CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022529Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From:	Amy M. Taylor, MD, MHS, Medical Officer Pediatric and Maternal Health Staff
Through:	Lisa Mathis, MD, OND Associate Director Pediatric and Maternal Health Staff
NDA Number:	22-529
Drug:	Belviq (lorcaserin HCl)
Sponsor:	Arena Pharmaceuticals
Proposed indication:	Weight management in obese patients with an initial body mass index ≥ 30 kg/m^2 and overweight patients with a body mass index ≥ 27 kg/m^2 in the presence of at least one weight related comorbid condition.
Dosage form and route of administration:	10 mg oral capsules
Division Consult Request:	The Division of Metabolic and Endocrine Products (DMEP) requests assistance with preparation for PeRC review and input regarding labeling.

PMHS worked with DMEP in preparing paperwork for the review of the pediatric plan by the Pediatric Review Committee (PeRC) which took place on May 16, 2012. The PeRC agreed with the Division's plan to waive the required studies under PREA in pediatric patients less than 7 years because the product does not represent a meaningful benefit and is not likely to be used by substantial numbers in this age group and to defer studies in patients 7 to 17 years because the product is ready for approval in adults. In addition, the PeRC recommended that:

- studies include an assessment of the effect of the drug on cognition and learning, monitoring of prolactin serum levels and hemoglobin A1C

- investigators use a standardized approach to Tanner staging
- the juvenile rat study include a post-natal dose at day 14
- reproductive performance be requested in the animal studies

PMHS participated in the labeling meetings for lorcaserin and provided the following recommendation for the Highlights section and section 8.4 Pediatric Use.

> **Highlights:**
> Pediatric Use: Safety and effectiveness not established and use not recommended in 7-17 year olds; should not be administered in 0 to 6 year olds (8.4)
>
> **8.4 Pediatric Use**
>
> Safety and effectiveness of BELVIQ in pediatric patients below the age of 18 years have not been established, and the use of BELVIQ is not recommended in pediatric patients.
>
> (b) (4)

The above language reflects that which was reviewed by PeRC. The Division may wish to edit this language. However, a statement that "safety and effectiveness of Belviq in pediatric patients below the age of 18 years have not been established" must be included in section 8.4 Pediatric Use.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY M TAYLOR
06/26/2012

LISA L MATHIS
06/28/2012

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 022529
Name of Drug: Belviq (lorcaserin hydrochloride) tablets, 10 mg
Applicant: Arena Pharmaceuticals

Labeling

Submission Date: **May 23, 2012**
Receipt Date: **May 24, 2012**

Background and Summary Description:
Belviq (lorcaserin hydrochloride) is a new molecular entity that is a 5-hydroxytryptamine 2C ($5HT_{2C}$) receptor agonist affecting those receptors in the appetite center of the brain. The indication is as an adjunct to diet and exercise for weight management, including weight loss and maintenance, in obese patients with an initial body mass index greater than 30 kg/m^2, 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, cardiovascular disease, glucose intolerance, sleep apnea, type 2 diabetes). The NDA was originally submitted on December 18, 2010 and, after extensive review and an advisory committee meeting, the application received a complete response (CR) letter on October 22, 2011. The company resubmitted a complete response on December 23, 2011 (received December 27, 2011). The resubmission underwent an intense 6-month review and was taken to another advisory committee meeting. The resubmission addressed all concerns stated in the CR letter and the second advisory committee voted for approval

Review

Based on comments received at the May 10, 2012, advisory committee meeting, the applicant submitted a revised draft package insert (PI) and patient package insert (PPI). These documents were subjected to in-depth review and substantially revised by the entire Belviq review team. On June 26, 2012, the FDA revised version of the PPI was sent to Arena Pharmceuticals. The company agreed to all the revisions. On June 27, 2012, the final iteration of the FDA revised PI was sent to Arena and they agreed to all FDA proposed changes. There was no document from the company for this project manager to review.

Please note that Ann Marie Trentacosti from the SEALD labeling team was involved in all aspects of formatting and content of the PI and PPI. The format conforms to PLR.

Recommendations

Arena Pharmaceuticals accepted the FDA revised PI and PPI. These were attached to the approval letter

Regulatory Project Manager: Pat Madara Date: June 28, 2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA J MADARA
06/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	022529
Product Name:	Belviq (lorcaserin hydrochloride) tablets
PMR/PMC Description:	A clinical pharmacology trial under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic parameters related to Belviq dosing in pediatric patients ages 12 to 17 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	03/31/2013
	Study/Trial Completion:	12/31/2013
	Final Report Submission:	03/30/2014
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Belviq is ready for approval in adults and the pediatric studies have not been completed.

Because Belviq has been associated with neuropsychiatric adverse events and increases in prolactin, pediatric safety and efficacy studies cannot be initiated until the results of the juvenile animal study PMR have been submitted and reviewed; however, a single dose pharmacokinetic study to determine dose(s) for the safety and efficacy study can proceed in the pediatric patients ages 12 to 17 (inclusive).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to establish the pharmacokinetics of Belviq in the pediatric subpopulation, ages 12 to 17 (inclusive), to determine appropriate dosing in this age group for the safety and efficacy study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology trial under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic parameters related to Belviq dosing in pediatric patients ages 12 to 17 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in pediatric patients ages 12 to 17 (inclusive).

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	022529
Product Name:	Belviq (lorcaserin hydrochloride) tablets
PMR/PMC Description:	A clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic parameters related to Belviq dosing in pediatric patients ages 7 to 11 (inclusive). Data from the study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population. This study may not be initiated until the results from the Belviq clinical pharmacology study in pediatric patients ages 12 to 17 (inclusive) have been submitted and reviewed by the Agency.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	09/30/2014
	Study/Trial Completion:	06/30/2015
	Final Report Submission:	09/30/2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Belviq is ready for approval in adults and the pediatric studies have not been completed.

   Because Belviq has been associated with neuropsychiatric adverse events and increases in prolactin, pediatric safety and efficacy studies cannot be initiated until the results of the juvenile animal study PMR have been submitted and reviewed. In addition, this single dose pharmacokinetic study to determine dose(s) for the safety and efficacy study in the pediatric patients ages 7 to 11 (inclusive), should not be intitiated until after the pharmacokinetic results from the adolescent (12-17 years of age) clinical pharmacology study have been submitted and reviewed by the Agency.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to establish the pharmacokinetics of Belviq in the pediatric subpopulation, ages 7 to 11 (inclusive), to determine appropriate dosing in this age group for the safety and efficacy study.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical pharmacology study under the Pediatric Research Equity Act (PREA) to assess pharmacokinetic parameters related to Belviq dosing in pediatric patients ages 7 to 11 (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population. This study may not be initiated until the results from the Belviq clinical pharmacology study in pediatric patients ages 12 to 17 (inclusive) have been submitted and reviewed by the Agency.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
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PMR/PMC Development Coordinator:

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PMR/PMC Development Template

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NDA/BLA #	022529
Product Name:	BELVIQ (lorcaserin hydrochloride) tablets
PMR/PMC Description:	A 52-week randomized, double-blind, placebo-controlled pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of Belviq for the treatment of obesity in pediatric patients ages 12 to 17 years (inclusive). This study may not be initiated until the juvenile animal study PMR and the clinical pharmacology study (pediatric patients ages 12 to 17 years) PMR have been submitted and reviewed.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/30/2015
	Study/Trial Completion:	09/30/2017
	Final Report Submission:	03/30/2018
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Belviq is ready for approval for use in adults. However, pediatric studies have not been completed.

   Belviq has been associated with neuropsychiatric adverse events and increases in prolactin. Studies in this age group should not be initiated until the results of the juvenile animal study PMR have been submitted and reviewed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to establish the safety and efficacy of Belviq in the pediatric subpopulation after 1 year of treatment

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 52-week randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of Belviq in adolescents, ages 12 – 17 years (inclusive) with age- and sex-matched BMI ≥ 95th percentile or BMI ≥ 30 kg/m^2 (whichever is lower), and at least one major co-morbidity (such as type 2 diabetes, pre-diabetes, sleep apnea, dyslipidemia, essential hypertension or non-alcoholic fatty liver disease). Subjects with obesity associated with known chromosomal, endocrine or metabolic causes will be excluded. This study may not be initiated until the results of the juvenile animal study PMR and the clinical pharmacology study (pediatric patients ages 12 to 17 years) PMR have been submitted and reviewed.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Subpopulation: Pediatric patients 12-17 (inclusive) with obesity with co-morbidities

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
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☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

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NDA/BLA #	022529
Product Name:	Belviq (lorcaserin hydrochloride) tablets
PMR/PMC Description:	A 52-week randomized, double-blind, placebo-controlled pediatric study under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of Belviq for the treatment of obesity in pediatric patients ages 7 to 11 (inclusive). This study may not be initiated until results from the Belviq adolescent safety and efficacy study and the clinical pharmacology study (pediatric patients ages 7 to 11 years) have been submitted and reviewed by the Agency.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/30/2018
	Study/Trial Completion:	10/31/2020
	Final Report Submission:	04/30/2021
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Belviq is ready for approval for use in adults. However, pediatric studies have not been completed.

   Belviq has been associated with neuropsychiatric adverse events and increases in prolactin. Studies in this age group should not be initiated until results from the Belviq adolescent safety and efficacy study have been submitted and reviewed by the Agency.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to establish the safety and efficacy of Belviq in the pediatric subpopulation after 1-year of treatment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

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     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A 52-week randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of Belviq in children, ages 7 - 11 years (inclusive) with age- and sex-matched BMI ≥ 99th percentile with a major co-morbidity (such as type 2 diabetes, pre-diabetes, sleep apnea, dyslipidemia, essential hypertension or non-alcoholic fatty liver disease). Subjects with obesity associated with known chromosomal, endocrine or metabolic causes will be excluded. This study may not be initiated until results from the Belviq adolescent safety and efficacy study have been submitted and reviewed by the Agency.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
Subpopulation: Pediatric patients ages 7-11 (inclusive) with obesity with co-morbidities

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
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PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	022529
Product Name:	Belviq (lorcaserin hydrochloride) tablets
PMR/PMC Description:	Lorcaserin juvenile animal study with behavioral, neurological, (b) (4) (b) (4) assessment.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	06/30/2013
	Study/Trial Completion:	09/30/2014
	Final Report Submission:	12/31/2014
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The current clinical indication excludes pediatric use. Pediatric clinical studies are planned for patients ages 7-17 years old (inclusive). Neurobehavioral and sexual development continue throughout childhood and adolescence and drug-related toxicity in adults may differ for these endpoints. Juvenile animal studies with lorcaserin administration are required prior to multiple dose pediatric clinical trials to investigate effects on behavior, learning and memory, and general nervous system and reproductive organ development.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

(b) (4) The juvenile animal study will assess physical development, sexual maturation, reproductive performance, and histological assessment of endocrine tissues, (b) (4), to address this risk. As a CNS active drug, alteration of serotonin synaptic activity could potentially have long lasting neuronal behavioral effects later in life. The juvenile animal study will also assess neurobeharvioral endpoints including those that address learning, memory, and motor development, as well as histological assessment of brain tissue.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☒ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study in juvenile male and female rats administered lorcaserin from post-natal day 14 to 90, at exposures ranging from 1x to 20x clinical exposure. A non-dosing recovery period should be included in the study design.

- Assess neurobehavioral endpoints, including those addressing learning, memory, and motor development (modified Irwin's, motor activity, passive avoidance, water maze or tail suspension test)

- Assess physical development and sexual maturation during treatment, and mating and fertility (i.e., reproductive performance) after treatment.

- Conduct histological assessment of brain (multiple brain sections capturing all major areas) and endocrine tissues (b) (4)) after dosing and recovery periods.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	022529
Product Name:	Belviq (lorcaserin hydrochloride) tablets
PMR/PMC Description:	A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with Belviq on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese subjects with cardiovascular disease or multiple cardiovascular risk factors. Serial echocardiographic assessments should also be included.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/31/2013
	Study/Trial Completion:	12/31/2017
	Final Report Submission:	12/31/2018
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

In a cohort of overweight and obese adults with mostly low-to-moderate baseline cardiovascular risk treated with Belviq, the observed changes in blood pressure and post-hoc analyses of major adverse cardiovascular events (MACE) were directionally favorable and similar to placebo. Mean heart rate decreased with Belviq treatment versus placebo. It is unknown what the clinical significance of Belviq's cardiovascular and metabolic effects will be in subjects at high risk for cardiovascular events treated long-term with Belviq. Ultimately, only a long-term, cardiovascular outcome trial can define the effect of Belviq treatment on risk for MACE in an obese at-risk population.

At clinical doses, lorcaserin is a selective 5HT2C receptor agonist. The 5HT2C receptor is a member of the family of serotonin receptors that includes 5HT2B – agonism of which has been identified as the likely culprit for fenfluramine-, dexfenfluramine-, and ergotamine-associated valvular heart disease (VHD). In the pooled analysis of the Phase 3 echocardiographic data, the relative risk for FDA-defined valvular heart disease (VHD), defined as mitral regurgitation greater than mild or aortic regurgitation greater than trace was 1.16, with a 95% confidence interval (CI) of 0.81 to 1.67. This upper bound exceeds the 1.5 upper bound requested by FDA to rule out an excess risk of VHD.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The primary objective of a cardiovascular outcome trial is to evaluate the effect of long-term treatment with Belviq on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese subjects with cardiovascular disease or multiple cardiovascular disease risk factors. Serial echocardiographic assessments should also be included to assess for valvular regurgitation associated with Belviq.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, double-blind, placebo-controlled trial to evaluate the effect of long-term treatment with (b) (4) on the incidence of major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) in obese subjects with cardiovascular disease or multiple cardiovascular risk factors.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
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☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

AMY G EGAN
06/22/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DCDP)
Division of Consumer Drug Promotion (DCDP)

****Pre-decisional Agency Information****

Memorandum

Date: June 22, 2012

To: Patricia Madara – Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah – Regulatory Review Officer, DCDP
Kendra Y. Jones – Regulatory Review Officer, DPDP

Subject: NDA 022529
OPDP labeling comments for BELVIQ (lorcaserin hydrochloride) tablets, for oral use

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In response to DMEP's January 17, 2012, consult request, OPDP has reviewed the proposed draft Prescribing Information (PI) and Patient Information (PPI) for BELVIQ (lorcaserin hydrochloride) tablets, for oral use.

