CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Options Review

Date:	June 8, 2012
Reviewer(s):	Joyce Weaver, Pharm.D., Risk Management Analyst (RMA) Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., RMA Team Leader, DRISK
Division Director:	Claudia Manzo, Pharm.D., Division Director, DRISK
Drug Name(s):	Lorcaserin
Therapeutic Class:	Anorectic
Dosage and Route:	10mg lorcaserin tablet orally twice daily
Application Type/Number:	NDA 22529
Submission Number:	Class 2 Resubmission of Original Application
Applicant/sponsor:	Arena Pharmaceuticals
OSE RCM #:	2012-172

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EXECUTIVE SUMMARY

Lorcaserin is a drug under consideration as an adjunct to diet and exercise for the treatment of obesity and for the treatment of overweight patients with two or more weight-related comorbid conditions. In the pooled analysis of the clinical echocardiographic data, the relative risk for FDA-defined valvular heart disease[1] was 1.16, with a 95% confidence interval of 0.81 to 1.67. The upper bound of the confidence interval exceeded the 1.5 upper bound specified by the FDA to rule out cardiac valvulopathy. At the May 10, 2012 meeting of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC), valvulopathy was identified by some committee members as a risk that might require a REMS. The issue was discussed at a meeting of the CDER Medical Policy Council on May 29, 2012. The Medical Policy Council concluded that a REMS is not appropriate at this time to mitigate the potential risk of valvulopathy. We agree with this decision because the evidence to date suggests the risk of valvulopathy is unlikely. Following patients with echocardiography to assess the potential of the drug to cause valvulopathy on a population basis would be better accomplished within a controlled trial.

1 INTRODUCTION

1.1 BACKGROUND

Lorcaserin is under consideration as an adjunct to diet and exercise for the treatment of obesity and for the treatment of overweight patients with two or more weight-related comorbid conditions.

1.2 REGULATORY HISTORY

The application for lorcaserin was originally filed December 22, 2009. The Agency issued a complete response letter for the application on October 22, 2010. The CR letter cited a concern for a pre-clinical signal for breast and brain tumors, and the need to submit the final study report for an ongoing trial of lorcaserin in overweight and obese individuals with type 2 diabetes to better assess the risk-benefit profile of lorcaserin. A complete, class 2 response to the October 22, 2010, action letter was filed December 27, 2011. In the resubmission, the sponsor submitted reassuring data regarding the pre-clinical signal for breast and brain tumors. According to the pre-clinical review, the safety margin supported by the data is regarded as having negligible risk to patients.

The user fee goal date for the resubmitted application is June 27, 2012.

The EMDAC met on May 10, 2012 to consider the application. The committee voted 18-4 with one abstention for approval.

1.3 PRODUCT LABELING

[1] FDA-defined valvular heart disease is mitral regurgitation greater than mild, or aortic regurgitation greater than trace

The proposed labeling includes a warning/precaution for valvular heart disease:

> Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in patients who took [redacted] serotonergic drugs [redacted] The etiology of the regurgitant valvular disease is thought to be by activation of 5-HT2B receptors. BELVIQ is selective for 5-HT2C receptors as compared to 5-HT2B receptors; [redacted]. In [redacted] clinical trials, [redacted] of patients receiving BELVIQ and 2.0[redacted]% of patients receiving placebo developed echocardiographic criteria for [redacted] valvular regurgitation at one year: none of these patients was symptomatic.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- October 20, 2010 Fred Alavi, Ph.D. lorcaserin pharmacology/toxicology NDA review and evaluation
- October 20, 2010 Todd Bourcier, Ph.D. secondary lorcaserin pharmacology/toxicology NDA review and evaluation
- FDA briefing document for May 10, EMDAC Meeting

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The three major trials with lorcaserin are summarized below:

- A placebo-controlled two-year trial was conducted in 3182 obese or overweight adult patients to assess the effect of lorcaserin on weight. Patients were randomized 1:1 to lorcaserin 10 mg BID or placebo. After one year of treatment, the lorcaserin group was re-randomized 2:1 to lorcaserin 10 mg BID or placebo, stratified by 5% weight loss responder status. The placebo group remained on placebo for the second year.
- A placebo-controlled one-year trial was conducted in 4008 obese or overweight adult patients. Patients were randomized 2:1:2 to lorcaserin 10 mg BID, lorcaserin 10 mg QD, or placebo.
- A placebo-controlled one-year trial was conducted in 604 obese or overweight adult patients with type 2 diabetes mellitus managed with oral hypoglycemic agents.

