CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	June 27, 2012
From	Curtis J. Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	NDA 22529
Applicant Name	Arena Pharmaceuticals, Inc.
Proprietary / Established (USAN) Names	Belviq Lorcaserin hydrochloride
Dosage Forms / Strength	Tablet 10 mg BID
Proposed Indication(s)	Weight management
Action:	*Approval*

Introduction and Discussion

This review is of the complete response (CR) for lorcaserin and will be a brief summary of the basis for regulatory action. Please refer to the reviews in the action package and to my previous review for the first cycle action for more detailed discussion. Lorcaserin is a new molecular entity that is a 5-hydroxytryptamine 2C (5HT2C) receptor agonist affecting those receptors in the appetite center of the brain. The proposed indication by the sponsor is:

- BELVIQ is indicated as an adjunct to diet and exercise for weight management, (b) (4) in obese patients with an initial body mass index greater than 30 kg/m , or in overweight patients with a body mass index greater than or equal to 27 kg/m^2 in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4) (b) (4) type 2 diabetes).

Obesity is a growing epidemic in the United States and epidemiologic data indicate it is associated with a myriad of adverse health outcomes that greatly impact obese people's lives and quality of life while also creating great cost to the health care system. Currently, only one drug, orlistat, is approved (approval 1999) for the chronic treatment of obesity. The focus of most poor health outcomes associated with obesity are related to the development of diabetes and cardiovascular disease, but other associated diseases are also important and include sleep apnea, osteoarthritis and some types of cancer.

Weight management is therefore focused on weight loss in obese patients with the goal of decreasing these adverse outcomes and improving quality of life. Since there are epidemiologic data that indicate that as weight increases so do the poor outcomes mentioned above, it would seem intuitive that weight loss will reverse these poor

outcomes and can be used as a surrogate to indicate probable decreases in obesity-related diseases. This may be true for weight loss that is achieved through non-pharmacologic means; however, history has taught us that many marketed weight-loss drugs (and some reviewed for possible marketing), also had 'off-target' activity that could adversely affect the outcomes above, or result in other unforeseen adverse effects not associated with obesity, such that an unfavorable risk:benefit ratio has not allowed initial, or continued, marketing. Such was the case for fenfluramine (a component of 'fen-phen') and dexfenfluramine where there were unexpected cases of primary pulmonary hypertension and valvular regurgitation associated with drug use thought to be due to effects on serotonin receptors (thought to be 5HT2B).[1] This adverse event profile, in the context of fairly marginal weight loss and inability to identify those that may be at risk, was deemed too unsafe to allow continued marketing. Sibutramine is also an example of a medication having an off-site activity (SCOUT trial) resulting in cardiovascular harm thought due to increases in blood pressure.[2] Just as in the case of fen-phen, a population could not be identified where weight loss with sibutramine was significant enough to overcome the risk caused from off-site activity. Other applications, such as rimonabant, have not received approval, and was removed from foreign markets because of suicidality concerns.

As such, while we have a great desire to try to find effective medications for weight management, there is little tolerance for potential devastating adverse effects, even if rare, in the environment of modest weight loss. Into this environment have come several agents seeking approval for marketing including lorcaserin, which is the subject of this NDA.

During the first review cycle review for lorcaserin, several areas of safety concern were identified that led to a CR action.

A pre-clinical concern from rat carcinogenicity studies demonstrated the incidence and proportion of female rats with mammary adenocarcinoma was higher at all doses of lorcaserin in updates provided to us from week 55 to 96. Thereafter, and to submission of the final study report, the incidence of mammary adenocarcinoma decreased in an imbalanced manner favorable to lorcaserin. Records documenting the reason and rationale for the change in each diagnosis between groups were lacking. This was identified as a deficit in the CR action and led to a re-evaluation of all relevant tissues by an independent panel of pathologists, re-adjudicating all mammary tissue. Also of concern, astrocytomas were demonstrated at mid- and high doses in male rats, and incomplete information existed regarding central nervous system (CNS) levels in humans to assure an adequate margin of safety existed. This led to investigations by the sponsor to supply adequate information regarding CNS partitioning of lorcaserin in humans to define a no-adverse effect level (NOAEL). Both of these concerns, as I will discuss below, have been adequately addressed by the sponsor.

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[1] Curfman GD. Diet pills redux. N Engl J Med 1997; 337:629-30.
[2] James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010; 363:905-17.