Comments on the proposed draft PI and PPI are provided directly on the attached marked version below.

Thank you for the opportunity to comment on this label.

If you have any questions regarding the proposed draft PI, please contact Kendra Jones at 301-796-3917 or Samuel.Skariah@fda.hhs.gov.

If you have any questions regarding this proposed draft PPI, please contact Kendra Jones at 301-796-3917 or Kendra.Jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
06/22/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 21, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Patricia Madara, DMEP

Subject: QT-IRT Consult to (application number)

This memo responds to your consult to us dated June 15, 2012 regarding sponsor's proposed labeling for NDA 22529. The QT-IRT reviewed the following materials:

- Your consult
- Sponsor's proposed labeling
- IRT QT review for IND 69888 dated 01/07/2008

QT-IRT Comments for DMEP

QT-IRT has reviewed the TQT study for lorcaserin under IND 69888 and concluded that lorcaserin does not have a QT prolongation effect. Sponsor has proposed the following labeling language in the package insert:

QT-IRT has the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

Cardiac Electrophysiology: The effect of multiple oral doses of lorcaserin 15 mg and 40 mg once daily on QTc interval was evaluated in a randomized, placebo- and active- controlled

(moxifloxacin 400 mg) four-treatment arm parallel thorough QT study in 244 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. The dose of 40 mg is expected to cover the high exposure clinical scenario for lorcaserin.

BACKGROUND

The information about hepatic, renal or drug-drug interactions was not available at the time of review of the study report submitted under IND 69888. Based on the information submitted in the NDA 22529, the dose of 40 mg q.d. appears to be adequate to cover the worst case exposure scenario for lorcaserin following a therapeutic dose of 10 mg b.i.d. :

- Hepatic impairment: There is no significant effect of mild or moderate hepatic impairment on PK of lorcaserin. The half-life is increased from 12 h in healthy controls to 17 and 19 h in mild or moderate hepatic impairment, respectively. No dose adjustment is recommended for mild or moderate hepatic impairment. Lorcaserin has not been evaluated in subjects with severe hepatic impairment.
- Renal impairment: There was no significant effect of renal impairment on lorcaserin exposures. However, metabolites for lorcaserin accumulate substantially in patients with severe and end-stage renal impairment. Label recommends using caution if lorcaserin is to be used in moderate renal impairment and also mentions that lorcaserin is not appropriate for patients with severe renal impairment.
- (b) (4) [redacted]

The therapeutic dose of lorcaserin is 10 mg b.i.d. The C_{max} achieved with 40 mg q.d. in the TQT study (307 ng/mL) is ~7-fold the mean C_{max} observed with 10 mg b.i.d at steady state. The mean C_{max} (SD) of metabolite (HSO3-APP356) at 40 mg q.d. dose in the TQT study at steady state is 579 (414) ng/mL which is ~17 and 6-fold the metabolite concentrations observed in moderate and severe renal impairment, respectively after single 10 mg dose of lorcaserin. The C_{max} of HSO3 metabolite was similar (34 ng/mL) in normal and moderate renally impaired subjects after a single dose. The half-life of HSO3 metabolite increases from 36 h to 70 h when comparing normal to moderate renally impaired individuals. Considering a half life of 70 h and expecting a 9-fold accumulation in moderate renal impairment, the HSO3 metabolite exposures in moderate renal impairment should be covered by the exposures of HSO3 metabolite observed with 40 mg q.d. at steady state in the TQT study.

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

NITIN MEHROTRA
06/21/2012

MONICA L FISZMAN
06/21/2012

NORMAN L STOCKBRIDGE
06/21/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**June 15, 2012**
To:	Mary Parks, MD, Director **Division of Metabolism and Endocrinology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, BSN, MSBA Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, RN, BSN, MSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	BELVIQ (lorcaserin hydrochloride)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 22529
Applicant:	Arena Pharmaceuticals, Inc.

1 INTRODUCTION

On December 18, 2009, Arena Pharmaceuticals, Inc. submitted an original New Drug Application (NDA) indicated for weight management, including weight loss and maintenance of weight loss, used in conjunction with a reduced-calorie diet and a program of regular exercise.

On October 22, 2010, the agency issued a Complete Response (CR) letter to the applicant based on clinical, non-clinical, and safety concerns. On December 22, 2011 the applicant resubmitted the NDA as a complete response to the deficiencies outlined in the Agency's CR action letter.

This review is written in response to a request by the Division of Metabolic and Endocrinology Products (DMEP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for BELVIQ (lorcaserin hydrochloride) tablets.

2 MATERIAL REVIEWED

- Draft BELVIQ (lorcaserin hydrochloride) PPI received on December 22, 2011 and received by DMPP on June 12, 2012
- Draft BELVIQ (lorcaserin hydrochloride) Prescribing Information (PI) received December 22, 201, revised throughout the review cycle and received by DMPP on June 12, 2012

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the PPI is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
06/15/2012

MELISSA I HULETT
06/15/2012

LASHAWN M GRIFFITHS
06/15/2012

SAFETY REVIEW MEMO

FROM:	Amy G. Egan, M.D., M.P.H. Deputy Director for Safety Division of Metabolism and Endocrinology Products (DMEP)
TO:	Curtis J. Rosebraugh, M.D., M.P.H. Director Office of Drug Evaluation II Eric Colman, M.D. Deputy Director DMEP
DATE:	June 8, 2012
SUBJECT:	Recommendation on patient labeling for BELVIQ (lorcaserin hydrochloride)
NDA #:	NDA 022529

BACKGROUND

BELVIQ (lorcaserin hydrochloride) is a new molecular entity developed for weight management. It is a first-in-class 5-hydroxytryptamine 2C (5-HT_{2C}) receptor agonist. It is believed that BELVIQ's effect on decreasing food consumption occurs by selectively activating the 5-HT_{2C} receptors in the hypothalamus. Activation of central 5-HT_{2C} receptors is associated with decreases in food intake by increasing meal-related satiety, reducing pre-meal hunger, and reducing intra-meal food intake.

BELVIQ's weight loss efficacy is modest. In three Phase 3 trials, placebo-subtracted weight loss at Week 52 was between 3.0-3.7%. Approximately 47% of patients without type 2 diabetes who were treated with Belviq lost at least 5% of their baseline body weight compared with about 23% of patients treated with placebo. In patients with type 2 diabetes, approximately 38% of patients treated with Belviq and 16% treated with placebo lost at least 5% of baseline body weight. In a dedicated trial in type 2 diabetic patients, BELVIQ produced a mean placebo-subtracted reduction in HbA1c of 0.49%.

The Agency issued a Complete Response letter after the initial review cycle due to safety concerns, including uncertainty regarding a preclinical signal for breast and brain tumors. Fenfluramine and dexfenfluramine, non-specific 5-HT_2 agonists for the treatment of obesity were removed from the U.S. market due to the occurrence of valvular heart disease, now believed to have been due to the effect of the drugs at the 5-HT_{2B} receptor. The uncertainty regarding lorcaserin's receptor selectivity, and an imbalance in FDA-defined valvulopathy not favoring BELVIQ observed in the sponsor's Phase 3 clinical trials, led to the Agency's heightened concern that use of BELVIQ may be associated with the development of valvular heart disease.

The sponsor's resubmission included receptor potency data that indicated that therapeutic exposure of lorcaserin was within the selective range for activation of 5-HT_{2C}, and that activation of 5-HT_{2A} and 5-HT_{2B} was unlikely either in the CNS or peripheral tissues.

Additional non-clinical data was submitted that identified a sufficient safety margin (24x the clinical dose) for lorcaserin-induced increases in mammary adenocarcinoma. There was no safety margin (<7x the clinical dose) for fibroadenoma; however, mechanistic studies identified prolactin as a plausible tumorigenic mode of action. And, a 70x safety margin for brain tumors was identified based on lorcaserin levels in the cerebrospinal fluid of humans.

Additional clinical data showed that the relative risk of FDA-defined valvular heart disease (VHD) at Week 52, excluding patients with baseline VHD, comparing BELVIQ-treated patients to placebo-treated patients was 1.16 (95% CI: 0.81, 1.67). While this finding was not statistically significant, it exceeded the FDA's requirement that the sponsor exclude a 50% increase in risk.

Other safety concerns that remain with BELVIQ include serotonin syndrome/neuroleptic malignant syndrome-like adverse reactions, psychiatric effects, and cognitive impairment.

At the time of NDA resubmission, the sponsor submitted a Package Insert (PI) and a Patient Package Insert (PPI). The sponsor did not propose a REMS or a Medication Guide. At the May 10, 2012 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), several committee members who voted for approval of BELVIQ indicated that the drug should be approved with a REMS. The basis for the recommendation stemmed from lingering concerns regarding the potential for BELVIQ to induce valvular heart disease given the "signal" from the clinical trial data. However, the type of REMS seemed more focused on physician education regarding the need to monitor patients for valvulopathy, and to discontinue drug should no weight loss benefit be achieved.

Subsequent to the EMDAC meeting, two meetings were held with the Division of Risk Management (DRISK) to discuss the possible need for a REMS for BELVIQ, the first on May 16th and the second on May 24th. The issue was also discussed at a Medical Policy Council meeting on May 29th.

Please refer to Dr. Joyce Weaver's June 8, 2012 REMS Options review for a complete discussion of the basis for DRISK's opinion. Dr. Weaver concludes:

> 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.

The Medical Policy Council also determined that a REMS for BELVIQ was unnecessary. Minutes from the May 29, 2012 meeting note the following:

> *Do you believe that there is justification for a REMS for Belviq?*
>
> The Council did not believe that there is a justification for a REMS for Belviq based on the efficacy and safety presented and the meeting discussion.

This memo will serve to address whether a Medication Guide, outside of a REMS, should be required for BELVIQ.

DISCUSSION

According to CFR § 208.1 (a), a Medication Guide should be required for drug products that FDA determines pose a "serious and significant public health concern." Such products typically have a Boxed Warning, or a serious side effect in the Warnings and Precautions section of the PI.

BELVIQ does not pose a serious and significant public health concern. Safety concerns identified and/or investigated with BELVIQ include:

Valvular heart disease: The preponderance of evidence is that BELVIQ is not associated with a risk for valvulopathy. This is based on our current understanding of

drug-induced valvulopathy and lorcaserin's known receptor selectivity, and on the results of echocardiographic evaluation of heart valve function in nearly 8000 patients in the BELVIQ development program that did not show a statistically significant difference in the development of FDA-defined valve abnormalities between BELVIQ- and placebo-treated patients. The serious risk of valvulopathy remains theoretical and should be addressed with physician labeling and further assessed in the sponsor's cardiovascular outcomes trial and through enhanced pharmacovigilance (as 15-day alert reports and in PADERS as an adverse event of special interest).

Serotonin syndrome/NMS: There were 2 cases of "serotonin syndrome" in the BELVIQ clinical development program. A patient in a Phase 2 study developed symptoms (tremor, palpitations, headache, and vomiting) compatible with a mild form of serotonin toxicity. A second patient in the Phase 3 BLOSSOM trial developed serotonin syndrome after initiating guaifenisin with dextromethorphan while on treatment with BELVIQ. This patient was successfully rechallenged with BELVIQ after guaifenisin and dextromethorphan were discontinued.

FDA has been inconsistent in its use of a Medication Guide to warn of the serious risk of serotonin syndrome. All currently approved selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) have Medication Guides (predicated on a Boxed Warning for suicidality), but there is inconsistency as to the inclusion of information on serotonin syndrome. Celexa (citalopram), Luvox (fluvoxamine), Lexapro (escitlopram), and Paxil (paroxetine) all include serotonin syndrome under the "What is the most important information I should know about DRUG?" section of the MG, while Pexeva (paroxetine), Prozac (fluoxetine), Sarafem (fluoxetine), and Zoloft (sertraline) do not. A Medication Guide warning of serotonin syndrome exists for Treximet (sumatriptan and naproxen sodium), but not for Imitrex (sumatriptin). The monoamine oxidase inhibitors (MAO-I) have Medication Guides for the risk of suicidality, but do not mention serotonin syndrome. Anti-psychotic medications also have Medication Guides warning of multiple risks, including mortality risk in elderly patients with dementia-related psychosis, hyperglycemia, weight gain, and lipid abnormalities, but the risk of serotonin syndrome is not mentioned. Linezolid and tramadol do not have Medication Guides, nor does lithium.

It is believed that serotonin syndrome is related primarily to overstimulation of the 5-HT_{2A} receptor. Given BELVIQ's low potential for activation of the $5HT_{2A}$ receptor at clinically relevant doses, and given the paucity of clinical trial data to support a serious safety concern at this time, this risk should be addressed with physician labeling and further assessed in the sponsor's cardiovascular outcomes trial – which will enroll patients taking pro-serotonergic medications - and through enhanced pharmacovigilance (as 15-day alert reports and in PADERS as an adverse event of special interest).

