CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Summary Review for Regulatory Action

Date	24 June 2012
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	22-529
Applicant Name	Arena Pharmaceuticals
Date of Re-Submission	December 27, 2011
PDUFA Goal Date	June 27, 2012
Proprietary Name /Established Name	Lorcaserin/Belviq
Dosage Forms / Strength	Tablet/10 mg BID
Proposed Indication(s)	Chronic Weight Management
Recommended Action for NME:	Approve

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Julie Golden, MD
Statistical Review	Janice Derr, PhD/Xiao Ding, PhD
Pharmacology/Toxicology Review	Fred Alavi, PhD/Todd Bourcier, PhD
CMC Review/OBP Review	Olen Stephens, PhD/John Duan, PhD/Raanan Bloom, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Immo Zdrojewski, PhD
OPDP	Sam Skariah, PharmD
OSI	Kassa Ayalew, MD/Leonard Lavi
OSE/DMEPA	Lubna Najam, MS, PharmD/Reasol Agustin, PharmD
OSE/DEPI	Christian Hampp, PhD
OSE/DRISK	Joyce Weaver, PharmD
OSE/DMPP	Sharon Williams, RN
Thorough QT Consult	Christine Garnett, PhD
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PMHS	Jeanine Best, RN, PNP

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DEPI=Division of Epidemiology
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
DMPP=Division of Medical Policy Programs
PMHS=Pediatric and Maternal Health Staff

1. Introduction and Background

Lorcaserin is a first-in-class, relatively selective oral agonist of the 5HT2c receptor, which as of this writing, has not been approved by any regulatory body in the world. Activation of 5HT2c receptors, which densely populate areas of the brain controlling appetite, has been shown in animal models to reduce caloric intake and decrease body weight. The sponsor is seeking approval of lorcaserin 10 mg BID for weight management in obese (BMI $\geq$ 30 kg/m^2) or overweight (BMI (b) (4) kg/m^2) individuals with at least one weight-related comorbidity.

The application was first submitted on 28 December 2009. During the first review cycle, it was concluded that the lorcaserin 10 mg BID dose satisfied the categorical efficacy criterion as outlined in the FDA's draft obesity guidance document (2007). The mean placebo-subtracted weight loss at one year was, however, only -3.3% based on data from two phase 3 clinical studies. Thus, lorcaserin did not satisfy the mean efficacy criterion of the obesity draft guidance. Safety issues raised during the initial review cycle included a slight imbalance in the percentage of patients treated with lorcaserin versus placebo who developed FDA-defined valvular heart disease (VHD). Two findings from preclinical evaluation were especially worrisome: an increase in the proportion of rats treated with lorcaserin that developed mammary adenocarcinoma/fibroadenoma and brain astrocytomas.

At a 16 September 2010 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting, the panel voted against approval due to concerns about the preclinical carcinogenicity findings and the marginal weight loss demonstrated in the phase 3 clinical trials.

On 28 October 2010, the sponsor was issued a Complete Response Letter (CRL). The deficiencies noted in the CRL were: 1) diagnostic uncertainty regarding classification of mammary adenocarcinoma and fibroadenoma in rats treated with lorcaserin in the two-year carcinogenicity study; 2) uncertainty regarding the exposure-response relationship for mammary adenocarcinoma in rats treated with lorcaserin in the two-year rat carcinogenicity study; and 3) an unknown safety margin and tumorigenic mode of action for astrocytoma in male rats treated with lorcaserin in the two-year carcinogenicity study. The CRL also requested that the sponsor submit the final report for the BLOOM-DM study, a phase 3 placebo-controlled clinical trial of lorcaserin in overweight and obese subjects with type 2 diabetes.

This memorandum summarizes the review findings from the principal review disciplines following evaluation of the complete response data submitted by the sponsor on 27 December 2011. Newly-submitted data include a readjudication of the preclinical mammary tumor data by a group of pathologists; clinical data regarding levels of lorcaserin in human cerebrospinal fluid versus plasma; and a final report for the phase 3 clinical trial in diabetics, BLOOM-DM.

No review discipline is recommending that lorcaserin not be approved at this time.

2. CMC/Biopharmaceutics

The CMC and biopharmacuetics reviewers state that there are no pending deficiencies to resolve and recommend that the application be approved. I agree that there are no outstanding CMC or biopharmaceutical issues at this time.

3. Nonclinical Pharmacology/Toxicology

In response to the CRL, the sponsor convened a pathology working group (PWG) composed of five veterinary pathologists. The PWG blindly readjudicated the mammary tumor data. The below table, reproduced from Dr. Alavi's review, provides the original and re-adjudicated mammary tumor results.

