
3/7/2013

Drug Information Assignment	Drug generic name: **Lorcaserin Hydrochloride** Brand name: Belviq (upon approval), Lorqess (during development) 
Description/ Classification [1]	Locaserin is a serotonin 5-HT_{2C} Receptor Agonist Belviq is manufactured by Arena Pharmaceuticals GmbH of Zofingen, Switzerland
Pathophysiology of Disease State [2,3,4]	Obesity is highly linked to genetic factors. An increase in body fat (both visceral and nonvisceral [subcutaneous]) requires that energy intake be increased over energy expenditure. Energy regulation in our bodies is mainly done by neuroendocrine system consisting of afferent system (in the hypothalamus), and efferent system (concerned of appetite and energy expenditure). The afferent system reflects signals of hunger (low blood sugar or cortisol) and fullness (gastric distension) peripherally. Furthermore, these signals can be received by hypothalamus centrally from via neurotransmitters and hormones. Dopamine, gamma-amino butyric acid, neurotensin and corticotropin-releasing hormone have an inhibitory effect on appetite. Moreover, serotonin and norepinephrine have effect in inducing fullness. Focusing on **serotonin** effects, it can be peripherally via intestinal serotonin. Afferent signals received by hypothalamus are processed to promote or reduce food intake and energy expenditure. This is carried out by a central processing unit containing neurons that express the POMC (proopiomelanocortin) peptide branch and express NPY (neuropeptide Y) and AgRP (agouti gene-related protein) branch. POMC induces loss of appetite and fullness (satiety) while the other branch antagonize the melanocortin receptors to prevent induction of satiety. Disturbance of such balance leads to a positive energy balance, causing excessive weight gain and obesity. Please refer to appendix 1
Mechanism of Action	Lorcaserin is believed to activate serotonin 5-HT_{2C} receptors, which stimulate pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, leading to increased alpha-melanocortin stimulating hormone release at melanocortin-4 receptors and resulting in satiety and decreased food intake. At recommended doses, lorcaserin has greater affinity for 5-HT_{2C} receptors compared to other 5-HT receptor subtypes (including 5-HT2A and 5-HT_{2B}), the 5-HT receptor transporter, and 5-HT reuptake sites.
Current Medications of Choice for Disease State [5]	Currently the main agents used for longterm anti-obesity management is Xenical® (orlistat), which reduces intestinal fat absorption by inhibiting pancreatic lipase. It received its FDA approval Apr 1999. Please refer to appendix 2

Pharmacokinetics	**Absorption: Time to peak:** 1.5-2 hours **Distribution:** Distributes to the CNS and cerebrospinal fluid **Protein binding**: ~70% to plasma proteins **Metabolism:** Extensive hepatic metabolism, via multiple enzymatic pathways, producing two major metabolites (inactive), lorcaserin sulfamate (M1) and N-carbamoyl glucuronide lorcaserin (M5), as well as minor metabolites (glucuronide and sulfate conjugates) **Half-life elimination:** ~11 hours, and 19hours with moderate hepatic impairment **Excretion:** Urine (92.3%, as metabolites); feces (2.2%, as metabolites), not dialyzed
Administration	It is administered orally with or without food
Dosage/ Indication	**Indication:** chronic weight management **Dose:** 10 mg twice daily orally (maximum: 10 mg twice daily); response should be evaluated by week 12; if patient has not lost ≥5% of baseline body weight, therapy should be discontinued **Dosage adjustment:** **Renal Impairment:** (renal function was estimated based on Cockcroft-Gault formula) • Mild impairment (Cl_{cr} >50 mL/minute): No dosage adjustment necessary. • Moderate impairment (Cl_{cr} 30-50 mL/minute): use with caution; serum concentrations and half-life of major metabolites are increased. • Severe impairment (Cl_{cr} <30 mL/minute): NOT recommended to use. • ESRD: NOT recommended to use. **Hepatic Impairment** • Mild-to-moderate impairment (Child-Pugh score 5-9): No needed dose adjustment • Severe impairment: it has not been studied , should be used with caution; undergoes extensive hepatic metabolism