Breast neoplasms and other malignancies: Adequate safety margins for astrocytoma and breast adenocarcinoma have been established.

Psychiatric effects: While imbalances occurred in the clinical trials for serious adverse events of depression and suicidal ideation, no clear safety signal emerged. Because of BELVIQ's mechanism of action, this remains a potential adverse effect of the drug which should be addressed with physician labeling and further assessed in the sponsor's cardiovascular outcome trial and through enhanced pharmacovigilance (as 15-day alert reports and in PADERS as an adverse event of special interest).

Cognitive dysfunction: Cognitive adverse events such as impairment in attention and memory occurred 3-4 times more frequently in BELVIQ-treated versus placebo-treated patients in the Phase 3 trials. Somnolence and sedation were also reported more frequently in BELVIQ-treated versus placebo-treated patients. There were 2 cognitive-related serious adverse events in the pooled Phase 3 trials – one of "dysphasia" and one of "amnesia". These serious adverse events did not lead to study drug discontinuation. This risk should be addressed with physician labeling and further assessed in the sponsor's cardiovascular outcome trial and through enhanced pharmacovigilance (in PADERS as an adverse event of special interest).

CONCLUSION

I concur with DRISK and the Medical Policy Council that there is no basis for a REMS for BELVIQ given that the evidence to date does not suggest that BELVIQ is associated with a serious risk.

Furthermore, at this time BELVIQ does not meet the regulatory definition of a drug product for which FDA should require a Medication Guide. It is recommended that information regarding the potential for serotonin syndrome be conveyed in the PPI along with a list of medicines that should be avoided while taking BELVIQ to help mitigate this potential risk. If additional data become available that raise the level of concern regarding the risk for this toxicity, or other toxicities for which patient labeling could help mitigate risk, then FDA should consider requiring a Medication Guide.

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/s/

AMY G EGAN
06/18/2012

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

Label, Labeling and Packaging Review

Date:	May 31, 2012
Reviewer:	Reasol S. Agustin, PharmD Division of Medication Error and Prevention Analysis
Acting Team Leader	Yelena Maslov, PharmD Division of Medication Error and Prevention Analysis
Division Director	Carol Holquist, RPh Division of Medication Error and Prevention Analysis
Drug Name and Strength:	Belviq (Lorcaserin Hydrochloride) Tablets, 10 mg
Application Type/Number:	NDA 22529
Applicant/Sponsor:	Arena Pharmaceuticals Inc
OSE RCM #:	2012-172

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Belviq (Lorcaserin HCl) Tablets NDA 022529 for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted a request for an assessment of the container label, carton, and insert labeling for the proposed proprietary name, Belviq (Lorcaserin HCl) Tablets, 10 mg, NDA 022529 on December 23, 2011.

The Applicant initially submitted Application for Lorcaserin Hydrochloride tablets, 10 mg under NDA 022529 on December 18, 2009. The Application received a Complete Response on October 22, 2010 due to clinical and non-clinical reasons. On December 23, 2011, the Applicant resubmitted the Application for review after a Complete Response.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 2, 2012 NDA submission:

- Active Ingredient: Lorcaserin
- Indication of Use: For the management of obesity including weight loss and the maintenance of weight loss in conjunction with a reduced-calorie diet and a program of regular exercise.
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 10 mg
- Dose and Frequency: 10 mg by mouth twice daily
- How Supplied: Packaged in bottles of 100 tablets and sample blister card of 10 tablets per carton
- Storage: Store at 15º- 30ºC (59º- 86ºF) [See USP Controlled Room Temperature]. Protect from heat and moisture
- Container and Closure Systems:
  - Bottle of 100: 60 cc HDPE, round, white, (b) (4) Child-resistant closure (CRC), (b) (4)
  - Blister card: (b) (4) and (b) (4) heat seal coated foil backing material

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Belviq container labels as well as carton and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 25, 2012 (Appendix A)
- Professional Sample Blistercards Label submitted April 25, 2012 (Appendix B)
- Professional Sample Carton Labeling April 25, 2012 (Appendix C)
- Insert Labeling submitted April 20, 2012 (no image)

2.2 PREVIOUSLY COMPLETED REVIEWS

As a part of the original Application review process, DMEPA previously reviewed container labels as well as carton and package insert labeling in OSE Review #2010-142, dated March 19, 2010 and August 27, 2010. In August 27, 2010 labels and labeling review, DMEPA noted that the majority of the labeling issues noted in March 19, 2010 review were addressed.

Additionally, the proposed proprietary name, Belviq, for this product was found acceptable in OSE Review #2012-333, dated May 1, 2012.

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

The principle display panel (PDP) of the container labels appears cluttered due to excessive information that takes away from the important information such as manufacturer's information and distracting images and graphics.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label (100-count)

1. Ensure the presentation of the established name is at least ½ the size of the proprietary name and has a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast and other printing features as stated in 21 CFR 201.10 (g)(2).
2. The finished dosage form (i.e. Tablets) is part of the established name. Therefore we request you include "Tablets" following (Lorcaserin HCl) on the PDP.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3. Remove or reduce the prominence of the graphic located beside the proprietary name as it distracts from the most important information such as the proprietary name, established name, and strength statements.
4. Relocate or reduce the prominence of the Manufacturers and Distributors logo located on the principal display panel (PDP) and on the lower portion of the carton labeling as it distracts from the most important information such as the proprietary name, established name, and strength statements.

B. Carton Labeling (10-count professional sample)

1. See Comments A1 though A4 and revise the carton labeling for the professional sample accordingly.

C. Professional Sample Blister cards

1. Ensure that the sample blister card incorporate the expiration date and lot number.
2. Add the phrase "per tablet" after the strength is space permits (e.g., 10 mg per tablet).

If you have further questions or need clarifications, please contact Ermias Zerislassie, project manager, at 301-796-0097.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

REASOL AGUSTIN
06/01/2012

YELENA L MASLOV
06/01/2012

CAROL A HOLQUIST
06/01/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 30, 2012

TO: Pat Madara, Project Manager
Division of Metabolic and Endocrine Products

FROM: Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Lauren Iacono-Connors, Ph.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22-529

APPLICANT: Arena Pharmaceuticals
Craig Audet, Vice President, Global Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121
Tel: (858) 453-7200 ext. 1612
Fax: (858) 667-0065
caudet@arenapharm.com

DRUG: Lorqess (lorcaserin hydrochloride)

NME: Yes

THERAPEUTIC CLASSIFICATIONS: (Resubmission; 6-month clock)

INDICATION: An adjunct to diet and exercise for weight management in patients with a BMI of 27 kg/m2 or greater with a weight-related co-morbidity or BMI of 30 kg/m2 or greater

CONSULTATION REQUEST DATE: January 20, 20122
INSPECTION SUMMARY GOAL DATE: May 30, 2012
DIVISION ACTION GOAL DATE: June 27, 2012
PDUFA: June 27, 2012

I. BACKGROUND:

The sponsor, Arena Pharmaceuticals, Inc. submitted a New Drug Application (NDA) for Lorquess (lorcaserin hydrochloride) tablets, 10 mg, pursuant to the Food and Drug Administration's (FDA) Complete Response Letter (CRL) for lorcaserin dated October 22, 2010. Arena Pharmaceuticals, Inc. (Arena) is providing this resubmission of NDA 22-529 as a complete response (CR) to the deficiencies outlined in the action letter for this NDA. The CRL included a request that the sponsor submit the final study report for the trial of lorcaserin in overweight and obese individuals with type 2 diabetes (BLOOM-DM) and to describe in detail any significant changes or findings in the safety profile. The CRL also stated that the sponsor should provide case report forms and narrative summaries for each patient who died during the clinical trial or who did not complete the trial because of an adverse event, as well as narrative summaries for serious adverse events.

The product Lorquess (lorcaserin hydrochloride) has never been marketed in the United States. Lorcaserin hydrochloride (hereafter, lorcaserin) is designed to activate 5-HT2C receptors. It is a potent and selective agonist for the 5-HT2C receptor that has no serotonin-releasing properties. A common risk associated with serotonin 2C agonist therapy is Serotonin Syndrome. Serotonin syndrome requires immediate medical attention and may include one or more of the following symptoms: mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in otherwise healthy persons who took non-selective serotonergic drugs such as fenfluramine or dexfenfluramine for weight loss.

To support the approval, the sponsor has provided the Clinical Study Report for Study ADP356-010, "Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus (BLOOM-DM): A 52-Week, Double- blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Safety and Efficacy of Lorcaserin Hydrochloride in Overweight and Obese Patients with Type 2 Diabetes Mellitus Managed with Oral Hypoglycemic Agent(s)" which details the findings from this study. The addition of the phase 3 study APD356-010 to the lorcaserin safety and efficacy database is intended to strengthen the overall benefit/risk profile of lorcaserin.

The protocol inspected was Protocol APD356-010. The study was conducted between December 27, 2007 (first patient enrolled) and June 21, 2010 (last patient completed). Subjects were to be included in the study if they were overweight/obese male and female patients with type 2 diabetes mellitus between 18 and 65 years of age, inclusive. Patients were considered obese if they had a body mass index (BMI) of 27 to 45 kg/m^2. All females, regardless of childbearing potential, were required to have a negative pregnancy test at Screening (by serum hCG) and on Day 1 (by urine dipstick). Females of childbearing potential were required to use adequate means of contraception.

Patients screened and enrolled into the study were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: placebo, lorcaserin 10 mg once-a-day (QD), or lorcaserin 10 mg twice-a-day (BID). Due to slow enrollment, the total enrollment target was reduced by discontinuing randomization to the low dose group. Patients screened after the implementation of Protocol Amendment 03 were randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or lorcaserin 10 mg BID. Patients randomized into the lorcaserin 10 mg QD group prior to the implementation of Amendment 03 remained enrolled in the trial to complete all planned study procedures. The study duration per patient was approximately 52 weeks total: 4 weeks for screening followed by 52 weeks on study medication plus a 2 week post-study contact by telephone.

The primary endpoints for primary efficacy assessment:

- Proportion (%) of patients achieving ≥ 5% weight reduction at the end of 52 weeks of treatment
- Change in body weight (kg) from Baseline to the Week 52 visit
- Proportion (%) of patients achieving ≥ 10% weight reduction at the end of 52 weeks of treatment

The secondary endpoints include change from baseline in HbA1c, total fat and lean body mass, and blood pressure (systolic and diastolic) at Week 52. For the lipid profile (LDL, total cholesterol, HDL, TG), percent change from baseline was examined.

Safety assessment included clinical laboratory tests, vital signs, physical examination findings, 12-lead electrocardiograms (ECGs), echocardiograms, Beck Depression Inventory–II, including assessments of suicidal ideation in any patient who indicates suicidal thoughts on the questionnaire, and adverse events.

Two domestic clinical investigators were selected for inspection, mainly due to high enrollment, high number of INDs, and absence of previous inspectional history.

II. RESULTS (by Site): There were 2 sites inspected:

Name of CI	Protocol # and # of Subjects:	Inspection Date	Final Classification
Dan A. Streja M.D Infosphere Clinical Research 7345 Medical Center Drive, Suite 430 West Hills, CA 91307 Site #1174	APD356-010 (BLOOMDM) 51subjects	2/13/2012- 2/14/2012	NAI
Stephen Aronoff M.D Research Institute of Dallas 10260 N. Central Expressway, Suite 100-N Dallas, TX 75231 Site #1105	APD356-010 (BLOOMDM) 30 subjects	3/27/2012- 3/30/2012	Pending (Preliminary classificationVAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **Dan A. Streja M.D**
   Infosphere Clinical Research
   7345 Medical Center Drive, Suite 430
   West Hills, CA 91307

a. What was inspected: This inspection was conducted in accordance with Compliance Program 7348.811 between February 13, 2012 and February 14, 2012.

This inspection was performed as a data audit for Protocol #APD356-010 submitted in support of NDA #22529. At this site, 153 subjects were screened, 51 enrolled, and 34 subjects completed the study. One hundred two (102) Subjects failed screening.

For 18 enrolled subjects a review of the informed consent documents verified that subjects signed consent forms prior to enrollment.

The inspection included review the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequacy of adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were

compared with the sponsor supplied line listings. There were no limitations to the inspection.

b. General observations/commentary: In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

c. Assessment of data integrity: Based on the provided EIR for this site, data derived from Dr. Dan A. Streja's site are considered acceptable.

2. **Stephen Aronoff M.D**
Research Institute of Dallas
10260 N. Central Expressway, Suite 100-N
Dallas, TX 75231

a. What was inspected: This inspection was conducted in accordance with Compliance Program 7348.811 between March 27, 2012 and March 30, 2012.

At this site, a total of 58 subjects were screened, 30 subjects were enrolled, 7 subjects withdrew, and 23 subjects completed the study. The inspection evaluated informed consent and included review of source documents for 10 subjects. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting, and 5) handling of pharmacokinetic samples. All primary efficacy endpoint data were compared with the line listings. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary: In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued to this investigator for:

1. Failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically,

- The study protocol required that an echocardiogram be conducted at Baseline, Week 24, and Week 52/EarlyTermination. Echocardiograms were not always performed as required by the protocol. The following subjects did not have protocol-required echocardiograms performed: Subject #029, Week 52; Subject #032, Early Termination Visit; Subject #012, Week 24; Subject #016, Early Termination Visit; and Subject #014, Week 24.