Mammary Tumors in Female Rats – Original and Readjudicated

		Lorcaserin Dose mg/kg AUC Exposure Multiple			
		0	10	30	100
		-	7x	24x	82x
Number of Adenocarcinoma	Original	28	34	35	60*
	PWG	27	21	24	50*
Number of Fibroadenoma	Original	20	47*	53*	51*
	PWG	23	53*	55*	51*

*p<0.0001

While the number of adenocarcinomas decreased by one in the control group, the number in the lorcaserin-treated groups decreased by a much larger extent upon reevaluation by the PWG. Relative to control, only the high-dose lorcaserin group had a statistically significant increase in adenocarcinomas. The readjudicated data provide a safety margin of 87-times based on the proposed clinical dose of lorcaserin 10 mg BID.

The number of fibroadenomas in all three lorcaserin-treated groups remained statistically significantly higher relative to control-treated animals following readjudication. However, given that fibroadenomas do not represent premalignant tumors in rats, the mammary tumor data submitted in the complete response alleviate the concern raised by the data in the original application.

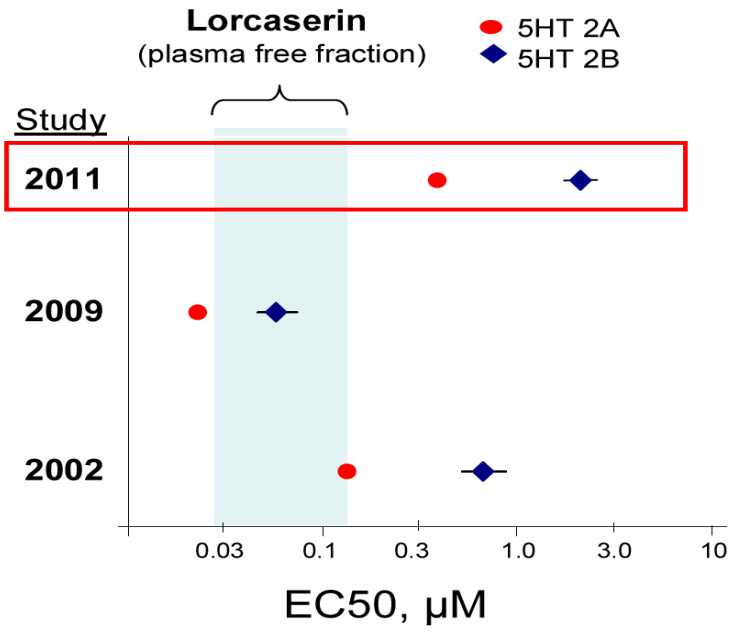
The sponsor continues to assert that the increase in adenocarcinomas in the high-dose group and fibroadenomas in all lorcaserin groups is the result of lorcaserin-induced elevations in plasma prolactin. Dr. Alavi felt that the data provided in the original application did not support this hypothesis. Additional prolactin data were submitted in the sponsor's complete response. Following review of these data, Dr. Alavi concluded that "these studies appear to support a plausible prolactin role in lorcaserin-induced increase in mammary tumors in female rats, but fall short of providing definitive evidence."

Based on information submitted in the complete response I do not believe that lorcaserin poses a risk for mammary adenocarcinoma in humans. The sponsor has adequately addressed two of the deficiencies noted in the CRL: diagnostic uncertainty regarding classification of mammary tumors in lorcaserin-treated rats and uncertainty regarding the exposure-response relationship for mammary adenocarcinomas in lorcaserin-treated rats.

Additional preclinical deficiencies included in the CRL were the unknown safety margin and tumorigenic mode of action for astrocytoma in male rats treated with lorcaserin. The sponsor chose to address these deficiencies by measuring the level of lorcaserin in cerebrospinal fluid (CSF) in humans.

As reviewed by Dr. Immo Zadezensky, clinical pharmacologist, 11 obese men and women received lorcaserin 10 mg BID for 10 days. Nine subjects completed the study. On Day 7, blood and CSF samples were collected. Plasma steady-state for lorcaserin was achieved by Day 4. The plasma C_{max} for lorcaserin was 63.1 ng/ml at 2 hours post-dose. The CSF C_{max} was 0.95 ng/ml at 6 hours post-dose. The CSF-to-plasma geometric mean ratios for AUC, C_{max}, and C_{min} were 0.017, 0.014, and 0.016, respectively. Dr. Zadezensky concluded that the lorcaserin CSF-to-plasma exposure ratio at steady-state in humans is less than 0.02. Based on these data, the safety margin for brain astrocytoma observed in male rats is 70-times the proposed clinical dose of lorcaserin 10 mg BID. The sponsor has adequately addressed the deficiencies related to brain astrocytoma in lorcaserin-exposed rats.