Interactions	Lorcaserin is associated with various drug interactions: **Antipsychotics:** due to enhancing the serotonergic effect of Serotonin Modulators, there is risk of serotonin syndrome • **Action:** monitor closely **BuPROPion:** it enhances effect of Lorcaserin, there is a risk of serotonin syndrome. • **Action:** avoid combination of two agents **Codeine:** CYP2D6 inhibitors may prevent metabolic of codeine to its active metabolite morphine which decreases codeine therapeutic effect. • **Action:** monitor closely **CYP2D6 Substrates:** CYP2D6 Inhibitors (Moderate) may decrease the metabolism of CYP2D6 Substrates. **Exceptions:** Tamoxifen. • **Action:** monitor closely **Ergot Derivatives:** Lorcaserin may enhance the adverse/toxic effect of Ergot Derivatives. Specifically, use of these drugs together may increase the risk of developing valvular heart disease. Lorcaserin may enhance the serotonergic effect of Ergot Derivatives. This could result in serotonin syndrome. • **Action:** avoid combination of two agents **Fesoterodine:** CYP2D6 Inhibitors may increase serum concentrations of the active metabolite(s) of Fesoterodine. • **Action:** monitor closely **Metoclopramide:** Serotonin Modulators may enhance the adverse/toxic effect of Metoclopramide. This may be manifest as symptoms consistent with serotonin syndrome or neuroleptic malignant syndrome. • **Action:** monitor closely **Metoprolol:** CYP2D6 Inhibitors may increase the serum concentration of Metoprolol. • **Action:** monitor closely **Nebivolol:** CYP2D6 Inhibitors (Moderate) may increase the serum concentration of Nebivolol. • **Action:** monitor closely **Phosphodiesterase 5 Inhibitors:** Lorcaserin may enhance the adverse/toxic effect of Phosphodiesterase 5 Inhibitors. Specifically, the risk of developing priapism may be increased. • **Action:** monitor closely **Propafenone:** May increase the serum concentration of CYP2D6 Inhibitors (Moderate). • **Action:** monitor closely **Serotonin Modulators:** May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. • **Action:** modify therapy **Tamoxifen (used for breast cancer):** CYP2D6 Inhibitors (Moderate) may decrease serum concentrations of the active metabolite(s) of Tamoxifen. Specifically, CYP2D6 inhibitors may decrease the metabolic formation of highly potent active metabolites. Management: Consider alternatives with less of an inhibitory effect on CYP2D6 activity when possible. • **Action:** monitor closely **Thioridazine:** CYP2D6 Inhibitors may decrease the metabolism of Thioridazine. • **Action:** avoid combination of two agents
Contraindication	Pregnancy

Adverse reaction	Most common adverse effect (>10 %): CNS: Headache (15% to 17%) Endocrine & metabolic: Hypoglycemia (diabetic patients 29%; severe: 2%) Hematologic: Lymphocytes decreased (12%) Neuromuscular & skeletal: Back pain (6% to 12%) Respiratory: Upper respiratory tract infection (14%), nasopharyngitis (11% to 13%)
Other safety issues	Look alike/sound alike drug: Lorcaserin hydrochloride may be confused with loratadine hydrochloride (Claritin®), losartan (Cozaar®) and Lotensin Hallucinogenic properties: Due to such properties, the Drug Enforcement Adminstration (DEA) is currently evaluating the drug as a controlled substance, and the **scheduling category IV** is being determined.
Pregnancy / Lactation	Pregnancy category: **X** (contraindicated in pregnancy) Fetal effect: the drug showed adverse effects on fetus in some animal studies with no clinical benefit of weight loss during pregnancy offers no clinical benefit. Lactation: it is not recommend since it was not well known. The drug may alter maternal serum prolactin concentrations.
Monitor Parameters	Body weight Waist circumference CBC (periodically during use) Blood glucose (in diabetics) prolactin levels (if galactorrhea, gynecomastia or other signs/symptoms of hyperprolactinemia arise) Depression or suicidal thoughts/behavior Signs/symptoms of SS/NMS-like reaction Signs/symptoms of valvular heart disease (dyspnea, dependent edema)
FDA indication [6]	**Dec 2009:** new drug application was submitted to FDA **Sep 2010:** FDA voted against the drug due to safety and efficacy concerns **May 2012**: New studies submitted by Arena company, and the drug was recommended by FDA **On 27 June 2012:** FDA approved lorcaserin for chronic weight management in patients with either an initial body mass index (BMI) of ≥30 kg/m2 or an initial BMI of ≥27 kg/m2 and at least one weight-related comorbid condition (eg, hypertension, dyslipidemia, type 2 diabetes). It should be used as an adjunct to a reduced-calorie diet and increased physical activity. It is considered the first agent approved for weight loss since 1999. Currently the drug generic is not yet available in US
Clinical Trials	**Efficacy studies**: The safety and efficacy of Belviq were evaluated in three randomized, placebo-controlled trials that included nearly 8,000 obese and overweight patients, with and without type 2 diabetes, treated for 52 to 104 weeks. All participants received lifestyle modification that consisted of a reduced calorie diet and exercise counseling. Compared with placebo, treatment with Belviq for up to one year was associated with average weight loss ranging from 3 percent to 3.7 percent. About 47 percent of patients without type 2 diabetes lost at least 5 percent of their body weight