  OSI Reviewer Comment: The investigator should have done echocardiogram as required by the protocol for the subjects listed above. Although the clinical investigator failed to conduct echocardiograms for individual subjects at Baseline,

Week 24, Week 52/EarlyTermination for 4 subjects, the protocol violations occurred in isolated visits.

Dr. Aronoff responded to the inspection findings in a letter dated April 13, 2012 and has plans to implement corrective actions.

- The study protocol required waist and hip circumference measurements to be recorded at different time points including at the time of randomization. Hip circumference measurements were not done for 4 subjects (Subjects #05, 012, 014, and 016) at the time of randomization.

  OSI Reviewer Comment: Although, the clinical investigator failed to measure hip circumference measurements for 4 subjects (Subjects #05, 012, 014, and 016) at the time of randomization the findings are isolated in nature and unlikely to impact data reliability. Dr. Aronoff responded to the inspection findings in a letter dated April 13, 2012, and he plans to implement corrective actions.

- The study protocol required the verification that the informed consent document was signed prior to the subject undergoing any study related procedures. Subject #024's informed consent was signed on April 9, 2008 after the patient had the Baseline echocardiogram, which occurred on March 19, 2008.

  OSI Reviewer Comment: The investigator should have complied with the applicable regulatory requirement and obtained informed consent prior to the subject undergoing the study related procedure.

  Although the clinical investigator failed to properly ensure the verification of informed consent prior to the patient undergoing echocardiogram (a non-invasive procedure), this regulatory violation is isolated and was the only study-specific procedure done prior to consenting. The violation is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study. Dr. Aronoff responded to the inspection findings in a letter dated April 13, 2012, and he plans to implement corrective actions.

- The study protocol required that serious adverse events (SAEs) be reported for any subject requiring hospitalization. Subject #027 was taken to the hospital and had surgery the next day for a broken left wrist and left forearm. An SAE was not reported for this hospitalization.

  OSI Reviewer Comment: This regulatory violation is an isolated finding and is unlikely to impact data reliability, safety and welfare of subjects in the study. Dr. Aronoff acknowledged the inspection findings in a letter dated April 13, 2012 and plans to implement corrective actions.

- Subject #049 was assigned the Investigation Drug Kit # 20839 at randomization; however, the subject received Kit# 24154 instead.

  OSI Reviewer Comment: Dr. Aronoff responded to the inspection findings in a letter dated April 13, 2012 and plans to implement corrective actions. According to the response to Form FDA 483, the above observation was reported to the IRB and the sponsor. The subject was later removed from the study, and the finding was reported to the NDA. Since correctional action was taken, this regulatory violation is unlikely to impact data reliability, or subject safety.

2. **Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation [21CFR312.62(b)].** Specifically,

   - Not all IVRS fax sheets were retained. As a result it was difficult to verify the correct kit assignment for some of the subjects.

   - Drug Accountability (Exposure) Logs were not completed and maintained.

     OSI Reviewer Comments: Based on the April 13, 2012 Form FDA 483 response, both drug accountability and IVRS fax sheets for all study participants for each visit were captured and recorded in the source documents from Week 2 to Week 52.

     The FDA form 483 does not show the exact number of subjects who had problem with IVRS fax sheets retention or drug accountability.

c. Assessment of data integrity: Based on the preliminary inspectional findings, efficacy and safety data obtained from this site can be considered reliable.

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The final classification of Clinical Investigator inspection of Dr. Dan A. Streja is No Action Indicated (NAI). The preliminary classification of the Clinical Investigator inspection of Dr. Stephen Aronoff is Voluntary Action Indicated (VAI). Although regulatory violations were noted at Dr. Stephen Aronoff's site, the violations reported on the Form FDA 483 appear isolated and the nature of the findings appears unlikely to significantly impact reliability of the data.

Note: The final classification for the inspection of Dr. Stephen Aronoff is pending and will be determined when the final EIR and associated exhibits are received and/or reviewed. Should the final classification for the clinical investigators be different from the current preliminary

classification, and overall conclusions change, DMEP will be notified and an inspection summary addendum will be generated.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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/s/

KASSA AYALEW
05/30/2012

SUSAN D THOMPSON
05/30/2012

LAUREN C IACONO-CONNORS
05/30/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
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Pediatric and Maternal Health Staff - Maternal Health Team Review

Date: May 30, 2012 **Date Consulted:** January 6, 2012

From: Jeanine Best, MSN, RN, PNP
Senior Clinical Analyst, Pediatric and Maternal Health Staff (PMHS)

Through: Melissa Tassinari, PhD, DABT, Acting Leader, Maternal Health
Pediatric and Maternal Health Staff

Lisa Mathis, MD
OND Associate Director, Pediatric and Maternal Health Staff (PMHS)

To: Division of Metabolic and Endocrine Products (DMEP)

Drug: Lorcarserin HCL tablets, NDA 022529

Sponsor: Arena Pharmaceuticals, Inc.

Subject: Pregnancy and Nursing Mothers Labeling, Pregnancy Planning and Prevention

Materials Reviewed:

- Sponsor's proposed labeling, December 23, 2011
- DMEP Pharmacology/Toxicology Review, October 20, 2010

Consult Question: DMEP requests that PMHS-Maternal Health comment on pregnancy and nursing mothers labeling and provide input on pregnancy planning and prevention for females of reproductive potential.

INTRODUCTION

On December 23, 2011, Arena Pharmaceuticals, Inc. submitted a Complete Response submission for lorcarserin HCL tablets, NDA 022529, in response to the Agency's October 22, 2010, Complete Response Letter. The Sponsor's proposed indication for locarserin is for use as an adjunct to diet and exercise for weight management, including weight loss and maintenance, in obese patients with an initial body mass index $\geq$30 kg/m^2, or overweight patients with a body mass index $\geq$27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).

On January 6, 2012, the Division of Metabolic and Endocrine Products (DMEP) consulted the Pediatric and Maternal Health Staff – Maternal Health Team (PMHS-MHT) to review and provide appropriate revisions to the pregnancy and nursing mothers subsection of labeling, and provide input on pregnancy planning and prevention for females of reproductive potential.

BACKGROUND

Lorcarserin

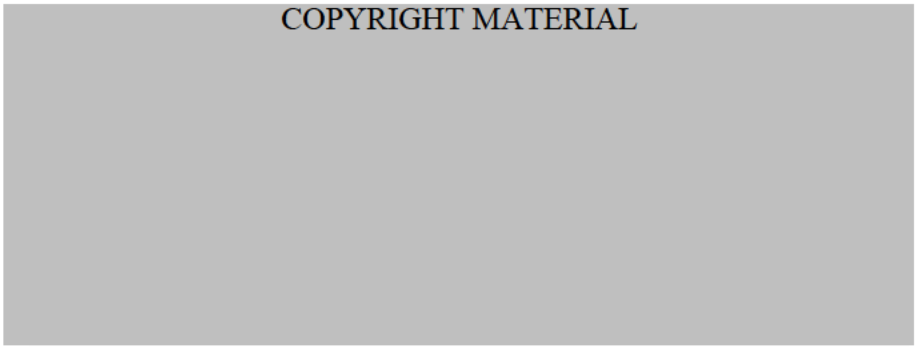
Lorcarserin, a selective agonist of the 5-HT$_{2C}$ receptor, is thought to mimic the hypophagic effect of serotonin through stimulation of pro-opiomelanocortin (POMC) neurons and produce weight loss with repeated administration as demonstrated in animal models.

An Advisory Committee Meeting was held on September 16, 2010 (during the initial review cycle), to discuss the safety and efficacy of lorcaserin. The Advisory Committee voted against lorcarserin approval due to marginal efficacy for weight loss and safety concerns of non-genotoxic carcinogencity and cardiac valvulopathy. The Sponsor responded to Complete Response issues and the Supplemental Application is under review. The Controlled Substance Staff is recommending DEA Scheduling of lorcarserin due to drug-seeking behavior observed in animal studies and adverse reactions of euphoria and hallucinations observed in the human clinical trials.

No teratogenicity was observed in animal reproduction studies in rats and rabbits. Lorcaserin was present in rat fetal tissues from in utero exposure. Rat milk samples were collected but not evaluated.

Pregnancy and Weight Gain Guidelines

Weight gain guidelines exist for pregnancy because both excessive weight gain and weight loss or poor weight gain during pregnancy have been associated with adverse maternal and fetal outcomes. The Institute of Medicine (IOM) published the following new pregnancy weight gain guidelines in May 2009, to address current research that had been conducted on the effects of weight gain in pregnancy on the health of both mother and baby:[1]



* Calculations assume a 0.5-2 kg (1.1-4.4 lbs) weight gain in the first trimester (based on Siega-Riz et al., 1994; Abrams et al., 1995; Carmichael et al., 1997).

An obligatory weight gain occurs in maternal tissues (the uterus, breasts, blood volume, and in the fetal-placental unit) during pregnancy. Weight gain in pregnancy is partly a gain in adipose tissue, accompanied by some degree of insulin resistance and other metabolic alterations that serve as an adaptive response to allow a more efficient transfer of fuels across the placenta to the fetus.

Excessive weight gain during pregnancy can lead to an increased risk of maternal insulin resistance and gestational diabetes mellitus, which can lead to fetal hyperglycemia and increased adiposity. In addition, these babies have a higher risk for childhood obesity and accompanying metabolic sequelae.[2] Pre-pregnancy obesity is associated with an increased risk of major malformations, including neural tube defects, omphalocele, heart defects, orafacial clefts, and others. The mechanism for these observed malformations and obesity is not known but may be due to severe metabolic and hormonal alterations including hyperglycemia, elevated insulin, and elevated estrogen levels; nutritional deficits from dieting or poor quality diets; and/or diabetes. [3]

Despite the association between obesity and major fetal malformations, a minimum weight gain (and no weight loss) is recommended during pregnancy for all women, including those who are already overweight or obese because of the obligatory weight gain that occurs in maternal tissues during pregnancy. The metabolic consequences of weight loss in pregnancy may be associated with adverse neurodevelopmental outcomes in childhood.[4]

---

[1] Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

[2] Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

[3] Watkins M, Rasmussen S, et al. Maternal obesity and the risk for birth defects. Pediatrics 2003; 111:1152-58

[4] Institute of Medicine of National Academy of Sciences. Weight gain during pregnancy: reexamining the Guidelines: http://www.nap.edu/catalog.php?record_id=12584#toc

SPONSOR PROPOSED LABELING (submitted December 21, 2012)

8 USE IN SPECIFIC POPULATIONS

(b) (4)

[redacted]

[5] See Appendix A for pregnancy category definitions table

[6] See Proposed Pregnancy and Lactation Labeling Rule, 73 FR 30831, May 29, 2008

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APPENDIX A:
FDA Pregnancy Category Definitions

Table 1. FDA Pregnancy categories (language summarized from 21 CFR 201.57)

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

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/s/

JEANINE A BEST
05/30/2012

MELISSA S TASSINARI
05/30/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 29, 2012
To:	Mary Parks, MD Director, Division of Metabolism and Endocrinology Products, Office of New Drugs
Through:	Tarek Hammad, MD, PhD, MSc, MS Deputy Director, Division of Epidemiology I Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology Diane K. Wysowski, PhD, MPH Team Leader, Division of Epidemiology I
From:	Christian Hampp, PhD Visiting Associate/Epidemiologist, Division of Epidemiology I
Subject:	Postmarketing Studies to Assess Fibroadenoma Risk with Lorcaserin
Drug Name(s):	Lorcaserin
Submission Number:	062
Application Type/Number:	NDA 22-529
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EXECUTIVE SUMMARY

Lorcaserin (NDA #22-529, Arena Pharmaceuticals) is a weight loss drug candidate currently under review by the Division of Metabolism and Endocrinology Products (DMEP). In preclinical studies, safety concerns arose about an imbalance in mammary fibroadenoma in female rats. On April 24, 2012, the sponsor submitted three briefly outlined study designs to evaluate lorcaserin-associated fibroadenoma in the postmarketing phase. This document formalizes the Division of Epidemiology-I opinion regarding feasibility of post-marketing studies on fibroadenoma in patients taking lorcaserin.

The brief outlines provided do not allow for a full assessment of study designs and several areas are unclear in the provided information. However, all of these approaches share limitations that are related to the nature of the outcome of interest. Because of the mostly benign nature of fibroadenoma and evidence that imbalances in animal studies may not translate into clinical events in humans, I recommend that DMEP reassess the need to study whether lorcaserin is associated with fibroadenoma in humans.

If DMEP concludes that additional clinical data on fibroadenomas are necessary to alleviate concerns, this review provides several considerations and study options. If DMEP requires a cardiovascular outcomes trial for lorcaserin, I recommend that DMEP consider the addition of breast cancer as an outcome of interest, with extended follow-up beyond trial completion, but limitations of this approach should also be taken into account.

Finally, in the case of lorcaserin approval, I recommend that DMEP consider adding language to the label that the drug be contraindicated or used with caution in women with a personal history of breast cancer and used with caution in women with a family history of breast cancer.

1 BACKGROUND

Lorcaserin (NDA #22-529, Arena Pharmaceuticals) is a weight loss drug candidate currently under review by the Division of Metabolism and Endocrinology Products (DMEP). In preclinical studies, safety concerns arose about an imbalance in mammary fibroadenoma in female rats. Thirty-seven percent of rats on vehicle control compared with 83%, 85%, and 68% of rats on 10, 30, and 100 mg/kg/day, respectively, developed fibroadenoma. An increase in mammary adenocarcinoma in female rats was only found at the highest dose, resulting in a safety margin of 24 times the plasma exposure in humans taking the maximum recommended dose. Since rats developed fibroadenoma at all doses of lorcaserin, a similar safety margin does not exist for fibroadenoma.