The sponsor's complete response submission included new data on lorcaserin's 5HT2 receptor binding and activation affinities. These data were reviewed by Dr. Todd Bourcier, supervisory pharmacology-toxicology reviewer. As shown in the below figure presented by Dr. Bourcier at the 10 May 2012, EMDAC meeting, the new information indicates that lorcaserin is notably less potent at the $5HT_{2A}$ and $5HT_{2B}$ receptors than previously reported. These data provide an added degree of comfort regarding lorcaserin's "off-target" potential to cause adverse reactions due to activation of the $5HT_{2A}$ (e.g., serotonin syndrome and psychiatric events) and $5HT_{2B}$ receptors (cardiac valvulopathy).



Lorcaserin concentration in human plasma compared to *in-vitro* 5HT2 receptor potency

4. Clinical Pharmacology

The clinical pharmacology reviewer concludes that the data submitted in support of the application are acceptable. I agree with the reviewer that there are no outstanding clinical pharmacology issues.

Based on review of the data from a thorough QT study, the agency's interdisciplinary review team for QT studies concluded that lorcaserin does not significantly prolong the QT interval. The largest upper bound of the 1-sided 95% CIs for the mean difference between lorcaserin 40 mg daily and placebo was below 10 ms, the regulatory threshold of concern.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

The efficacy of lorcaserin was assessed in two phase 3 placebo-controlled clinical trials – BLOOM and BLOSSOM - submitted in the original application. In BLOOM, the mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was -3.7% ($p<0.0001$). In BLOSSOM, mean adjusted placebo-subtracted weight loss following up to one year of treatment with lorcaserin 10 mg BID was -3.0% and -1.9% with lorcaserin 10 mg QD ($p<0.0001$ for both groups).

In BLOOM, the percentages of subjects achieving $\geq$ 5% weight loss following up to one year of treatment were 48% in the lorcaserin 10 mg BID group and 20% in the placebo group ($p<0.001$). In BLOSSOM, the percentages of subjects achieving > 5% weight loss following up to one year of treatment were 47% in the lorcaserin 10 mg BID group, 40% in the lorcaserin 10 mg QD group, and 25% in the placebo group ($p<0.0001$ for both groups vs. placebo).

Thus, the 10 mg BID dose of lorcaserin satisfied the categorical efficacy criterion set forth in the Agency's 2007 draft guidance document. The BLOOM and BLOSSOM trials excluded subjects with type 2 diabetes.

The CRL requested that the sponsor submit the results of BLOOM-DM, a phase 3 placebo-controlled trial of overweight and obese individuals with type 2 diabetes. A brief description of BLOOM-DM follows.

A total of 253 subjects were randomized to placebo and 256 to lorcaserin 10 mg BID. Due to slower than expected recruitment, randomization to a lorcaserin 10 mg QD group was terminated after 95 subjects. I will focus on the efficacy of the lorcaserin 10 mg BID dosing regimen. The mean age of the study subjects at baseline was approximately 53 years; 54% of the participants were female and the majority white. The average BMI was 36 kg/m^2 and the average HbA1c was 8.1%. More than 90% of the subjects were taking metformin at the start of

the study. One hundred fifty-seven subjects from the placebo group completed the one-year study, while 169 subjects from the lorcaserin 10 mg BID group completed the study.

In the modified intention-to-treat population, 37.5% of subjects in the lorcaserin 10 mg BID group lost at least 5% of baseline body weight versus 16.1% of subjects in the placebo group ($p<0.0001$). This compares with approximately 47% of non-diabetic subjects treated with lorcaserin 10 mg BID and 23% of placebo-treated subjects from the BLOOM and BLOSSOM trials. The placebo-subtracted mean percent weight loss in the lorcaserin 10 mg BID treatment arm from BLOOM-DM was 3.1% ($p<0.001$). This compares with approximately 3.3% for non-diabetics treated with lorcaserin 10 mg BID in the BLOOM and BLOSSOM trials. As might be expected, weight loss was greater in subjects with baseline HbA1c values below versus above 8.0%.

As depicted in the below table from Dr. Golden's review, treatment with lorcaserin 10 mg BID was associated with a statistically significant mean reduction in HbA1c from baseline to Week 52.