Another concern is that of valvulopathy. For the weight loss drugs fenfluramine and dexfenfluramine, valvulopathy was noted and felt to be related to activity at the serotonin receptor 5HT2B, a receptor in the same class as 5HT2C. Helpful to some extent in the evaluation of this concern is that receptor potency is helpful in predicting possible valvulopathy. Because the severe valvular problems reported with fenfluramine were somewhat rare, evaluating possible adverse valve effects in clinical trials is difficult because it is impossible to 'prove a negative' turning the evaluation instead into the degree of certainty that is acceptable. While no overt valvular damage was demonstrated during the development program, echocardiography evaluation revealed that a 50% increase for the development of FDA-defined valvular heart disease (VHD) could not be ruled out. It is important to emphasize that ruling out a 50% increase is not agency policy, or even an agreement we had made, rather it was a starting point in the sponsor's development program, as we were involved in uncharted territory, did not want to stall drug development, but at the same time could not determine what an appropriate margin may be without some initial data. Compounding our concern is that while the sponsor claims that lorcaserin is a specific 5HT2C receptor agonist which should avoid the valvular problems seen with other drugs, it is still somewhat permissive at other serotonin receptors, and with the original application there was conflicting pre-clinical data and uncertainty regarding the true functional potency at different serotonin receptors. The sponsor repeated these pre-clinical studies in a more rigorous fashion considered to be more appropriate and representative of true receptor potency by our pharmacology and toxicology reviewers who have concluded that the sponsor has adequately addressed this concern.

New to this review cycle and not identified in the CR action letter is an evaluation to exclude a certain degree of risk of cardiovascular (CV) thromboembolic events. The sponsor has successfully met these criteria as I will discuss below.

The efficacy of lorcaserin is not impressive but also is not out of line with other weight loss drugs. Placebo-subtracted mean differences in weight loss associated with lorcaserin treatment were 3.7% for one pivotal trial and 3.0 % for another pivotal trial. It should be noted however, that a small proportion of patients may achieve impressive and probably quite important weight loss. Unfortunately, this will not be the experience of the majority of users.

These issues, as well as evaluation for cardiovascular adverse event potential for drugs used in the treatment of obesity as discussed at the March 29, 2012 Advisory Committee (AC) meeting, were discussed at the May 10, 2012 AC meeting specific to lorcaserin. The committee voted 18 to four in favor of approval.

As briefly discussed above and upon which I will expand below, the sponsor has successfully addressed all the issues identified with the original review of this application and should receive an approval action.

Efficacy

Efficacy was originally evaluated based on two pivotal trials, BLOOM and BLOSSOM. The CR submission included new clinical data from Bloom-DM (Study APD356-010), a 52-week trial in overweight and obese subjects with type 2 diabetes mellitus. The top-line results are summarized in the tables below from Dr. Golden's review (page 32).

Table 1. 5% Weight Loss Responders at Week 52, BLOOM and BLOSSOM [Modified Intent to Treat (MITT) LOCF]

BLOOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1538	731 (47.5)
Pbo	1499	304 (20.3)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	27.2 (24.0, 30.5)	< 0.0001
BLOSSOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1560	737 (47.2)
Pbo	1539	385 (25.0)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	22.23 (18.94, 25.52)	< 0.0001
Pooled Non-Diabetes		
Treatment	**N**	**n (%)**
Lorc 10 mg BID	3098	1460 (47.1)
Pbo	3038	687 (22.6)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	24.52 (22.22, 26.82)	< 0.001

Source: NDA 022529 BLOOM CSR, Table 10; BLOSSOM CSR, Table 9; ISE Statistical Report, Table E1.0

Table 2. 5% Weight Loss Responders at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	251	94 (37.5)
Pbo	248	40 (16.1)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	21.3 (13.8, 28.9)	< 0.0001

Source: Dr. Janice Derr, statistical reviewer, OTS/OB/DBII

In addition, Dr. Golden's original review (page 33) noted other relevant features from the two pivotal trials:

In the first year of the BLOOM (APD356-009) trial:

- Patients treated with lorcaserin 10 mg BID lost 5.8 ± 0.16 kg body weight as compared to 2.2 ± 0.14 kg in the placebo group ($p < 0.001$)
- 22.6% of patients treated with lorcaserin 10 mg BID lost ≥ 10% weight loss from baseline to Week 52 as compared to 7.7% of patients treated with placebo ($p < 0.001$)

In the 1-year BLOSSOM (APD356-011) trial:

- Patients treated with lorcaserin 10 mg BID, lorcaserin 10 mg QD, and placebo lost 5.76 ± 0.17 kg, 4.72 ± 0.240, and 2.86 ± 0.154 kg body weight, respectively ($p<0.001$ for lorcaserin 10 mg BID vs. placebo; $p<0.001$ for lorcaserin 10 mg QD vs. placebo)

- 22.6% of patients treated with lorcaserin 10 mg BID, 17.4% of patients treated with lorcaserin 10 mg QD, and 9.7% of patients treated with placebo lost ≥ 10% of body weight after 52 weeks of treatment ($p<0.001$ for lorcaserin 10 mg BID vs. placebo; $p<0.001$ for lorcaserin 10 mg QD vs. placebo)

In the second year of the BLOOM trial:

- 67.9% of lorcaserin-treated patients who completed Year 1 of BLOOM and were ≥ 5% weight loss "responders" maintained at least a 5% weight loss from baseline (beginning of the study) at Week 104 as compared to 50.3% of placebo-treated ≥ 5% responders ($p < 0.001$)
- All treatment groups regained body weight from Week 52 to Week 104: those lorcaserin-treated patients who were randomized to remain on lorcaserin in Year 2 regained 2.53 ± 0.19 kg, those lorcaserin-treated patients who were re-randomized to placebo regained 4.76 ± 0.31 kg, and those who were randomized to placebo for the first and second years of the trial regained 1.00 ± 0.61 kg body weight from Week 52

The 1-year pooled data from BLOOM and BLOSSOM demonstrated that the placebo-subtracted mean body weight change in the lorcaserin 10 mg BID treatment group was -3.25 kg. Approximately 47% of patients on lorcaserin 10 mg BID and 23% of patients on placebo lost at least 5% of baseline body weight at Week 52.