On April 23, 2012, the sponsor submitted three briefly outlined study designs to evaluate lorcaserin-associated fibroadenoma in the postmarketing phase. DMEP asked the Division of Epidemiology I (DEPI I) to review these study designs for feasibility in

advance of an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting on May 10, 2012. DEPI-I staff met with DMEP and provided informal communication before the EMDAC meeting. This document formalizes DEPI-I's opinion regarding feasibility of post-marketing studies on fibroadenoma in patients taking lorcaserin.

2 METHODS

This review is based on the sponsor's submission of three briefly outlined study designs ("Potential Post Marketing Observational Study Designs," dated April 23, 2012, submitted April 24, 2012), to evaluate lorcaserin-associated fibroadenoma in the postmarketing phase. In addition, the medical literature was reviewed for information on epidemiology, diagnosis, and clinical significance of fibroadenoma in humans. Personal communication with two Medical Officers in the Breast Oncology Group, Division of Oncology Products-I, Tatiana Prowell, M.D., and Nancy S. Scher, M.D., provided further background and some pertinent medical literature references on fibroadenoma.

3 RESULTS

3.1 PROPOSED STUDY SYNOPSES

The sponsor submitted three brief outlines of study designs to investigate lorcaserin-associated fibroadenoma in women during the postmarketing phase. The outlines are summarized below:

The first design is a pharmacoepidemiology study based on claims data and medical records. The population will be divided into three cohorts: lorcaserin exposed (stratified by current or recent use), age-matched general population, and age-matched overweight/obese patients. The proposed outcome is biopsy-proven fibroadenoma identified in claims data and validated in medical records.

The second design was described as a retrospective/prospective cohort study based on two complementary data collection approaches: (a) electronic medical records (EMR) and (b) surveys of physicians who care for the patients identified under (a). Control patients will be matched based on age, race, and body mass index. The proposed outcome is biopsy-proven fibroadenoma identified in EMR and/or physician surveys.

Finally, the third design is a prospective cohort study (registry) in a pharmacy benefit management database. Subjects will be users of lorcaserin matched by propensity scores to users of other weight loss agents who provide verbal consent for participation and from whom baseline data, including body mass index, can be obtained. Follow-up information will be done quarterly via telephone survey, even after discontinuation of therapy. If patients report a diagnosis of fibroadenoma, their physicians will be contacted to provide a pathological diagnosis.

3.2 CRITIQUE OF PROPOSED STUDIES

The brief outlines provided do not allow for a full assessment of study designs and several areas are unclear in the provided information. However, all of these approaches share limitations that are related to the nature of the outcome of interest.

Fibroadenoma is a fairly common condition, especially among women in their second or third decades of life, where prevalence estimates range from 2.2% to 23% (1). Many women between 20 and 40 years of age do not perform breast self-examinations (BSE) (2) and most do not have regular clinical breast examinations (CBE). In young women, CBE includes manual exam and ultrasound as indicated. Because of the absence of regular testing in this age range, incident cases may not be distinguishable from prevalent cases in a retrospective design. In addition, fibroadenomas in young women are typically not biopsied (1, 3) and applying this requirement to existing data may miss many, if not most, cases.

Any observational design could suffer from detection bias, as a consequence of possible label language indicating a signal of fibroadenoma in pre-clinical studies. If more physicians advise lorcaserin patients to perform BSE or obtain CBE compared to users of other anti-obesity drugs, more diagnoses of fibroadenoma and other lesions would be expected.

4 RECOMMENDATIONS TO DMEP

Fibroadenoma is a benign condition and is not associated with an increased risk for breast cancer when the fibroadenoma is noncomplex and no family history of breast cancer exists (relative risk, 1.08 (95% CI, 0.79-1.49). These conditions were met by two thirds of patients with fibroadenoma in a retrospective cohort study (4). The same study found an increased risk for the 23% of patients with complex fibroadenoma (relative risk, 3.10 (95% CI, 1.9-5.1), histologically defined as containing cysts greater than 3 mm in diameter, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes. In another study, 16% of fibroadenoma cases were complex (5). The distribution of complex versus non-complex fibroadenoma in rats exposed to lorcaserin is not known.

At the EMDAC meeting, the sponsor provided evidence for a prolactin-dependent tumor mechanism in rats and emphasized that levels of circulating prolactin were *not elevated* in women taking lorcaserin. Furthermore, the clinical trials on lorcaserin detected no cases of fibroadenoma in women and no imbalance in breast cancer, but follow-up duration may not have been sufficient to detect lorcaserin-related fibroadenoma or malignancy. Because of the mostly benign nature of fibroadenoma and evidence that preclinical imbalances may not translate into clinical events, I recommend that DMEP reassess the need to study fibroadenoma in humans.

If DMEP concludes that additional clinical data on fibroadenomas are necessary to alleviate concerns, the following should be taken into consideration. A prospective observational or experimental study with baseline clinical breast examinations, including

regular manual exams and ultrasound if indicated for diagnostic certainty, could potentially overcome some of the shortcomings discussed above, but it would have to include a control group, preferably another weight-loss drug. Also, to minimize detection bias, regular screening of all participants by breast cancer specialists may be necessary, but would complicate the study with regard to logistics, ability to enroll sufficient numbers of patients, and cost.

If DMEP requires a cardiovascular outcomes trial (CVOT) for lorcaserin, I recommend that DMEP consider the addition of breast cancer as an outcome of interest, which is clinically more significant and has better diagnostic accuracy than fibroadenoma. Baseline CBE assessment could assure that detected cases are incident cases and prespecified diagnostic criteria could increase the validity of the outcome. In addition, given randomization and double-blinding, detection bias could be minimized. To account for the long latency, follow-up for breast cancer should be extended beyond the trial's duration.

In the case of prospectively identifying fibroadenoma, limitations need to be considered, including limited sensitivity and reliability of CBEs if not conducted by breast cancer specialists (1), added anxiety and cost of conducting repeated CBEs, the problem of ascertaining a benign condition, and potentially added difficulty in recruitment if CBE is required. Also, more weight loss in one group could facilitate the detection of breast nodules, introducing detection bias despite double-blinding. Lastly, enrichment of a CVOT study with patients at higher cardiovascular risk may result in underrepresentation of young women, thus reducing expected case counts of fibroadenoma.

Finally, in the case of approval, I recommend that DMEP consider adding language to the label that the drug be contraindicated or used with caution in women with a personal history of breast cancer and used with caution in women with a family history of breast cancer.

Christian Hampp, PhD

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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 30, 2012

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
J.P. Gong, M.D., Medical Officer
Controlled Substance Staff

Subject: Lorcaserin (b) (4) NDA 22-529
Indication: Weight Management
Dose: 20 mg/day; 10 mg BID
Sponsor: Arena Pharmaceuticals

Materials reviewed: NDA 22-529 (resubmission, 12/27/11); scientific and medical literature

Table of Contents

I. SUMMARY

A. Background

This memorandum summarizes our findings related to the abuse potential of lorcaserin [redacted] NDA 22-529), as requested by the Division of Metabolism and Endocrinology Products. The NDA for lorcaserin was previously reviewed by FDA in 2010, and the NDA received a Complete Response letter on October 22, 2010.

Lorcaserin is a new molecular entity that has high affinity as an agonist for $5HT_{2C}$ and $5HT_{2A}$ receptors in human brain tissue. The Schedule I hallucinogens, lysergic acid diethylamide (LSD), psilocybin and 2,5-dimethoxy-4-methamphetamine (DOM) have the same mechanism of action.

The proposed indication for lorcaserin is weight management, including weight loss and maintenance of weight loss, in conjunction with reduced-calorie diet and regular exercise. The proposed dose range is 20 mg/day (10 mg BID). Lorcaserin is not marketed in any country.

The Sponsor states that, "The available data support a recommendation that lorcaserin be unscheduled, or that scheduling no more restrictive than Schedule V be applied."

B. Conclusions from NDA Reviews

In the resubmitted NDA, CSS evaluated two new abuse-related animal studies. We also re-evaluated the psychiatric and neurological AEs associated with lorcaserin administration in the previously-submitted clinical studies as well as the new Phase 2 clinical study data. From these analyses, we conclude that:

1. Acute administration of lorcaserin to rats produces behaviors that are associated with activation of 5HT2A receptors (wet dog shakes and back fasciculations) as well as behaviors that are associated with activation of 5HT2C receptors (penile grooming and inactivity). These behaviors were also produced in this study by the DOM (a $5HT_{2A}$ and $5HT_{2C}$ receptor agonist that is a Schedule I hallucinogen), as well as by dexfenfluramine (a Schedule IV drug that acts at the serotonin transporter but does not have direct activity at $5HT_{2A}$ and $5HT_{2C}$ receptors).

2. In a test of drug discrimination in rats trained to recognize DOM (a $5HT_{2A}$ and $5HT_{2C}$ receptor agonist that is a Schedule I hallucinogen), individual data show that lorcaserin fully generalizes to the DOM cue in 7 of 9 rats following administration of at least one dose of lorcaserin (ranging from 0.1 to 10.0 mg/kg). These data show that lorcaserin produces interoceptive responses that are similar to those of the Schedule I hallucinogen, DOM.

3. The overall incidence of euphoria in Phase 1 and Phase 2/3 clinical efficacy and safety studies following administration of therapeutic doses of lorcaserin is low (0.7%), but is greater than that observed following administration of placebo (0.06%). The ability of lorcaserin to produce euphoria is dose-dependent, with supratherapeutic doses producing the highest incidence of the AE. Individuals treated with lorcaserin showed a higher incidence of other prominent safety or abuse-related AEs (such as feeling jittery, psychomotor hyperactivity, paresthesia, abnormal dreams, and confusional state) than subjects treated with placebo.

4. In contrast to the low overall incidence of the AE euphoria in Phase 1, 2 and 3 studies, lorcaserin produces a high rate of the AE euphoria (6-19%) in a human abuse potential study with drug abusers. The incidence of euphoria in this study resulting from lorcaserin administration is similar to that reported following administration of zolpidem (Schedule IV; 13-16%), lower than that reported following administration of ketamine (Schedule III; 50%), and higher than that reported following administration of placebo (0%). The duration of euphoria in lorcaserin treatment groups (12.2 hrs, 7.2 hrs, and 8.5 hrs for 20 mg, 40 mg, and 60 mg, respectively) was much longer than the duration of euphoria produced by the two positive controls, ketamine (1.6 hrs) and zolpidem (3.0 hrs and 2.0 hrs for 15 mg and 30 mg, respectively). Lorcaserin also produced a high rate of headache (61-84%), nausea (21-45%) and dizziness (13-19%), abdominal discomfort (9-26%), hot flush (3-19%), decreased appetite (3-19%), paresthesia (3-16%), anxiety (3-10%) and depressed mood (3-9%).

The data summarized above from the present NDA were considered in conjunction with conclusions from our September 3, 2010 review of abuse-related clinical and preclinical data in the previous NDA, which included:

1. Lorcaserin is a high-affinity agonist at $5HT_{2A}$ and $5HT_{2C}$ receptors. This mechanism of action is identical to that of Schedule I hallucinogenic drugs. Lorcaserin does not have high affinity for other binding sites in the brain.

2. Phase 1 clinical pharmacokinetic studies show that the major metabolite of lorcaserin in humans is lorcaserin sulfamate (M1). The M1 metabolite is pharmacodynamically inactive, based on binding studies. The Tmax of lorcaserin is approximately 2 hours, with a half-life of 11 hours.

3. In the human abuse potential study in recreational abusers of psychedelic drugs and CNS depressants (n = 28), lorcaserin (40 and 60 mg, p.o.) and the positive control drugs, zolpidem and ketamine, produced statistically significant increases on certain positive subjective measures ("High", "Good Drug Effects" and "Good Drug Effects"), as well as a numerical increase in "Hallucinations" compared to placebo. Lorcaserin, as well as zolpidem and ketamine, produced statistically significant increases in "Sedation" compared to placebo. The subjective response data suggest that lorcaserin produces effects that are similar to those of ketamine and zolpidem, drugs with hallucinogenic and euphorigenic properties. However, lorcaserin did not produce statistically significant

increases in ratings on other positive control drugs compared to placebo ("Drug Liking", "Overall Drug Liking", "Euphoria", "Take Drug Again"), although zolpidem and ketamine did. Additionally, lorcaserin produced statistically significant increases in certain negative subjective effects ("Overall Dislike Drug", "Bad Effects"). On the VAS-Drug Similarity scale, subjects identified the two highest doses of lorcaserin as similar to "LSD" and "MDMA," while subjects identified ketamine as "ketamine" and zolpidem as "benzodiazepine." However, since zolpidem and ketamine have different mechanisms of action from that of lorcaserin, they are not ideal comparators for determining the hallucinogenic profile of lorcaserin.

4. The ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses, in healthy individuals and in obese patients, at doses greater than the proposed therapeutic dose of 20 mg suggests that lorcaserin can produce psychic dependence similar to that of other 5HT2 agonist hallucinogens.

Overall Conclusion

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. These conclusions are different than those drawn by the Sponsor (see below under **Discussion**).

C. Conclusions and Recommendation (to be conveyed to Sponsor):

Following our review of the abuse-related data submitted in the NDA, we conclude that:

- Lorcaserin has abuse potential most similar to that of zolpidem (Schedule IV)
- Lorcaserin will be recommended for placement in Schedule IV of the Controlled Substances Act.