Mean Change in HbA1c from Baseline to Week 52

Treatment	**N**	**Baseline Mean (SD)**	**Adjusted Change from Baseline (SE)**	
Lorcaserin 10 BID	251	8.05 (0.92)	-0.93 (0.06)	
Placebo	248	8.03 (0.92)	-0.44 (0.06)	
Between treatment difference			**Difference in LS means (95% CI)**	**p value**
Lorcaserin 10 BID vs. placebo			-0.49 (-0.65, -0.33)	<0.001

Seventeen percent of lorcaserin 10 mg BID-treated subjects had a decrease in dosage of anti-diabetic medication during the trial versus 12% of placebo-treated subjects. A larger percentage of subjects randomized to the lorcaserin 10 mg BID group had their anti-diabetic medication(s) withdrawn or stopped compared with subjects randomized to placebo.

The mean changes from baseline to Week 52 in cardiometabolic parameters were small, but for the most part, numerically in favor of the lorcaserin 10 mg BID group compared with the placebo group.

7. Safety

Valvular Heart Disease

The weight-loss drugs dexfenfluramine and fenfluramine were removed from the United States market in 1997 due to reports implicating their involvement in the development of left-sided VHD. Research conducted subsequent to this discovery suggested that dexfenfluramine and fenfluramine's activation of the $5HT_{2B}$ receptor on valvular tissue was the mechanism responsible for the VHD. In a 2002 meta-analysis of nine cross-sectional studies, the incidence of FDA-defined VHD (at least mild aortic regurgitation or at least moderate mitral regurgitation) in subjects exposed to fenfluramine or dexfenfluramine for more than 3 months was calculated to be 12% versus 6% in unexposed or control subjects [OR = 2.2 (95% CI 1.7,

2.7].[1] Subjects exposed to fenfluramine or dexfenfluramine for less than 3 months did not appear to have an increased risk for FDA-defined VHD.

Given that lorcaserin targets the serotonergic system, VHD was identified as a leading safety concern requiring extensive evaluation during the drug's clinical development. Although the results of *in-vitro* studies indicate that lorcaserin's binding affinity for and activation of the $5HT_{2B}$ receptor are lower than those of dexfenfluramine and fenfluramine, the Division requested that the sponsor conduct echocardiographic evaluation of heart valves in all subjects participating in long-term lorcaserin clinical trials.

Arena proposed that the phase 3 clinical development program be powered to rule out a doubling of the risk for FDA-defined VHD. The Division believed that a doubling was too permissive and requested that the program be powered to rule out at least a 50% increase in risk (i.e., upper bound of the 95% CI 1.5 or less). This necessitated increasing the sample size of the phase 3 program from approximately 4000 to 7000 subjects. It was made clear to the sponsor that ruling out at least a 50% increase in the risk for FDA-defined VHD was an arbitrary benchmark and that the adequacy of the valvulopathy data would be determined by not only the data themselves, but lorcaserin's efficacy and overall safety profile as well.

All echocardiograms obtained in the BLOOM and BLOSSOM trials were over-read by 2 blinded central readers. Any discrepant readings between the two primary readers were adjudicated by a third reader. In BLOOM, echocardiograms were obtained at screening and at Weeks 24, 52, 76, and 104/exit. In BLOSSOM, echocardiograms were obtained at baseline and at Weeks 24 and 52/exit. The primary endpoint of the echocardiographic evaluations was the incidence of FDA-defined valvulopathy at Week 52.

The incidence rates and relative risks for FDA-defined VHD at Week 52 are shown below in a table modified from Dr. Golden's review. In BLOOM, the incidence rates for VHD in the safety population were 2.4% for placebo and 2.7% for lorcaserin 10 mg BID [RR 1.13 (95% CI 0.69, 1.85)]. In BLOSSOM, the incidence rates for VHD were 2.0% for placebo and 2.0% for lorcaserin 10 mg BID [RR 1.0 (95% CI 0.57, 1.75)]. In the analysis of pooled data, the RR for FDA-defined VHD was 1.07 (95% CI 0.74, 1.55). The kappa statistic was 0.32 for reading of the mitral valve and 0.38 for reading of the aortic valve. These values indicate that the echocardiographic readings from the two primary readers were in fair agreement.

Given that the upper bound of the 95% confidence interval for the relative risk for FDA-defined VHD with lorcaserin exceeded 1.5, albeit by a small amount, one cannot conclude that the lorcaserin is non-inferior to placebo. When the valvulopathy analysis is restricted to subjects who completed 52 weeks of treatment, the RR for FDA-defined valvulopathy was 0.90 (95% CI 0.59, 1.38). It should be noted, however, that the RR estimates for VHD in BLOSSOM are considerably different for the safety and completers populations. The reason for the discrepancy is unclear, but it was not observed in BLOOM.