Also noted by Dr. Golden are relevant findings from the Bloom-DM trial (Pages 27-28):

- At Week 52, mean placebo-subtracted weight loss from baseline for lorcaserin 10 mg BID was 3.1%
- At Week 52, 37.5% of patients on lorcaserin 10 mg BID and 16.1% of patients on placebo lost at least 5% of baseline body weight
- At Week 52, mean placebo-subtracted change in HbA1c for lorcaserin 10 mg BID was 0.49%
- At Week 52, more patients on lorcaserin 10 mg BID than placebo achieved HbA1c < 7% (50.4% vs. 26.3%), HbA1c < 6.5% (23.9% vs. 8.6%), fasting plasma glucose < 126 mg/dL (42.2% vs. 29.1%), and fasting plasma glucose < 100 mg/dL (14.1% vs. 5.7%)
- For unclear reasons, a dose-response was not seen for efficacy between the BID and QD doses, unlike in the larger BLOSSOM trial and Phase 2 dose-ranging trials

The above demonstrates that lorcaserin 10 mg BID treatment on average resulted in 3.25 kg (about 7 lbs.) greater weight loss than placebo in non-diabetic subjects.

The two tables below from Dr. Golden's review demonstrates the percentage of subjects experiencing at least a 10% weight loss (Pages 36-37).

Table 3. 10% Weight Loss Responders at Week 52, BLOOM and BLOSSOM (MITT/LOCF)

BLOOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1538	347 (22.6)
Pbo	1499	115 (7.7)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	14.9 (12.4, 17.4)	< 0.001
BLOSSOM		
Treatment	**N**	**n (%)**
Lorc 10 BID	1560	353 (22.6)
Pbo	1539	150 (9.7)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	12.88 (10.33, 15.43)	< 0.001
Pooled Non-Diabetes		
Treatment	**N**	**n (%)**
Lorc 10 mg BID	3098	695 (22.43)
Pbo	3038	264 (8.69)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	13.75 (11.97, 15.52)	< 0.001

Source: NDA 022529 BLOOM CSR Table 12; BLOSSOM CSR Table 12; ISE Statistical Report Table E3.0

Table 4. 10% Weight Loss Responders at Week 52, BLOOM-DM (MITT/LOCF)

Treatment	**N**	**n (%)**
Lorc 10 BID	251	41 (16.3)
Pbo	248	11 (4.4)
Between Treatment Comparison	**Difference in Proportion (95% CI)**	**p-value**
Lorc 10 BID vs. Pbo	11.90 (6.66, 17.14)	<0.001

Source: NDA 022529 BLOOM-DM CSR, Table 11

In summary, one of the two efficacy benchmarks identified in our draft guidance was achieved (categorical-proportion of subjects losing 5% or more of body weight in drug group is at least 35% and approximately double the proportion in the placebo-treated group) in BLOOM, with BLOSSOM narrowly missing.[3] BLOOM-DM also achieved the categorical criteria. The other criteria that are evaluated are whether the mean weight loss between drug and placebo-treated groups is at least 5%. The two lorcaserin trials in the initial NDA submission had mean weight loss placebo subtraction loss of 3.7% and 3.0% whereas it was 3.1% in BLOOM-DM. These efficacy results are in line with other weight loss drugs that have been approved in the past. The mean placebo-subtracted HbA1c demonstrated in BLOOM-DM was -0.49.

Safety

The main concerns with safety are pre-clinical carcinogenicity findings in rats, and evaluation of the potential for clinically important valvular heart disease (VHD).

Regarding the pre-clinical findings, lorcaserin has been associated with non-genotoxic carcinogenic findings of multiple tumor types. Among the multiple tumor types,

[3] FDA Guidance for Industry: Developing Products for Weight Management. February 2007. http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf

mammary and brain tumors are the most concerning as the others could potentially be monitored clinically (i.e. squamous cell cancer of the skin) or have adequate safety margins.