The mean placebo-subtracted weight loss with lorcaserin in the trials was 3.0% to 3.7% (thus not achieving the FDA efficacy criteria of 5%). The FDA categorical weight loss efficacy criteria was met, with 47% of lorcaserin patients compared with 23% of placebo patients losing 5% or more of their baseline body weight.

3.2 SAFETY CONCERNS

The safety issue cited by members of the advisory committee as possibly requiring mitigation with a REMS is valvular heart disease, a known safety issue with a related drug, fenfluramine. However, the valvulopathy that occurs with fenfluramine is thought to be associated with activity at the 5-hydroxytryptamine 2B (5HT2B) receptor. Lorcaserin is a 5-hydroxytryptamine 2C (5HT2C) agonist. The lingering concern regarding valvulopathy stemmed from uncertainty over the specificity of lorcaserin for the 5HT2C receptor.

In his 2010 pharm/tox review, Dr. Alavi noted that rat heart tissue was examined for potential evidence of valvulopathy. He stated that there was no evidence of valvulopathy in rats treated with lorcaserin doses up to 50 mg/kg, a dose 24 to 40 times the proposed human clinical dose. In his secondary pharm/tox review, Dr. Bourcier agreed, but noted that there are limitations in the ability to screen for drug-induced valvulopathy in animals, and that the tissue examinations were not definitive. Additional pre-clinical data provided with the 2011 resubmission indicate that therapeutic doses of lorcaserin are expected to remain selective 5HT2C. According to Dr. Alavi's review, lorcaserin preferentially activates 5HT2C with 45- to 90-fold greater potency compared to 5HT2B.

In the pooled analysis of the clinical echocardiographic data, the relative risk for FDA-defined valvular heart disease[2] was 1.16, with a 95% confidence interval of 0.81 to 1.67.

4 DISCUSSION

The preponderance of evidence regarding cardiac valvulopathy shows that lorcaserin is unlikely to cause valvulopathy at clinically relevant doses. Nevertheless, because the point estimate for FDA-defined valvular heart disease was 1.16 in the pooled clinical echocardiographic data, and the upper bound of the 95% confidence interval was 1.67, a lingering concern remains that there might some risk of valvulopathy.

The applicant did not propose a REMS for lorcaserin. During the May 10, 2012 EMDAC meeting discussion regarding the lorcaserin application, four of the 22 EMDAC members considering the application voiced support for approving the application with a REMS to mitigate the possible risk of valvulopathy. The committee members did not agree on the elements of a REMS, with one committee member supporting an education program, one member supporting the use of elements to assure safe use, including following patients with echocardiograms to monitor for the development of valvulopathy, and two members supporting the idea of REMS without specifying the elements they thought would be appropriate.

REMS should be used when there is the potential to mitigate a serious risk. At this point we do not see value in requiring a REMS to monitor patients for a potential risk particularly since the evidence to date suggests the risk of valvulopathy is unlikely. Following patients with echocardiography to assess the potential of the drug to cause valvulopathy on a population basis would be better accomplished within a controlled trial. We recommend that patients who participate in the lorcaserin cardiovascular outcomes trial (to be conducted in the post-marketing setting) be followed with echocardiography, if this element is feasible in the context of this trial.

[2] FDA-defined valvular heart disease is mitral regurgitation greater than mild, or aortic regurgitation greater than trace

The issue was discussed at a meeting of the CDER Medical Policy Council on May 29, 2012. Participants concluded that a REMS is not needed to mitigate the potential risk of valvulopathy because the evidence suggests there is unlikely to be such a risk.

5 CONCLUSION

We agree with the recommendation of the CDER Medical Policy Council to not institute a REMS for lorcaserin. Should new safety information emerge regarding this risk, we ask that you consult us regarding the need for a REMS.

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/s/

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06/08/2012

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