[1] Sachdev M, et al. Effect of fenfluramine-derivative diet pills on cardiac valves: A meta-analysis of observational studies. Am Heart J 2002; 144:1065-73.

Incidence of FDA-Defined Valvulopathy at Week 52

	BLOOM		BLOSSOM			POOLED	
	Pbo	**Lorc 10 BID**	**Pbo**	**Lorc 10 QD**	**Lorc 10 BID**	**Pbo**	**Lorc 10 BID**
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 (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 (95% CI)		1.12 (0.65, 1.95)			0.63 (0.32, 1.27)		0.90 (0.59, 1.38)

Although the VHD associated with dexfenfluramine and fenfluramine was predominately left-sided, use of other $5HT_{2B}$ agonists has been associated with abnormalities of the right-sided heart valves. It is therefore of interest to examine the proportion of subjects who experienced any increase from baseline in valvular regurgitation of any cardiac valve at Week 52 (excluding absent to trace) was 33% in the lorcaserin 10 mg BID group and 28% in the placebo group (see following table from Dr. Golden's review).

Proportion of Subjects with an Increase from Baseline in Valvular Regurgitation at Week 52 Excluding Absent to Trace

	Lorcaserin 10 BID	Placebo	Relative Risk (95% CI)	P value
Aortic	1.25%	1.54%	0.81 (0.51, 1.30)	0.384
Mitral	9.99%	8.47%	1.18 (0.99, 1.41)	0.066
Pulmonic	17.48%	15.32%	1.14 (1.00, 1.30)	0.042
Tricuspid	12.25%	10.03%	1.22 (1.04, 1.43)	0.014
Any Valve	32.76%	28.42%	1.15 (1.06, 1.25)	0.001

The increases in the proportion of subjects exposed to lorcaserin 10 mg BID versus placebo that had increases in regurgitation of the pulmonic and tricuspid valves were of nominal statistical significance. The clinical significance of these findings is unknown.

Importantly, there were no cases of moderate or severe aortic regurgitation or severe mitral regurgitation observed in the BLOSSOM or BLOOM trials.

Additional echocardiographic data were included in the sponsor's complete response. These data from the BLOOM-DM trial, in which approximately 400 subjects with type 2 diabetes were randomized to lorcaserin 10 mg BID or placebo and treated for up to one year. The incidence of FDA-defined VHD at Week 52 in lorcaserin-treated subjects was 2.86% versus 0.48% in placebo-treated subjects (RR=5.97; 95%CI, 0.7, 49.2). The below table taken from Dr. Golden's review provides the pooled RR for FDA-defined VHD for the three pivotal clinical studies.

FDA-Defined VHD at Week 52 in BLOOM, BLOSSOM, and BLOOM-DM

	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)**					

Although the risk estimate for VHD in BLOOM-DM is much higher compared with the other two studies, this is due to a notably lower incidence of VHD in the placebo-group from BLOOM-DM. The risk estimate of 5.97 would be concerning if it was due to an increase in the incidence of VHD in the lorcaserin group relative to the comparable groups in BLOOM and BLOSSOM.

With respect to the 16% increase in the risk estimate for FDA-defined VHD based on the three pivotal clinical trials, Dr. Golden notes in her review that some observational data suggest that there is an inverse relationship between BMI and degree of valvular regurgitation, at least at the mitral valve.[2] In line with this, the relative risk for moderate or greater mitral regurgitation in lorcaserin-treated subjects was 1.95 (1.05, 3.59) and for mild or greater aortic regurgitation the relative risk was 0.89 (0.56, 1.42). Moreover, the average weight loss in subjects (in both the lorcaserin and placebo groups) who developed FDA-defined VHD was higher than the average weight loss in subjects who did not develop VHD. Change in body weight or BMI may explain the higher incidence of FDA-defined VHD in lorcaserin-treated subjects.

While it is true that the upper bound of the 95% confidence interval for FDA-defined VHD exceeds the 50% threshold the Division initially set as an acceptable level of risk, on the whole, the echocardiographic data from the lorcaserin program provide reasonable assurance that this drug is not associated with the degree of risk for VHD observed with dexfenfluramine or fenfluramine.

Taking into account the *in-vitro* receptor, nonclinical, and clinical data, I do not believe that lorcaserin is associated with a prohibitive risk for FDA-defined VHD. However, I do believe additional echocardiographic data should be obtained to provide a more precise estimate (i.e., tighter confidence interval) of lorcaserin's effect on valvular morphology and function. This could be done in a postmarking cardiovascular outcomes trial.