D. Discussion

The Sponsor makes the following assertion in the NDA regarding the abuse potential of lorcaserin: "Evaluation of all lines of evidence required for the 8 factor analysis places lorcaserin in the category of a drug with a very low abuse liability based upon the chemistry and nonclinical and clinical data, including the human abuse potential study data indicating lower abuse potential relative to ketamine (Schedule III) and zolpidem (Schedule IV). The available data support a recommendation that lorcaserin be unscheduled, or that scheduling no more restrictive than Schedule V be applied."

The Sponsor draws this conclusion based on the following assertions about lorcaserin:

- It has $5HT_{2A}$ receptor binding and functional activity but no in vivo $5HT_{2A}$ activity like that associated with hallucinogens

- It has no structural similarity to controlled substances, including hallucinogens

- The adverse event profile is similar to that of unscheduled serotonergic drugs (such as serotonin selective reuptake inhibitor antidepressants)

- Subjective responses in the human abuse potential study are similar to those reported for varenicline (unscheduled) and for pregabalin and lacosamide (Schedule V)

- It does not produce physical dependence, based on the lack of a withdrawal syndrome upon discontinuation

We disagree with the Sponsor that lorcaserin has low abuse potential and should either not be scheduled or should be placed into Schedule V. These conclusions are based on the following:

- Although the binding of lorcaserin is numerically greater at $5HT_{2C}$ receptors than at $5HT_{2A}$ receptors, the affinity of lorcaserin is still relatively high for both receptor subtypes. As discussed below in the review section, the receptor binding profile of lorcaserin is identical to that of Schedule I hallucinogens (Nichols, 2006).

- A substance's lack of similarity in chemical structure to scheduled drugs of abuse, including hallucinogens, does not predict its pharmacological or behavioral activity.

- The overt behavioral study shows that lorcaserin produces both $5HT_{2A}$-associated behaviors and $5HT_{2C}$-associated behaviors, similar to the Schedule I hallucinogen, DOM, and the Schedule IV controlled substance, dexfenfluramine.

- The drug discrimination study showed that lorcaserin produced full generalization to the interoceptive cue produced by the Schedule I hallucinogen, DOM, in the majority of rats tested.

- In a human abuse potential study, lorcaserin produces some, but not all, of the positive subjective responses in the human abuse potential study produced by zolpidem and ketamine, including an increase in measures of "High", "Good Drug Effects" and "Hallucinations". However, it is to be expected that these three drugs would produce different behavioral responses in humans, given that lorcaserin is a $5HT_2$ receptor agonist, while zolpidem is a GABA agonist and ketamine is an NMDA antagonist. It is important to recognize that zolpidem and ketamine are not the ideal positive control drugs for a $5HT_2$ agonist like

lorcaserin. Instead, the optimum positive control would be a $5HT_2$ agonist hallucinogen such as LSD. However, given that there has been limited research conducted with Schedule I $5HT_2$ agonist hallucinogens using modern clinical methodology, this class of drugs was not considered appropriate for use as a positive control in regulatory studies

- The data from the human abuse potential study with lorcaserin cannot be compared with data from human abuse potential studies with varenicline, pregabalin or lacosamide because a direct experimental comparison between these drugs has not been conducted.

- The incidence of the AE euphoria following administration of supratherapeutic doses (40 and 60 mg) of lorcaserin ranged from 15-19%.

- The ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at therapeutic and supratherapeutic doses in healthy individuals and in obese patients suggests that lorcaserin can produce psychic dependence similar to that of other 5HT2 agonist hallucinogens.

Given that lorcaserin has a mechanism of action identical to that of 5HT2 hallucinogens, it was specifically of interest to determine whether lorcaserin produces hallucinogenic-like effects. After a review of the adverse events produced by lorcaserin in clinical studies (euphoria, hallucinations, paresthesias, nausea, abdominal discomfort, hot flush, dizziness, anxiety and decreased appetite) and the subjective responses observed in the human abuse potential study ("High," "Good Drug Effects," "Hallucinations"), we conclude that lorcaserin has hallucinogenic properties.

Lorcaserin produces modest weight reduction at the proposed therapeutic dose. However, the risk-benefit calculation should consider that lorcaserin produces psychiatric adverse events, including euphoria and hallucinations, beginning at twice the proposed therapeutic dose. This suggests that patients risk exposing themselves to serious psychiatric AEs if they double their lorcaserin dose, by choosing to ignore the recommended dose (because they desired a greater weight loss response, for example), by inadvertent mistakes in dosing (forgetting a dose and then taking twice as much subsequently) or by deliberate misuse for abuse purposes (taking higher doses for recreational or experimental purposes to elicit euphoric or hallucinatory responses).

Additionally, given that data from the 2010 National Survey on Drug Use and Health shows that hallucinogens rank second with cocaine as the most frequently used illicit drug class in the United States after marijuana (Substance Abuse and Mental Health Services Administration, 2011), it is likely that certain individuals may seek out lorcaserin for its ability to induce euphoria and hallucinations. This suggests that the risks of lorcaserin include the risk of drug abuse.

Thus, lorcaserin appears to have a narrow therapeutic window that may lead to considerable psychiatric risks related to abuse potential in the intended clinical

population. Given that drugs with hallucinogenic-like properties have known abuse potential, diversion of lorcaserin may occur from a patient population or a drug abusing population.

II. REVIEW

In the present NDA, there were two new animal abuse-related studies (an overt behavior study and a drug discrimination study). Additionally, there was a new Phase 2 clinical efficacy and safety study. The AEs in this study were reviewed in the context of the AEs reported in the previously submitted NDA for this drug.

Preclinical Abuse-Related Studies

a. Receptor Binding and Functional Studies

Receptor Binding

As noted in the previous NDA review, lorcaserin has relatively high affinity for only two human brain receptors: the 5-HT2C receptor (Ki = 13 nM) and 5-HT2A receptor (Ki = 92 nM). In contrast, the two major metabolites, M1 and M5, do not have measurable affinity for any receptors and transporters tested, including serotonin receptors.

Functional Assays at 5HT2A and 5HT2C Receptors

Human 5-HT2 receptors active second messenger signal transduction cascades via G proteins. Activation of these receptors leads to phospholipase-C phosphatidylinositol (PI) hydrolysis and phospholipase-A2-mediated arachadonic acid (AA).

As a measure of PI hydrolysis, the Sponsor assayed inositol phosphate (IP) accumulation to test functional activity of lorcaserin at 5-HT2 receptors. These studies were conducted in 2002-04, in 2009 and most recently in 2011. Although the data in earlier studies showed that lorcaserin stimulated IP accumulation with reasonable high activity at both 5HT2A receptors (EC50 of 14-133 nM) and 5HT2C receptors (EC50 of 1.8-9 nM), the 2011 data show that lorcaserin was much more potent at 5HT2C receptors (EC50 of 39 nM) than at 5HT2A receptors (553 nM) (see Table 1, below). The percent of Emax compared to serotonin (a measure of efficacy) was 81% at 5HT2C receptors but only 25% for 5HT2A receptors.

Table 1: Potency of lorcaserin in inositol phosphate assays at 5HT2A, 5HT2B and 5HT2C receptors (data from studies conducted in 2002/04, 2009, 2011)

	Lorcaserin, EC50, nM		
Study date	**5HT2A**	**5HT2B**	**5HT2C**
2002/04	133	811	9
2009	14	82	1.8
2011*	**553 (%Emax = 25%)**	**2380**	**39 (%Emax = 81%)**

5HT2 receptor-associated IP accumulation is coupled to calcium release, so calcium release was also measured at each of the 5HT2 receptor subtypes. Similar to the IP accumulation data, the 2002-04 data showed high activity of lorcaserin at stimulating calcium release at 5HT2A and 5HT2C receptors (EC50 of 52 nM and 6 nM, respectively) (see Table 2, below). However, when the assays were conducted in 2011, the EC50 of lorcaserin at stimulating calcium release had increased from 6 nM to 146 nM, while the EC50 at 5HT2A receptors had increased from 52 nM to 948 nM. Similar to IP accumulation data, the percent of Emax compared to serotonin (a measure of efficacy) for calcium release was 86% at 5HT2C receptors but only 26% for 5HT2A receptors.

Table 2: Potency of lorcaserin in calcium release assays at 5HT2A, 5HT2B and 5HT2C receptors (data from studies conducted in 2002/04, 2009, 2011)

	Lorcaserin, EC50, nM		
Study date	**5HT2A**	**5HT2B**	**5HT2C**
2002/04	52	350	6
2011*	**948 (%Emax = 26%)**	**1040**	**146 (%Emax = 86%)**

Overall, the data from IP accumulation and calcium release functional assays suggest that lorcaserin is acting as an agonist at 5HT2C receptors with relatively high activity but slightly less than full agonist efficacy. In contrast, lorcaserin has low activity at 5HT2A receptors in these same functional assays, with very low agonist efficacy.

It is notable that the Sponsor did not conduct functional assays with AA, since this is the other major second messenger system associated with both 5HT2A and 5HT2C receptors. With 5HT2 receptors, agonist-directed trafficking of receptor stimuli can result in differential efficacy depending on which second messenger system was measured (Berg and Clarke, 2006). Since agonist-directed trafficking cannot occur between two responses that are sequentially connected, it would be expected that there would be a good correlation between IP accumulation and calcium release in these assays. However, it is often the case that the rank order of agonist relative efficacy can reverse when two second messenger systems associated with a receptor are assayed. This is specifically often the case with 5HT2A and 5HT2C receptors. So, although IP accumulation and calcium release showed that lorcaserin preferentially activated 5HT2C receptors, it is possible that AA assays would have shown the opposite response, with 5HT2A receptors activated preferentially over 5HT2C receptors.

More importantly, however, drugs that are hallucinogenic in humans (2,5-dimethoxy-4-iodoamphetamine (DOI; Shulgin and Shulgin, 1991) and LSD), in which the hallucinogenic activity is reliant on 5HT2A activation, have variable efficacy at 5HT2A and 5HT2C receptors when second messenger system activation is assayed (see Table 3, below) (Berg and Clarke, 2006).

Table 3: Efficacy of DOI and LSD in AA release and IP accumulation at $5HT_{2A}$ and $5HT_{2C}$ receptors *(Berg and Clarke, 2006).*

Drug	Efficacy at $5HT_{2A}$-associated AA release	Efficacy at $5HT_{2A}$-associated IP accumulation	Efficacy at $5HT_{2C}$-associated AA release	Efficacy at $5HT_{2C}$-associated IP accumulation
DOI	~60%	~50%	~90%	~60%
LSD	~50%	~15%	~40%	~15%

These data show that the hallucinogen DOI acts as a partial agonist at $5HT_{2A}$ sites (as measured by AA release and IP accumulation), a partial agonist at $5HT_{2C}$ sites (as measured by IP accumulation) and as a full agonist at $5HT_{2C}$ sites (as measured by AA release). In contrast, the Schedule I hallucinogen LSD acts as a partial agonist at $5HT_{2A}$ and $5HT_{2C}$ sites when AA release is measured, but had extremely low efficacy (~15%) at $5HT_{2A}$ and $5HT_{2C}$ sites when IP accumulation is measured.

Thus, it is not possible to determine the full functional activity of lorcaserin at $5HT_{2A}$ and $5HT_{2C}$ receptors, given that AA was not assayed. More critically, however, based on comparisons with known $5HT_2$ agonist hallucinogens, these functional assays do not necessarily provide useful information about whether drugs that have relatively high binding affinity at these $5HT_2$ receptor subtypes will produce hallucinogenic-like behavioral responses in animals or humans.

b. Overt Behavioral Responses to Lorcaserin (Study #DBR-11-001; "Effect of Lorcaserin, Dexfenfluramine, and 2,5-Dimethoxy-4-methylamphetamine (DOM) on Behavioral Signs Indicative of 5-HT_{2C} and 5-HT_{2A} Activation in the Male Rat")

The overt behavioral response study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail.

Methods

Rats (n = 6/group) received intraperitoneal injections of lorcaserin HCl hemihydrate (0.3, 1, 3, or 10 mg/kg, dose expressed as base), dexfenfluramine (1 or 10 mg/kg, dose expressed as base), or DOM (0.01, 0.1, or 1 mg/kg, dose expressed as salt). Observations were made for 60 minutes for signs of $5HT_{2A}$ activation (wet dog shakes, back muscle contractions) and $5HT_{2C}$ activation (penile grooming and inactivity). For analysis of inactivity, scores of "active", "sleeping", or "resting/inactive" were recorded as being present (1) or absent (0) within five-minute time bins, resulting in a maximum possible score of twelve for each activity category.

Results

As shown in Table 4 (below), behavioral profiles for each of the drugs were similar. Lorcaserin significantly increased both $5HT_{2A}$-associated behavior (wet dog shakes and back muscle fasciculations) as well as $5HT_{2C}$-associated behaviors (penile grooming and inactivity) compared to placebo. Lorcaserin did not alter back muscle fasciculations at any dose. DOM significantly increased $5HT_{2A}$-associated behaviors (wet dog shakes and back muscle fasciculations) and a $5HT_{2C}$-associated behavior (penile grooming) compared to placebo. DOM did not alter inactivity levels. Dexfenfluramine significantly increased a $5HT_{2A}$-associated behavior (wet dog shakes) and $5HT_{2C}$-associated behaviors (penile grooming and inactivity) compared to placebo. Dexfenfluramine did not alter back muscle fasciculations.