Mammary Carcinoma

In the original submission, lorcaserin caused mammary gland tumors in both sexes of rodents at clinically relevant exposures. Mammary gland tumors were comprised of both adenocarcinoma and fibroadenoma, and there were unclear criteria regarding adjudicating the tumors as malignant (adenocarcinoma) or non-malignant (fibroadenoma) and imbalanced diagnostic changes occurred over time, favoring lorcaserin. As part of the NDA resubmission, the sponsor was required to commission an independent pathology working group (five members) to readjudicate the mammary tumors in a blinded fashion. The blinded readjudication provided by this group had 92% consensus and panel members seemed able to confidently discriminate malignant from benign tumors. These efforts resulted in mitigation of the diagnostic uncertainty and provided an adequate safety margin of 24-fold. The sponsor has proposed that the formation of fibroadenoma is on the basis of circulating prolactin. The pharmacology/toxicology reviewers find that the data supporting their contention as plausible but not definitive. There were a limited number of breast neoplasms noted in the clinical trials and were balanced between lorcaserin and placebo groups.

Astrocytomas

The sponsor determined cerebrospinal fluid (CSF) concentrations in humans and non-clinical brain:CSF ratios were used to project human brain exposure. The clinical study conducted demonstrates lower cerebrospinal fluid (CSF) levels in humans than predicted based on monkey or rodent studies. Based upon this data and the relatively constant relationship of CSF to total brain levels of drug (measured in monkeys and rodents), the level where astrocytoma were not seen in male animals provides an exposure ratio of 70-fold and the level of drug exposure in animals where astrocytomas were first noticed provided an exposure ratio of 342-fold. In female animals where there were no astrocytomas noted the exposure margin is greater than 1000-fold.

VHD

In the original submission the selectivity of lorcaserin at the 5HT2C receptor compared to the 5HT2B (implicated in valvulopathy) at clinically relevant doses was unclear. Data included in the CR response has provided clarification, at least in terms of preclinical pharmacology/toxicology receptor potency data. The original NDA had two different groups of data revealing disparate results such that there was a potential for lorcaserin concentrations in patients to approach levels of concern in regard to activating the 5HT2B receptor. New studies were conducted that modulated receptor densities between relevant human tissues and the cells used in the *in vitro* potency assays. These studies demonstrated that lorcaserin is 3- to 5-fold less potent than originally reported at all three 5HT2 receptor subtypes. As such the human plasma levels are many fold lower for EC50

activation of 5HT2A and 2B, leaving an adequate margin of safety. Based on these estimates, doses of 40 mg might result in activation of the 5HT2A and doses in excess of 200 mg might activate 5HT2B. Please refer to Dr. Bourcier's review for further details.

The clinical safety assessment of lorcaserin focused on concerns related to potential valvular heart disease. Echocardiographic assessments were designed to rule out a 50% or greater increase in the relative risk for FDA-defined valvular heart disease (mild or greater aortic regurgitation and/or moderate or greater mitral regurgitation). This 50% increase was arbitrarily chosen as a starting point, with the concept that more data may be needed depending on the results. The sponsor performed echocardiography in approximately 4800 subjects and at week 52 had a RR of 1.07 (95% C.I.: 0.74, 1.55). The greatest proportion of lorcaserin-treated VHD occurred at Week 24 and seemed to attenuate somewhat by Week 52. This is highlighted in the table below from Dr. Golden's original review (page 80).

Table 5. FDA-Defined VHD

	BLOOM		**BLOSSOM**			**POOLED**	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 QD**	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
Week 24							
Safety pop N	1089	1213	1103	601	1170	2192	2383
Safety pop n (%)	21 (1.9)	25 (2.1)	20 (1.8)	12 (2.0)	27 (2.3)	41 (1.87)	52 (2.18)
Relative Risk (90% CI)		1.07 (0.66, 1.73)		1.27 (0.79, 2.06)	1.10 (0.61, 2.00)		1.17 (0.83, 1.64)
Relative Risk (95% CI)		1.07 (0.60, 1.90)		1.27 (0.72, 2.26)	1.10 (0.61, 2.00)		1.17 (0.78,1.75)
Completers pop N	709	882	797	447	863	1506	1745
Completers pop n (%)	14 (2.0)	20 (2.3)	17 (2.1)	9 (2.0)	20 (2.3)	31 (2.06)	40 (2.29)
Relative Risk (90% CI)		1.15 (0.65, 2.02)			1.09 (0.64, 1.86)		1.12 (0.76, 1.65)
Relative Risk (95% CI)		1.15 (0.58, 2.26)			1.09 (0.57, 2.06)		1.12 (0.70, 1.77)
Week 52							
Safety pop N	1191	1278	1153	622	1208	**2344**	**2486**
Safety pop n (%)	28 (2.4)	34 (2.7)	23 (2.0)	9 (1.4)	24 (2.0)	**51 (2.18)**	**58 (2.33)**
Relative Risk (90% CI)		1.13 (0.75, 1.71)		0.73 (0.38, 1.38)	1.00 (0.62, 1.60)		**1.07 (0.78, 1.46)**
Relative Risk (95% CI)		1.13 (0.69, 1.85)		0.73 (0.34, 1.56)	1.00 (0.57, 1.75)		**1.07 (0.74, 1.55)**
Completers pop N	698	857	790	448	853	1488	1710
Completers pop n (%)	21 (3.0)	29 (3.4)	19 (2.4)	7 (1.6)	13 (1.5)	40 (2.69)	42 (2.46)
Relative Risk (90% CI)		1.12 (0.71, 1.79)			0.63 (0.35, 1.14)		0.90 (0.63, 1.29)
Relative Risk (95% CI)		1.12 (0.65, 1.95)			0.63 (0.32, 1.27)		0.90 (0.59, 1.38)