Primary Pulmonary Hypertension

Some anorexigens, including dexfenfluramine and fenfluramine, have been associated with an increased risk for the development of primary pulmonary hypertension (PPH), a rare but usually fatal disease.[3] As Dr. Golden discusses in her review, it is estimated that no more than 1 in 1000 individuals exposed for more than 3 months to fenfluramine or dexfenfluramine developed PPH. The mechanism(s) responsible for fenfluramine and dexfenfluramine-

[2] Singh JP, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999 Mar 15; 83(6): 897-902.
[3] Abenhaim L, et al. Appetite-suppressant drugs and the risk for primary pulmonary hypertension. International Primary Pulmonary Hypertension Study Group. N Engl J Med August 29;335:609-616.

associated PPH are not well defined. Yet, some evidence suggests that activation of the $5HT_{2A}$ or $5HT_{2B}$ receptors may play a causative role. Although cardiac catheterization is required to definitively diagnose PPH, pulmonary artery systolic pressure (PASP) of 27-50 mmHg suggest *possible* PPH and values greater than 50 mmHg suggest *likely* PPH.

As shown in the following table extracted from Dr. Golden's review, there was a slightly higher percentage of lorcaserin- compared with placebo-treated subjects who developed elevated PASP values during BLOOM and BLOSSOM.

Subjects with Elevated PASP Values

	Lorc 10 BID	**Pbo**
Week 52	N=1838	N=1632
≥ 35 mmHg	35 (1.9)	24 (1.5)
≥ 40 mmHg	5 (0.3)	3 (0.2)
≥ 45 mmHg	2 (0.1)	1 (0.1)
≥ 50 mmHg	2 (0.1)	0
≥ 55 mmHg	0	0
≥ 60 mmHg	0	0

In her review, Dr. Golden evaluates the case narratives for the two lorcaserin-exposed subjects who developed PASPs > 50 mmHg. Based on this information, it is difficult to conclude that lorcaserin was a probable or even possible cause of the increased PASP readings.

As noted by Dr. Golden, one patient from the BLOOM-DM trial who was treated with lorcaserin 10 mg once daily had an increase from baseline in PASP ≥ 60 mmHg. Given this patient's ostensible history of COPD it is difficult to assess lorcaserin's role in the elevation of PASP.

Given the size and duration of the clinical development program, it is safe to assume that lorcaserin is not associated with an increase in the risk of PPH to a degree observed with fenfluramine and dexfenfluramine. But given the rarity of PPH, it would take wide-spread use of lorcaserin before one could determine if the drug is associated with a small or modest increase in risk for this condition. At this point, PPH remains a theoretical risk for lorcaserin.

Serotonin Syndrome

Serotonin syndrome presents as a constellation of signs and symptoms including agitation, tachycardia, hypertension, tremor, and hyperreflexia.[4] In its severest form serotonin syndrome can be fatal. A variety of mechanisms have been suggested to explain the pathophysiology of serotonin syndrome; however, activation of the $5HT_{2A}$ and $5HT_{1A}$ receptors is likely involved. Given lorcaserin's 5HT receptor binding and activation profile, serotonin syndrome is a potential risk, albeit perhaps a remote one. As noted in Dr. Golden's review, there were 2 cases from the lorcaserin development program that investigators considered to fall within the spectrum of serotonin toxicity. Both subjects were randomized to lorcaserin 10 mg BID. One subject was taking dextromethorphan, a serotonergic compound associated with serotonin

[4] Boyer EW., et al. The serotonin syndrome. N Engl J Med. 2005 March 17;352:1112-1120.

syndrome when used as monotherapy. It is worth noting that lorcaserin was shown in a drug-drug interaction study to double the plasma concentrations of dextromethorphan through its inhibition of CYP2D6-mediated drug metabolism.

In an attempt to reduce the risk for serotonin syndrome, it was considered prudent to limit the use of concomitant serotonergic drugs – e.g., SSRIs, SNRIs – during the lorcaserin phase 3 clinical trials. Therefore, until additional controlled clinical trial and real-world experience clarify the drug's potential to cause serotonin syndrome, the labeling will recommend extreme caution if coadministration of lorcaserin with other serotonergic compounds is clinically warranted.