Table 4: Rat Behaviors Following Administration of Vehicle, Lorcaserin, DOM and Dexfenfluramine

Drug	Wet Dog Shake	Back Muscle Fasciculations	Penile Grooming	Inactivity
Vehicle	4.0	2.7	0.3	2.2
Lorcaserin 0.3 mg/kg	4.5	1.0	**3.8 ****	2.3
Lorcaserin 1.0 mg/kg	**12.2 ****	0.2	**9.3 ****	2.7
Lorcaserin 3.0 mg/kg	1.2	0.3	**8.3 ****	**6.5 ****
Lorcaserin 10 mg/kg	0.8	2.3	0.3	**11 ** ##**
DOM 0.01 mg/kg	3.8	1.8	0.5	2.5
DOM 0.1 mg/kg	**15.5 ****	**8.8 ***	**4.3 ****	2.0
DOM 1.0 mg/kg	**27.3 ** ##**	**68.5 ****	0.7	2.2
Dexfenfluramine 1.0 mg/kg	**12.0 ****	2.2	**8.3 ****	2.8
Dexfenfluramine 10 mg/kg	**8.7 ***	7.2	**5.7 ****	**5.2 ****

* $p < 0.05$ compared to placebo; ** $p < 0.01$ compared to placebo
$p < 0.01$ significantly higher than any other treatments

Conclusions

The positive control drug, DOM, is an agonist at $5HT_{2A}$ receptors (Ki = 21 nM; Egan et al. 2000) and at $5HT_{2C}$ receptors (Ki = 41-372 nM; Boess et al., 1994). Therefore, the ability of the two highest doses of DOM to produce a significant increase in $5HT_{2A}$ and $5HT_{2C}$ associated behaviors compared to placebo in this study validates the methodology.

According to receptor binding data submitted in the NDA, lorcaserin is an agonist at both $5HT_{2A}$ receptors (Ki = 92 nM) and at $5HT_{2C}$ receptors (Ki = 13 nM). Given that the pharmacology of lorcaserin is similar to that of DOM, lorcaserin also produced a significant increase in $5HT_{2A}$ and $5HT_{2C}$ associated behaviors compared to placebo.

Dexfenfluramine is a serotonin releaser (Samanin and Garattini, 1993) that has no significant affinity for either $5HT_{2A}$ receptors (Ki > 2400 nM; Fitzgerald et al., 2000, Knight et al., 2004) or $5HT_{2C}$ receptors (Ki = 1400 nM; Fitzgerald et al., 2000, Knight et al., 2004). Despite a lack of direct activation of $5HT_2$ receptors, dexfenfluramine produced a significant increase in $5HT_{2A}$ and $5HT_{2C}$ associated behaviors compared to placebo.

Notably, there was little evidence for a dose-dependent increase in the four $5HT_2$–associated behaviors for any of the three drugs tested, with the exception of DOM with regard to wet dog shakes and back muscle fasciculations and for lorcaserin for inactivity. Instead, for the majority of behavioral responses, there was the appearance of an inverted U-shaped curve, with moderate doses producing the highest behavioral counts.

Finally, a justification was not provided for the drug doses selected or for the timing of the behavioral observations. It is possible that the drug doses do not produce plasma levels that are similar to those produced by human doses. It is also possible that the behavioral responses could have been measured at a time other than Cmax.

These data show that the ability of a serotonergic drug to induce wet dog shakes, back muscle contractions, penile grooming and inactivity is not necessarily reliant on direct activation of $5HT_2$ receptors. Thus, the usefulness of this behavioral test for distinguishing between pharmacological mechanisms of action (e.g., $5HT_{2A}$ vs. $5HT_{2C}$) is extremely limited.

c. Drug Discrimination Study in Rats (Study # TX-11-001; "Evaluation of Lorcaserin for Abuse Liability Using the Drug Discrimination Test in the Rat")

The drug discrimination study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail.

Study Design

Rats (n = 9) were trained to discriminate DOM (0.56 mg/kg), "or on a few occasions, 0.32 mg/kg", i.p., 75 minutes pretreatment time) from saline. The schedule of reinforcement increased to FR10 over the course of training. Drug training sessions occurred daily. The training session in the test cage lasted for either 15 minutes or for 50 responses, whichever occurred first.

Testing with lorcaserin, DOM and saline began when rats satisfied the following criteria for either 5 consecutive, or 6 of 7 consecutive, training sessions: a) at least 80% of the total responses on the training drug-associated lever and b) fewer than 10 (one FR) responses on the inactive lever prior to completion of the FR 10 on the active lever. During testing, sessions were conducted no more often than every third day and only so long as rats satisfied the same criteria during intervening training sessions and, minimally, for two days immediately preceding a test.

Test sessions were identical to training sessions except that rats received i.p. injections of saline, the training dose (0.56 mg/kg) of DOM, or a dose of the test substance (lorcaserin; 0.1, 0.3, 1.0, 3.0, and 10.0 mg/kg) 60 minutes prior to being placed into the chamber (i.e., 75 minutes before testing) and during those sessions 10 responses on either lever resulted in delivery of a food pellet.

In order to demonstrate adequate stimulus control for the training conditions before embarking on studies with the test substance, individual rats had to respond at criterion levels (i.e., at least 80% injection-appropriate responding for the session and fewer than 10 responses on the inappropriate lever before completion of the FR on the appropriate lever) in a test session with saline and a separate test session with the training dose of DOM. When a rat failed to respond at criterion levels in either of those test sessions, training and testing continued until individual rats satisfied those criteria in test sessions.

Next, different doses of lorcaserin were tested with the order of different doses varying nonsystematically among animals. Rats had to satisfy the criteria noted above for two consecutive training sessions prior to each test with lorcaserin. After four doses (0.1, 0.3, 1.0, and 3.0 mg/kg) of lorcaserin were studied, rats were retested with saline and with the training dose of DOM. Data are reported only from animals that responded at criteria levels in these saline and DOM test sessions. For this component of the study to be considered complete, a minimum of 8 rats had to complete all tests and respond at criterion levels in the second saline and DOM test sessions (9 of 12 animals satisfied these criteria).

To confirm consistency across the study, the nine rats that satisfied criteria for lorcaserin, saline and DOM after the initial studies were tested again with lorcaserin at 3.0 and 10.0 mg/kg and with saline and the training dose of DOM.

Results

In drug discrimination studies, animals must select the training drug-appropriate lever at least 80% in order for the test drug to be considered to have full generalization to the training drug. After receiving the training drug DOM, rats responded an average of 98% on the drug-associated lever at the beginning of the study and 99% at the end of the study. Conversely, saline administration produced less than 4% responding on the DOM-associated lever at the beginning of the study and less than 2% at the end of the study. This consistency across the study validates the methodology. Notably, this consistency was not fulfilled in the previously-conducted drug discrimination study submitted in the first NDA for lorcaserin (Study # TOX08040).

As shown in Table 5 (below), an evaluation of the individual response data shows that lorcaserin produces full generalization to DOM in certain individual rats at each of the doses tested.

Administration of lorcaserin produces generalization to the DOM cue that is less than 20% for the 0.1, 3.0 and 5.0 mg/kg doses. At the 0.3 and 1.0 mg/kg doses of lorcaserin, there is partial generalization to the DOM cue, at 25% and 38%, respectively. Administration of 10.0 mg/kg of the test substance eliminated or markedly decreased responding in all 9 rats as follows: 5 rats failed to make a single response, 3 rats made one response each, and 1 rat responded at a markedly reduced rate. The single rat that responded after receiving this dose of the test substance responded exclusively on the DOM-associated lever.

Table 5: Individual Rat Responding on the DOM-Associated Lever by Lorcaserin

Rat	Lorcaserin 0.1 mg/kg	Lorcaserin 0.3 mg/kg	Lorcaserin 1.0 mg/kg	Lorcaserin 3.0 mg/kg (test #1)	Lorcaserin 3.0 mg/kg (test #2)	Lorcaserin 10.0 mg/kg
#1	0%	4%	0%	100%	100%	0%
#2	1%	0%	1%	8%	46%	--
#3	0%	2%	76%	85%	8%	100%*
#4	2%	9%	0%	2%	93%	--
#5	2%	99%	7%	25%*	97%	--
#6	0%	0%	0%	0%	1%	--
#7	100%	0%	0%	--	14%	0%
#8	0%	0%	100%	100%	6%	--
#9	0%	0%	0%	100%	100%	100%
mean	**12%**	**13%**	**20%**	**56%**	**53%**	**100%**

(--) = animals failed to respond on either lever
** animal did not respond 10 times during session, but percent completed on DOM lever is recorded*

Conclusions

In a test of drug discrimination in rats trained to recognize DOM (a $5HT_{2A}$ and $5HT_{2C}$ receptor agonist), individual data show that lorcaserin fully generalizes to the DOM cue in 7 of 9 rats following administration of at least one dose of lorcaserin (ranging from 0.1 to 10.0 mg/kg). Following administration of the two highest doses of lorcaserin (3.0 and 10.0 mg/kg), 4 of 9 rats showed full generalization to the DOM cue that ranged from 93% to 100%. At the 10 mg/kg dose of lorcaserin, only one rat completed the trial and showed 100% generalization to the DOM cue. One other rat did not fully complete the trial, but the responses that were made were 100% on the DOM-associated lever. The other 7 rats were unable to finish the trial. The Sponsor acknowledges that these data "suggest some DOM-like activity" of lorcaserin.

Clinical Study AE Data

Abuse-Related AEs in Clinical Efficacy and Safety Studies

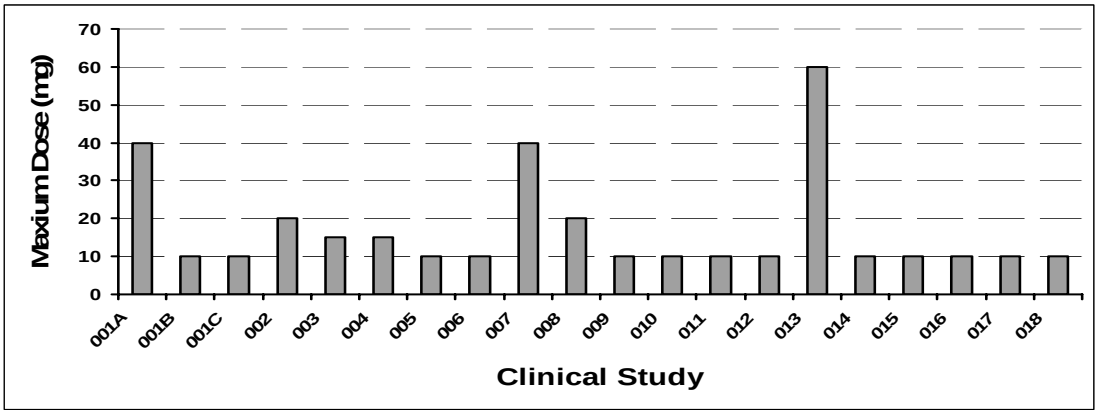
During lorcaserin development, the Sponsor conducted 13 Phase 1 clinical safety studies in healthy volunteers (n = 493) and 7 Phase 2/3 clinical safety and efficacy studies in obese patients (n = 8683). Since the Sponsor conducted most clinical trials with subtherapeutic doses, the overall abuse-related AE could be underestimated. Therefore, not only did we do the overall analysis for abuse related AEs in all clinical studies, but also for the high-dosage individual studies 001A and 013.

Our systematic analysis of abuse-related AEs, especially euphoria AE, indicates that lorcaserin show some abuse potential signals.

1. Limitation of the abuse-related AE data provided by the Sponsor due to subtherapeutic dosage in most clinical trials

In the "first study in human" Study #001A, the Sponsor's original plan was to test doses from 10 mg to 320 mg. This study was terminated at 40 mg dosage because of the unexpected serious abuse-related AEs. Since the conclusion of that study, the maximum acute oral dosages in the majority of the clinical studies (17 of 20) were limited to 10 or 15 mg of lorcaserin (Figure 1, below). Consequently, the outcome of the lorcaserin efficacy data analysis only met one of the Agency's two weight-loss efficacy requirements (CR letter).

Figure 1. Comparison of maximum dosage of lorcaserin in each clinical trial.



For lorcaserin, the incidence of efficacy and safety are dose-proportional. Thus, the reduction in the proposed therapeutic dose to 10-15 mg for safety reasons led to both a reduction in the incidence of AEs as well as a lower efficacy observed for weight loss.

Our concern is that the Sponsor underestimated the abuse-related AEs associated with lorcaserin with the lower dosage strategy in their clinical studies. If lorcaserin is approved for marketing, the obese patients may increase dosages to attempt greater therapeutic effects, with a subsequent increase in abuse related AEs.

Based on this concern, our analysis for abuse related AEs not only focuses on evaluation of the overall summary data of all clinical trials. We believe that those clinical studies with higher dosages, like study 001A, study 007, and study 013, would provide more valuable information for predicting the abuse potential of lorcaserin in a real world.