	compared with about 23 percent of patients treated with placebo. In people with type 2 diabetes, about 38 percent of patients treated with Belviq and 16 percent treated with placebo lost at least 5 percent of their body weight. Belviq treatment was associated with favorable changes in glycemic control in those with type 2 diabetes. The approved labeling for Belviq recommends that the drug be discontinued in patients who fail to lose 5 percent of their body weight after 12 weeks of treatment, as these patients are unlikely to achieve clinically meaningful weight loss with continued treatment. **Safety studies :** Two agents were withdrawn from the market because of their effects on serotonin 2 B receptors located in the heart causing heart valve damage. Lorcaserin didn't show effect on serotonin 2 B receptor in the dosage of 10 mg PO BID. **Summary about each study:** I. Phase 2 b trial: (drug groups: 10mg, 15mg, 20mg , and placebo studied over 12 weeks) • There were significant weight loss with the drug vs placebo, patients lost: • 10mg/ day → 4 pounds , 15mg/day → 5.7 pounds , 20mg/day → 7.9 pounds • Placebo → 0.7 pounds • However after 12 weeks, all groups regained weight rabidly II. Phase 3 trials: A. BLOOM trial; 2010: 3182 patients BMI 36.2, drug 10mg once or twice vs placebo for 52 weeks. Wt loss ≥ 5% → **NNT= 4,** Wt loss ≥ 10% → **NNT= 2** B. BLOSSOM trial; 2011: 4008 patients BMI 30-45 or 27-29.9 , drug 10mg once or twice vs placebo for 52 weeks Wt loss ≥ 5% → **NNT= 5,** Wt loss ≥ 10% → **NNT= 8** C. BLOOM- DM trial; July 2012, 604 overweight patients BMI 36 with T2DM, drug 10mg once or twice vs placebo for 52 weeks Wt loss ≥ 5% → **NNT= 5,** Wt loss ≥ 10% → **NNT= 4** **Future studies:** Drug's manufacturer will be required to conduct **six postmarketing studies**. Studies should mainly focus on safety aspects of long-term cardiovascular outcomes to further investigate drug effect on the risk for major adverse cardiac events such as heart attack and stroke.
Cost Information [7]	Pricing will range from $3.23 to $5.48.

References

1. Lexicomp database
2. www.uptodate.com
3. http://www.scielo.br/scielo.php?pid=S002175572004000100004&script=sci_arttext&tlng=en
4. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3104148/
5. Elie Dolgin. A history of drugs on the weight list. Nature Medicine June 6, 2012;18: 843
6. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm
7. http://en.wikipedia.org/wiki/Lorcaserin

Appendices:

Appendix 1: Pathophysiology of obesity

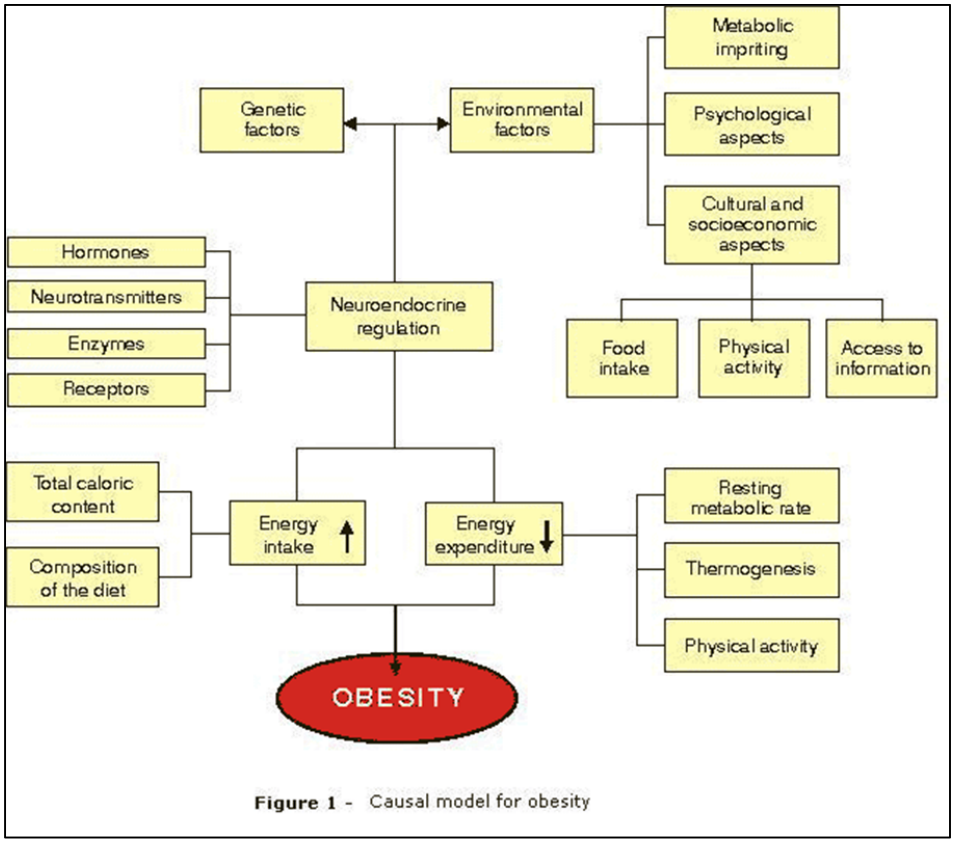

Figure 1 - Causal model for obesity

Appendix 2: Development of anti-obesity agents summary