Cardiovascular Risk

The Sibutramine Cardiovascular Outcomes (SCOUT) trial, published in 2010, found that sibutramine increased the risk for major adverse cardiovascular events in an at-risk population.[5] Based on these data the agency determined that sibutramine's benefit-risk profile was unfavorable. Abbott Laboratories removed sibutramine from the market in October 2010.

This experience heighted the Division's concern about the cardiovascular safety of drugs used for the long-term treatment of obesity. Of particular concern are sympathomimetics whose effect on body weight is not sufficient to reduce blood pressure relative to treatment with placebo, as was the case with sibutramine and another obesity drug recently reviewed by the Division.

Historically, patients enrolled in obesity drug clinical trials have largely been middle-aged Caucasian women at low short-term risk for cardiovascular disease. This was the case for the lorcaserin development program. Consequently, there were a small number of major adverse cardiovascular events recorded during the long-term clinical trials.

Nonetheless, given the recent concern surrounding sibutramine, the sponsor provided a post-hoc adjudication of major adverse cardiovascular events from BLOOM and BLOSSOM. An independent committee blindly evaluated 25 cases, including 19 potential ischemic events, four potential cerebrovascular events, and two deaths. Following adjudication there were 11 cases determined to reflect cerebrovascular or cardiac events. Based on these data, the odds ratio for major adverse cardiovascular events for lorcaserin versus placebo was 0.63 (95% CI, 0.19, 2.12).

Although there were too few events from the phase 3 clinical trials to draw definitive conclusion regarding lorcaserin's effect on risk for cardiovascular disease, the point estimate for cardiovascular risk was below unity and in general all the biomarkers of cardiovascular risk improved with lorcaserin compared with placebo treatment. The available data do not raise concern that lorcaserin will increase the risk for major adverse cardiovascular events.

[5] James WP., et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med. 2010 September 2;363:905-917.

Common Adverse Reactions

Commonly-reported adverse reactions from the phase 3 clinical trials that occurred more frequently in lorcaserin- versus placebo-treated subjects included nausea, diarrhea, constipation, dry mouth, headache, fatigue, dizziness, and hypoglycemia (in type 2 diabetics).

8. Advisory Committee Meeting

A second EMDAC meeting for lorcaserin was held on 10 May 2012. The meeting focused on the readjudicated preclinical mammary data, a study of lorcaserin levels in the plasma and cerebrospinal fluid of humans, and the results from BLOOM-DM.

When asked if they believed that the benefits of lorcaserin outweighed the risks when used in a population of overweight and obese subjects, 18 panel members voted "yes" and 4 voted "no", with one abstention. Several committee members who voted in favor of approval recommended that a risk evaluation and mitigation strategy (REMS) be instituted, primarily to monitor cardiac valve status. I address this recommendation in section 10 below.

Because a March 2012 EMDAC recommended that all future obesity drugs be formally evaluated for cardiovascular risk pre-approval, the 10 March 2012 EMDAC was asked if they thought that a pre-approval cardiovascular outcomes trial was justified for lorcaserin. The general consensus was that a pre-approval assessment was not justified and that a cardiovascular outcomes trial should be conducted in the post-approval setting. I agree with this judgment. Many of the committee members who were at the March 2012 EMDAC and recommended that obesity drugs be evaluated pre-approval for cardiovascular risk also took part in the second lorcaserin advisory committee meeting and were comfortable with a post-approval assessment of risk for lorcaserin.

As of this writing, the agency has not formulated an official policy regarding the March 2012 EMDAC recommendation that obesity drugs be assessed for cardiovascular risk in a manner similar to that for diabetes drugs - i.e., the ruling out of pre- and post-approval degrees of cardiovascular risk.

9. Pediatrics

Regarding the Pediatric Research Equity Act (PREA), a waiver was granted for the study of children ages 6 years and below, as medication is not the recommended modality of treatment for obese children in this age range. Deferrals were granted for the study of adolescents aged 12 to 17 years and children aged 7 to < 12 years. A juvenile animal study and single-dose pharmacokinetics studies in the pediatric population need to be completed prior to initiation of the clinical efficacy and safety studies in adolescents and children. The approach to the pediatric evaluation of lorcaserin was discussed with and approved by the Pediatric Review Committee (PeRC).

10. Other Relevant Regulatory Issues

The Office of Surveillance and Epidemiology and the Office of Prescription Drug Promotion evaluated the proposed tradename, Belviq. They found the name acceptable. I agree with this assessment.

Dr. Golden notes in her review that the sponsor has certified that no investigator from the phase 3 pivotal trials has entered into a financial agreement with the sponsor.

Routine inspection of clinical sites by the Office of Scientific Investigation did not uncover any significant deficiencies or irregularities in reporting of clinical data.