	BLOOM		BLOSSOM			POOLED	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 QD**	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
Exposed at least 3 months pop N	1028	1167	1059	574	1101	2087	2268
Exposed at least 3 months pop n (%)	26 (2.5)	33 (2.8)	23 (2.2)	9 (1.6)	22 (2.0)	49 (2.35)	55 (2.43)
Relative Risk (90% CI)		1.12 (0.73, 1.71)		0.72 (0.38, 1.37)	0.92 (0.57, 1.49)		1.03 (0.75, 1.41)
Relative Risk (95% CI)		1.12 (0.67, 1.86)		0.72 (0.34, 1.55)	0.92 (0.52, 1.64)		1.03 (0.70, 1.50)

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Including data from BLOOM-DM has increased the point estimate to 1.16 (95% CI 0.81-1.67). This is summarized in the table below from Dr. Golden's review (Page 66).

Table 6. Incidence of FDA-Defined VHD at Week 52 by Treatment Group, Patients with Baseline VHD Excluded (Safety Population, LOCF)

	BLOOM		**BLOSSOM**		**BLOOM-DM**	
	Lorc 10 BID N=1278	**Pbo N=1191**	**Lorc 10 BID N=1208**	**Pbo N=1153**	**Lorc 10 BID N=210**	**Pbo N=209**
FDA-VHD, n (%)	34 (2.66)	28 (2.35)	24 (1.99)	23 (1.99)	6 (2.86)	1 (0.48)
Relative Risk (95% CI)	1.13 (0.69, 1.85)		1.00 (0.57, 1.75)		5.97 (0.73, 49.17)	
Pooled RR (95% CI)	**1.16 (0.81, 1.67)**					

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Noted with fenfluramine-associated VHD was the predominance of involvement of the aortic valve as noted by Dr. Golden. Below are two tables from Dr. Golden's review (page 67) demonstrating that the aortic valve does not seem to be the predominant valve causing the 16% excess noted above.

Table 7. Incidence of Mild or Greater Aortic Regurgitation at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Patients*	**Number of Events**	**Incidence**	**RR** (95% CI)	**Pooled RR**** (95% CI)
BLOOM	**Lorc BID**	1278	18	1.41%	0.96 (0.69, 1.34)	0.89 (0.56, 1.42)
	Pbo	1191	18	1.51%		
BLOOM-DM	**Lorc BID**	210	4	1.90%	2.51 (0.43, 14.54)	
	Pbo	209	1	0.48%		
BLOSSOM	**Lorc BID**	1208	13	1.08%	0.84 (0.62, 1.13)	
	Pbo	1153	18	1.56%		
Total		5249	72	1.37%		

* Number without missing, excluding baseline valvulopathy
** Stratified Mantel-Haenszel approach

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

Table 8. Incidence of Moderate or Greater Mitral Regurgitation at Week 52 (LOCF) by Treatment Group (Safety Population, Subjects with Baseline Valvulopathy Excluded)

		Total Patients*	**Number of Events**	**Incidence**	**RR** (95% CI)	**Pooled RR**** (95% CI)
BLOOM	**Lorc BID**	1278	17	1.33%	1.31 (0.80, 2.14)	1.95 (1.05, 3.59)
	Pbo	1191	10	0.84%		
BLOOM-DM	**Lorc BID**	210	2	0.95%		
	Pbo	209	0	0%	-	
BLOSSOM	**Lorc BID**	1208	12	0.99%	1.67 (0.80, 3.48)	
	Pbo	1153	5	0.43%		
Total		5249	46	0.88%		

* Number without missing, excluding baseline valvulopathy
** Stratified Mantel-Haenszel approach

Source: Dr. Xiao Ding, Statistical Reviewer FDA DB7

There were not any cases of moderate or severe aortic regurgitation or severe mitral regurgitation. In the pooled analysis of BLOOM and BLOSSOM, 27 lorcaserin patients and

21 placebo patients who were diagnosed with FDA-defined VHD at Week 24 subsequently "reverted" back to no VHD at Week 52. It is difficult to know whether the slight imbalance in FDA-defined VHD is a result of drug use or ascertainment or weight loss bias (as Dr. Coleman points out there are some observational data suggesting an inverse relationship between BMI and the degree of valvular regurgitation). The 5HT2 receptor data resubmitted by the sponsor is reassuring, and the level of evaluation by the sponsor should assure us that rates associated with fenfluramine or dexfenfluramine have not occurred.[4]

There is probably a great deal of imprecision inherent in echocardiographic evaluation. Evidence to support this are the subjects who were diagnosed with VHD at Week 24 'reverted' back to non-VHD at Week 52 and the Kappa statistic between readers ranged from 0.32 to 0.38 depending on the valve evaluated, which is only fair agreement.[5] We have done multiple analyses in an effort to look for any bias such as the one below from Dr. Golden's review (Page 75).