The Controlled Substance Staff are recommending that lorcaserin be placed in Schedule IV of the Controlled Substance Act. As stated by Dr. Bonson in her review, "After review of all abuse-related data in the two submissions for NDA 22-529, CSS concludes that lorcaserin is a drug with hallucinogenic properties, that it has abuse potential and that it can produce psychic dependence." Lorcaserin cannot be legally marketed until the Drug Enforcement Agency makes its determination of lorcaserin's scheduling.

Although at least one advisory committee member at the 10 May 2012 meeting recommended that a risk evaluation and mitigation strategy (REMS) be instituted so that patients are followed with serial echocardiograms, as detailed in her memorandum of 18 June 2012, Dr. Amy Egan, the Deputy Division Director for Safety, does not believe that the available safety data for lorcaserin justify a REMS. This opinion is shared by colleagues in the Office of Surveillance and Epidemiology and by senior management in the Office of New Drugs and the Center for Drug Evaluation and Research who attended a Medical Policy Council meeting on 29 May 2012.

I agree that the totality of the lorcaserin nonclinical and clinical data do not support a REMS, specifically one related to routine echocardiographic monitoring. In addition to the data not supporting a REMS, one needs to consider the possibility that serial echocardiograms will have negative unintended consequences – e.g., detection of small amounts of transient valvular regurgitation that are not clinically significant but are sufficient to cause unnecessary additional testing and anxiety among healthcare providers and patients.

The sponsor will be required to conduct 6 postmarketing studies: a preclinical juvenile animal study; two pharmacokinetics studies in pediatric patients; two clinical efficacy and safety studies in children and adolescents; and a cardiovascular outcomes trial.

11. Labeling

Some key features of the approved labeling include:

The indication will be for chronic weight management (b) (4)

(b) (4)

[redacted] (b) (4) The newly-worded indication aligns with the recommendation made in the agency's 2007 draft drug guidance.

Limitations of use statements will highlight 1) that the safety of lorcaserin when used with other products intended for weight loss – prescription drugs, nonprescription drugs, and herbal or dietary supplements - has not been determined and, 2) that the effect of lorcaserin on cardiovascular morbidity and mortality has not been determined.

In an effort to limit unnecessary exposure to lorcaserin, the labeling will state that patients who do not lose at least 5% of baseline body weight by 12 weeks of lorcaserin therapy discontinue the drug, as it is unlikely that they will achieve and sustain clinically-meaningful weight loss with continued treatment.

12. Decision/Action/Risk Benefit Assessment

The data submitted in the original lorcaserin application did not support a favorable benefit-risk profile for the drug. The potential risks for breast and brain cancer outweighed lorcaserin's modest and perhaps transient weight-loss efficacy.

The blinded readjudication of the mammary tumor data by a five-panel PWG sufficiently clarified the uncertainty regarding lorcaserin's potential to cause breast cancer. The "new" data provide an adequate safety margin for breast adenocarcinoma and remove this issue as an obstacle to approval. With respect to astrocytomas, the data obtained from the 11 subjects who took lorcaserin and had drug levels measured in serum and cerebrospinal fluid, eliminates concern about lorcaserin's potential to increase the risk for brain cancer. The safety margin for astrocytomas is 70-times the proposed clinical dose of lorcaserin. Hence, brain cancer is no longer a concern.

In addition to the sponsor adequately addressing the safety concerns generated from the rat carcinogenicity study, the complete response submission included data from a long-term clinical study in subjects with type 2 diabetes. Although the weight loss effect of lorcaserin was modest in this population, the mean placebo-subtracted reduction in HbA1c of approximately 0.5% is similar to the efficacy observed with some approved anti-diabetic medications. The drug will benefit some obese and overweight patients with type 2 diabetes.

The clinical data from diabetics, together with the efficacy data from overweight and obese non-diabetics, are sufficient to offset the remaining known potential risks of lorcaserin. These include a slight numerical imbalance in the development of FDA-defined valvulopathy, a potential risk for serotonin syndrome, particularly if used in combination with other serotonergic medications, and an increased incidence of adverse reactions related to cognition and mood. As such, the drug should be approved.

In addition to providing a thorough assessment of lorcaserin's effect on the atherothrombotic process, a postmarking required cardiovascular outcomes trial will provide additional clarity regarding lorcaserin's effect on valvular regurgitation and its potential to cause serotonin

syndrome, particularly when coadministered with commonly-used antidepressants such as SSRIs and SNRIs.

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/s/

ERIC C COLMAN
06/26/2012