Table 9. Models to Test for the Association between Percent Weight Loss and VHD

Model 1. Placebo only	**Estimate**		**p-value**	**Risk Ratio**	**(95% CI)**
Age	0.0565	0.0145	0.0001	1.06	(1.03, 1.09)
Baseline weight	0.0009	0.0086	0.9194	1.00	(0.98, 1.02)
% weight loss at week 52	0.0215	0.0207	0.2993	1.02	(0.98, 1.06)
Model 2. Lorc BID only	**Estimate**		**p-value**	**Risk Ratio**	**(95% CI)**
Age	0.0491	0.0137	0.0003	1.05	(1.02, 1.08)
Baseline weight	-0.0102	0.0082	0.2167	0.99	(0.97, 1.01)
% weight loss at week 52	0.0281	0.0171	0.1003	1.03	(0.99, 1.06)
Model 3. Placebo and Lorc BID	**Estimate**		**p-value**	**Risk Ratio**	**(95% CI)**
Lorcaserin	0.0566	0.1934	0.7698	1.06	(0.72, 1.55)
Age	0.0529	0.01	<0.0001	1.05	(1.03, 1.08)
Baseline weight	-0.0048	0.0059	0.4235	1.00	(0.98, 1.01)
% weight loss at week 52	0.0256	0.0131	0.0513	1.03	(1.00, 1.05)

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

In summary, no matter what way the data is looked at, for the estimate when including all valves, the HR is usually slightly greater than one, not favoring drug.

I had noted in my original review that clarifying the permissiveness of lorcaserin binding to serotonin receptor subtypes and estimates of the incidence rates from fenfluramine/dexfenfluramine such that there was enough exposure in this database to screen for rates of this magnitude. Based on the CR submission augmenting the data from the original NDA, there is not evidence of valve damage. The point estimate always being slightly greater than one is slightly disconcerting, but it is mainly in the context of the prior history of drugs that have effects at the serotonin receptor. While it may not be totally clear that lorcaserin cannot 'absolutely' have cardiac valvular effects (it is hard to prove a negative), it is

[4] Jick H, et al. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. NEJM, 1998 sep 10;339(11):719-24. 35 per 10,000 subjects exposed for four or more months (95% CI, 16.4-76.2; p<0.001)

[5] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics, March 1977:159-174

clear that there are not effects to the level of those demonstrated by fenfluramine/dexfenfluramine.[6]

Cardiovascular (CV) Risk Assessment

Patients with obesity have greater baseline CV rates than the general population. There has been concern that some drugs used to treat obesity may have off-target effects actually increasing CV rates. The result of increasing CV events in a population that already has an increased rate would be a devastating public health impact. This same concern exists with drugs used to treat Type-2 diabetes mellitus (DM) as well and was the topic of an Advisory Committee (AC) meeting held in July 2008. At this meeting, recommendations were made for CV assessment in the pre- and post-approval setting. An AC meeting was convened on March 28-29, 2012 to discuss the CV safety requirements necessary for obesity drug approval. The results of the March 2012 meeting were the recommendations that drugs used in the treatment of obesity should undergo CV safety evaluation similar to that as put forth in the CV evaluation guidance of drugs used in the treatment of Type 2 diabetes.[7]

The CV safety assessment for drugs used in the treatment of Type 2 DM requires pre-approval CV assessment screening, with further post-approval definitive testing to determine that there are not increased cardiovascular risks associated with the medication. The diabetic assessment guidance allows for a two-step, 'step-wise' assessment of potential cardiovascular risk during drug development. The first step, 'step-one', is to make a determination that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.8 (goal-post) compared to a control group, with a point estimate near unity. Assuring that there is not an eighty percent increase in risk would allow marketing while a longer and larger outcome study, which would assure even less risk, is conducted. The boundary of 1.8 was chosen because a more conservative 'goal-post' to pre-approval testing would be too burdensome/prohibitive to drug develop, but this level of assurance (1.8) would be feasible and would provide some assurances (with a point estimate near unity) while further testing was underway. The 'step-two' testing would be accomplished by a larger outcome study that must demonstrate that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than 1.3 compared to a control group in order for marketing to continue. Although one could question whether ruling out an 80% increase for initial marketing and ultimately ruling out a 30% increase is enough assurance, the reality is that these goals are what is practical to actually test in a randomized trial and the practicality of the situation was instrumental in dictating the risk ratios described above. In fact, if a drug compared to the control group had a true effect that is 'neutral' (point estimate of one), it is impossible to have a study large enough for the upper bound of the confidence interval to be at one (certainty). It should also be noted that the upper bound of the CI is viewed in the context of the necessity that the point estimate is near unity. Also, these upper bounds were chosen based on the baseline rate of CV events in the diabetic

[6] Sachdev M, Miller WC, Ryan T, Jollis JG. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. Am Heart J. 2002 Dec; 144(6):1065-73

[7] Guidance for industry: Diabetes mellitus-evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. United States Food and Drug Administration, 2008. Http://www fda.gov/downloads/Drugs/GuidanceCompliance

population and consideration is given to the absolute number of 'excess events' that would be ruled-out.

Of relevance is that the recommendations for a 'diabetic-type' evaluation of drugs used in the treatment of obesity have come at a time when there are active applications in house under review. This situation is very similar to that of the diabetic drugs when we had (b) (4) active applications in house at the time that the AC gave recommendations and our guidance issued. At that time, we concluded that recommendations should apply to all ongoing programs including those with applications pending with the agency. We did make some concessions however due to the fact that these programs had not been designed to prospectively evaluate for CV events. At that time, we allowed the use of Standardized MedDRA Queries (SMQs) for CV event terms (to fulfill 'step-one'), utilizing the individual investigators original designation of an adverse event that may be associated with a thromboembolic event without formal adjudication. While not specifically fulfilling the recommendations in the CV evaluation of diabetic drugs guidance, this type of approach did fulfill the 'spirit' and does allow for, while not precise, an assessment of undue risk while not unduly delaying the availability of important therapeutics to those in need. The drugs that received approval were then required to perform a formal outcome trial as a post-marketing requirement (PMR). This approach was discussed for the pending diabetic drugs and agreed to at the time by the AC panel members.

We have also evaluated a similar approach in the case of lorcaserin. It is important to note that we have not yet made a formal policy decision upon the requirements necessary for CV evaluation of obesity drugs. Also, due to the different background rates of CV events in the obesity population compared to the diabetic population, different 'goal-posts' are necessary to allow for the same exclusion of 'excess-events'. We have already considered the 'goal-posts' in a dispute resolution with another obesity drug. For that drug, we determined that an initial (b) (4) This allows for a similar exclusion of 'excess-events' as that recommended for in the diabetic guidance (depending upon true background rates).

There are many different SMQs search terms that can be used ranging from broad to narrow. The review team has chosen a 'broad' group to encompass a spectrum of possible ischemic events and a 'narrow' group that may be more reflective of a stricter MACE definition. This also was similar to what was done for the (b) (4) diabetic drugs under review at time of the CV evaluation of diabetic drugs guidance issuance. The results of these two approaches are in the tables below from Dr. Golden's review (Pages 111 and 113).

Table 10. Broad Search, All Adverse Events

	Adverse Events in Broad[3] CV Search							
	Treatment	Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	8	5.05	1.37 (0.55, 3.41)	1.37 (0.55, 3.41)	1.08 (0.61, 1.91)	1.09 (0.64, 1.88)
	Lorc 10 BID	1593	11	6.91				
BLOOM-DM	Pbo	252	8	31.75	0.61 (0.20, 1.88)	0.89 (0.35, 2.30)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	5	52.63				
BLOSSOM	Pbo	1601	7	4.37	1.29 (0.48, 3.46)	1.05 (0.41, 2.71)		
	Lorc 10 BID	1602	9	5.62				
	Lorc 10 QD	801	2	2.50				

[1]Lorcaserin 10mg BID vs. placebo
[2]All lorcaserin vs. placebo
[3]Broad Search includes: Haemorrhagic cerebrovascular conditions SMQ, Ischaemic cerebrovascular conditions SMQ, and Ischaemic heart disease SMQ

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Table 11. Narrow Search, All Adverse Events

	Adverse Events in Narrow[3] CV Search							
		Total Subjects	Adverse Events	Events / 1000 subjects	Odds Ratio[1] (95% CI)	Odds Ratio[2] (95% CI)	Mantel-Haenszel OR[1]	Mantel-Haenszel OR[2]
BLOOM	Pbo	1584	7	4.42	0.57 (0.17, 1.94)	0.57 (0.17, 1.94)	0.78 (0.40, 1.54)	0.77 (0.40, 1.46)
	Lorc 10 BID	1593	4	2.51				
BLOOM-DM	Pbo	252	7	27.78	0.70 (0.22, 2.23)	0.82 (0.29, 2.28)		
	Lorc 10 BID	256	5	19.53				
	Lorc 10 QD	95	3	31.58				
BLOSSOM	Pbo	1601	5	3.12	1.20 (0.37, 3.94)	0.93 (0.30, 2.94)		
	Lorc 10 BID	1602	6	3.75				
	Lorc 10 QD	801	1	1.25				

[1]Lorcaserin 10mg BID vs. placebo
[2]All lorcaserin vs. placebo
[3]Narrow Search includes: Ischaemic cerebrovascular conditions SMQ, Myocardial infarction SMQ

Source: Dr. Eugenio Andraca-Carrera, Statistical Reviewer FDA DB7

Utilizing the same approach that was applied to pending agents used in the treatment of Type-2 DM, lorcaserin would make the goal-post of 2.0 that would allow marketing. It is interesting to note in the tables above that the upper bound of the CI actually decreases for the narrow CV search despite a decreased number of events which widens the CI. The decrease in the upper bound occurs because of a more favorable point estimate when using stricter criteria, which should be reassuring to the extent possible based on the limitations of this type of analysis. While this type of overall approach is not what would be expected of future applications, it is not without precedence as discussed above. The sponsor will be required to perform a formal CV outcome trial. These issues were also discussed at the AC meeting and were acceptable to members active in the discussion who also noted that lorcaserin did not have any concerning 'signals' such as increased blood pressure or adverse changes in biomarkers, also giving them some degree of reassurance to allow for formal evaluation as a post-marketing requirement. So the combination of no clear signal in the trial database combined with no concerning biomarker abnormalities will allow for a post-marketing trial to fully evaluate for CV effects.

Psychiatric effects and scheduling

Lorcaserin may be predicted, depending upon dose relative to receptor potency, to have effects similar to some psychedelic drugs that have activity through the 5HT2A receptor (the same receptor associated with effects of lysergic acid diethylamide-LSD). Because the potency at this receptor is less than predicted blood levels at clinical doses, most patients should not

develop adverse hallucinogenic reactions, euphoria or other dissociative symptoms. In clinical trials, most adverse events indicating the effects mentioned above were balanced. The controlled substance staff (CSS) has noted that acute administration of lorcaserin to rats produces behaviors that are associated with activation of 5HT2A. CSS also notes that the overall incidence of euphoria is low (0.7%), but greater than placebo (0.06%). Also noted is a high rate of euphoria (6-19%) in human abuse potential study with drug abusers. As such, CSS is recommending lorcaserin for placement in Schedule IV of the Controlled Substances Act. Please refer to Dr. Bonson's review for further details.

Serotonin Syndrome

As lorcaserin exerts its effects through serotonin receptors, serotonin syndrome adverse effects are a consideration. Noted in the safety data base are two subjects that had adverse effects that may fall into this category. As such, labeling will contain warnings to be alert for this syndrome if coadministration of other serotonergic drugs occurs.

Risk Evaluation and Mitigation Strategy (REMS)

The issue of a possible REMS was discussed at a meeting of the Medical Policy Council on May 29, 2012. The council concluded that a REMS is not appropriate at this time to mitigate the risk of valvulopathy as the risk is unlikely. This view is also proposed by The Office of Medication Error Prevention and Risk Management as they have recommended that further assessment of valvulopathy risk would be better accomplished within a large controlled safety trial, such as the planned CV outcome trial. This same sentiment is shared by the clinical reviewers from DMEP with which I agree. There was one panel member from the AC that suggested initial and yearly echocardiograms should occur in all patients receiving lorcaserin. This would not serve to mitigate any risk to individual patients and would instead serve as a type of uncontrolled population study. I do not agree with this approach as it does not protect individual patients, would have a tremendous cost to the health care system, and would not be as instructive as information obtained from planned safety trials.

Advisory Committee Meeting

An advisory committee meeting was held on September 16, 2010. The committee voted 18 to four in favor of approval. Dr. Golden has a summary of the votes and comments from the meeting in her review.

Conclusions and Recommendations

Obesity can be a devastating disease and has become an epidemic in this country creating a tremendous burden on our healthcare system. Obesity's causes are multi-factorial and it is instructive to look at the size of soft drinks now compared to 30 years ago. This is a simplistic but illustrative example that environmental factors are overwhelmingly responsible for obesity, consisting of easy and cheap access to high calorie foods and drinks, less physical activity as our population demographics have switched from a rural to urban setting combined with our natural instinct to obtain calories for survival. In this type of setting, it may be impractical that

any medication by itself will be a solution and to make true inroads into the obesity epidemic, thought needs to be given to wider interventions. However, within the agency our contribution is through drug regulation and we are aware of the urgency to try to provide aid and appropriate treatments. This urgency however has to be weighed against any potential medication induced adverse effects. Such considerations lead to a CR action for the first review cycle of Lorcaserin due to many concerning pre-clinical signals that was considered in the backdrop of fairly marginal efficacy findings.

With this CR submission, the sponsor has successful addressed the items identified in the CR letter. All of this material was presented at an AC meeting with the majority voicing support of approval, in large part due to the lack of effective therapies as was emotionally and movingly voiced during the open public session by many suffering from obesity. I agree with the advisory panel that this application should receive an approval action with appropriate labeling.

There is still work to do however. The sponsor should have a PMR to conduct a CV outcome trial. This trial should also be an opportunity to further supplement cardiac valve evaluation and other safety issues (mammary tumors) of concern.

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/s/

CURTIS J ROSEBRAUGH
06/27/2012