2. Overall analysis: abuse related AEs in all clinical studies

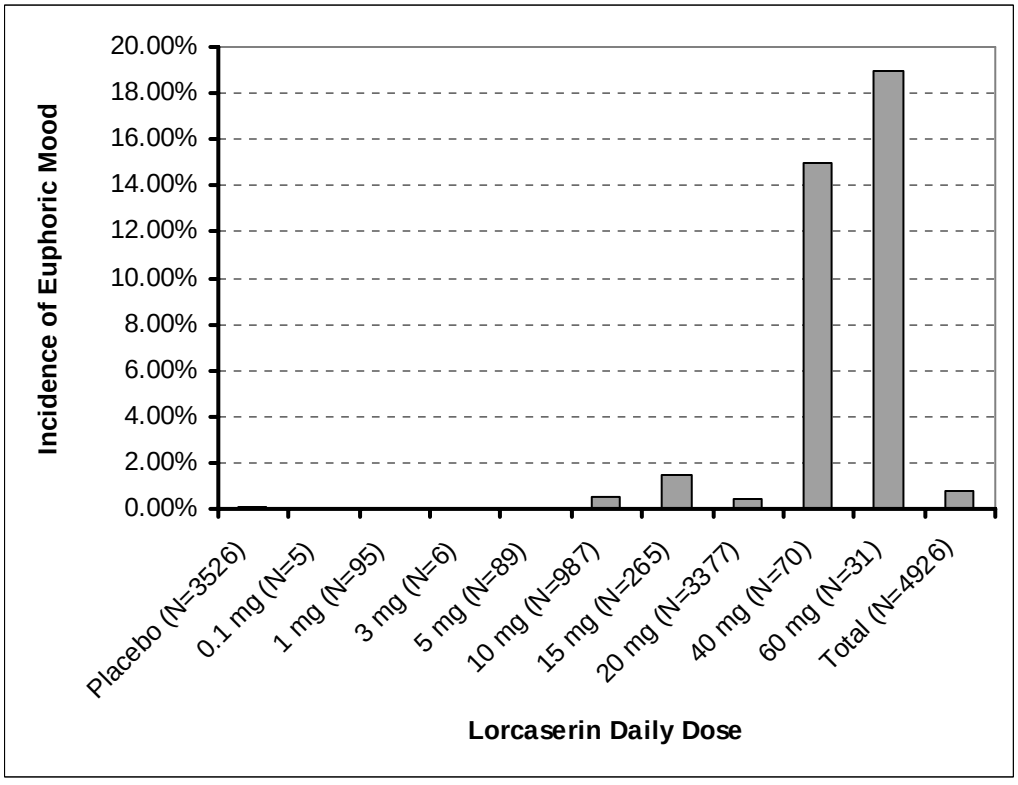
From the data the Sponsor provided, euphoric mood was evaluated as a primary AE indicative of abuse potential. These data show that lorcaserin-treated individuals had a higher incidence of euphoric mood than did placebo-treated individuals. Table 6 (below) presents a summary of euphoric mood reported in single and multiple dose studies conducted with lorcaserin in healthy volunteers (including polydrug abuser) and obese patients. Summed data from Phase 1 and Phase 2/3 studies show that the incidence of euphoric mood in the lorcaserin-treated group at doses ranging from 0.1 to 60 mg/day (0.8% overall; n = 38 of 4926 subjects) was dose dependent and almost 13 times higher than that reported in placebo-treated group (0.06%; n = 2 of 3526 subjects).

Figure 2 (below) demonstrates that the incidence of euphoric mood was dose-dependent. Individuals who received 40 mg lorcaserin (twice the proposed daily therapeutic dose and four times the proposed single therapeutic dose) reported a 16% incidence of euphoria (n = 11 of 70 subjects). When 60 mg lorcaserin (three times the proposed daily therapeutic dose and 6 times the proposed single therapeutic dose) was administered, there was a 19% incidence of euphoria (n = 6 of 31 subjects). Incidences of euphoria at the 40 and 60 mg doses are (respectively) 250 and 300 times greater than that reported following placebo administration.

Table 6: Incidence of Euphoric Mood across Phase 1 and Phase 2/3 Clinical Studies with Lorcaserin at 0.1 to 60 mg doses, relative to Placebo

Study	Dose	Placebo	Lorcaserin Daily Dose (mg)									
			0.1	1	3	5	10	15	20	40	60	Total
Phase I	Single	0 of 20 (0%)	0 of 5 (0%)	0 of 5 (0%)			0 of 35 (0%)		0 of 12 (0%)	4 of 6 (67%)	6 of 31 (19%)	
Phase I	Multiple	0 of 117 (0%)			0 of 6 (0%)		1 of 34 (2.9%)	4 of 60 (6.7%)	6 of 54 (11%)	7 of 64 (11%)		
Phase II & III	Multiple	1 of 3389 (0 03%)		0 of 90 (0%)		0 of 89 (0%)	4 of 918 (0.4%)	0 of 205 (0%)	6 of 3311 (0.18%)			
Total		2 of 3526 (0 06%)	0 of 5 (0%)	0 of 95 (0%)	0 of 6 (0%)	0 of 89 (0%)	5 of 987 (0.5%)	4 of 265 (1.5%)	12 of 3377 (0.4%)	11 of 70 (16%)	6 of 31 (19%)	38 of 4926 (0 8%)

Figure 2: Overview of Incidence of Euphoria Mood in Phase 1 and Phase 2/3 Clinical Studies with Lorcaserin in Healthy Volunteers and Obese Patients at 0.1 to 60 mg doses, relative to Placebo



3. Analysis of abuse related AEs in study 001A.

As we mentioned before, this "first study in human" 001A was not finished at its maximum dosage 320 mg. Expectedly, the Sponsor had to terminate it at 40 mg dosage due to the serious abuse related AEs.

Table 2 (below) shows data from Study 001A (as presented in the Sponsor's "Adverse Event Listing by Treatment" of Study #APD356-001 in NDA 22-529). The Sponsor reported an incidence of euphoric mood in 4 of 6 healthy individuals (67%) who were treated with 40 mg/day lorcaserin. In this group, another subject who didn't report euphoria had some other abuse-related AEs, such as mood altered. Therefore, 83% (5 of 6) healthy volunteers with 40 mg/day lorcaserin treatment reported various abuse-related AEs (Table 7).

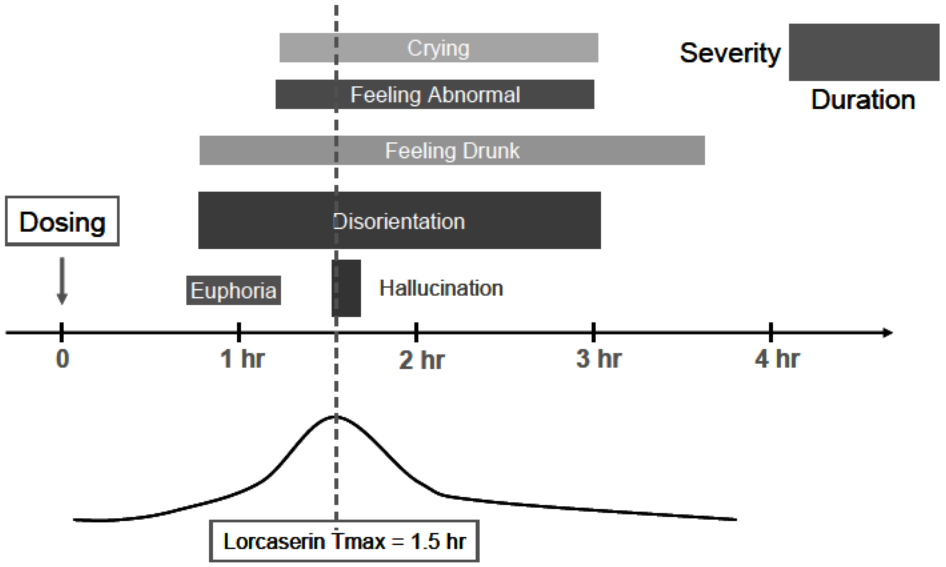
The most critical AE case report related to abuse potential occurred in a female obese patient who received 40 mg lorcaserin in Study 001A (Subject #25). On Day 1 of lorcaserin treatment, this woman experienced numerous abuse-related AEs, including euphoria, disorientation, and hallucination. The moderate euphoria began ~40 minutes after her morning dose of lorcaserin and persisted for ~30 minutes. She concurrently experienced severe disorientation that persisted for 140 minutes. Approximately 90 minutes after lorcaserin administration, she experienced severe hallucinations (loss of arm awareness) that persisted for 10 minutes.

Table 7: Abuse-Related AEs Patients Receiving 40 mg/day Lorcaserin (Study 001A)

Subject #	Euphoric Mood	Mood Altered	Disorientation	Feeling Drunk	Hallucination
19	+				
21	+				
23	+				
24		+			
25	+		+	+	+
27					

These AEs resulting from lorcaserin administration are of particular note because they are consistent with the behavioral profile of other 5HT2 agonists such as the hallucinogens, LSD, psilocybin, and DOM. It is noteworthy that these AEs occurred on the first day of lorcaserin administration, before 5HT2 receptor down-regulation and subsequent tolerance develops to lorcaserin. These data suggest that a motivated individual would be able to use lorcaserin for abuse purposes on an acute basis. More importantly, the multiple abuse-related AEs, like severe hallucination, severe disorientation, feeling drunk, feeling abnormal, all occurred in the period when the subject had highest blood concentration of lorcaserin (Figure 3). The good correlation of PK and AE here provided strong evidence to support that lorcaserin induced all those abuse related AEs in this subject.

Figure 3. Diagram showing the relationship of abuse-related AEs and PK for subject 25 in study 001A.



4. Analysis of abuse related AEs in study 013.

Study 013 is the human abuse potential study. It is the only study that reached the highest dosage 60 mg of lorcaserin in all clinical studies. It was conducted in a population of polydrug abusers. It is the only clinical study the Sponsor conducted to test the relative abuse potential of lorcaserin by comparing with other scheduled substances, such as ketamine (Schedule III) and zolpidem (Schedule IV). We analyzed and described euphoria in two aspects: incidence and duration.

Incidence of euphoria

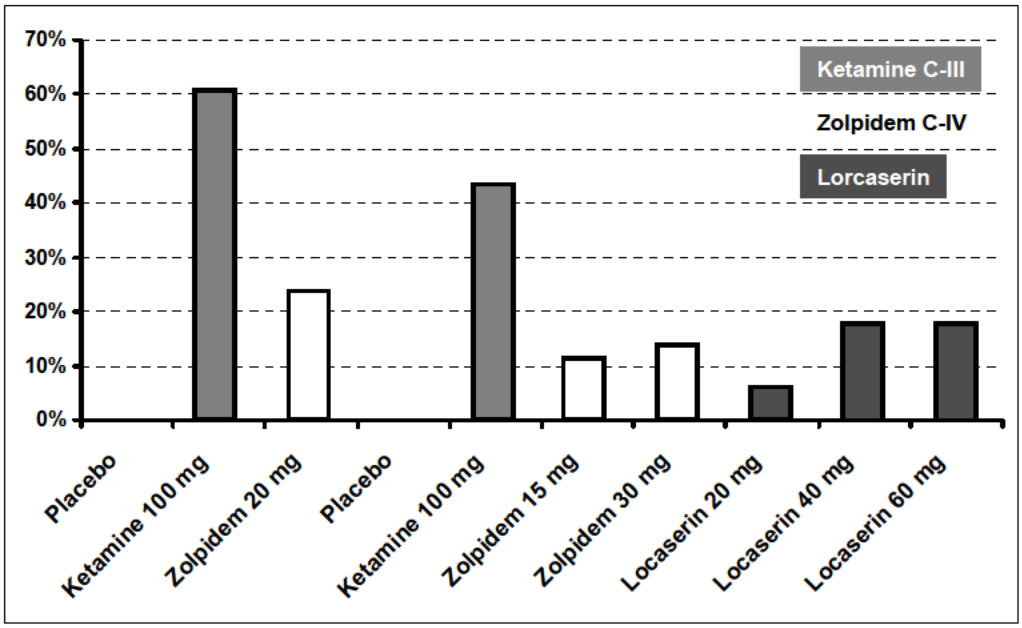
Table 8 shows the individual subject profile of euphoria AE in each treatment group of clinical study 013. Fewer subjects reported euphoria in the lorcaserin treatment groups than in the 2 positive control groups, ketamine and zolpidem. However, incidences of euphoria in response to both positive controls were lower in evaluation phase than in the qualification phase. Lorcaserin 40 mg and 60 mg had higher incidence of euphoria that Lorcaserin 20 mg.

The incidences of euphoria in each treatment group were showed as percentage in Figure 4. Overall, the incidence of euphoria in lorcaserin treatment groups (6-19%) was less than that of ketamine treatment groups (50%), but equal or slight higher than zolpidem treatment groups (13-16%) (Figure 4).

Table 8. Individual profile of euphoria AE in each treatment group of clinical study 013 (Pbo=Placebo, Q=Qualification Phase, L=Lorcaserin, K=Ketamine, Z=Zolpidem, T=Test Phase)

Subject ID	Pbo Q	K 100 Q	Z 20 Q	Pbo T	K 100 T	Z 15 T	Z 30 T	L 20 T	L 40 T	L 60 T
9004		●							●	
9006		●	○		●	○		●	●	●
9009		●	○		●					
9012		●			●					
9014			○		●	○	○			●
9024		●								
9027		●			●		○			●
9032		●			●		○			
9039		●			●				●	●
9041										
9042					●					
9043					●					
9050										
9054		●	○					●		
9056		●								
9059		●			●				●	
9068		●			●					●
9071		●	○							
9072					●	○			●	
9079		●								
9080		●							●	
9081		●	○		●					
9084										
9088		●	○							
9096										
9104										
9107					●					
9110						○	○			
9112										
9115		●			●		○			
9124		●								
9135		●	○							
9146		●								
9171										●
9178										

Figure 4. Incidence of euphoria in each treatment group of clinical study 013.

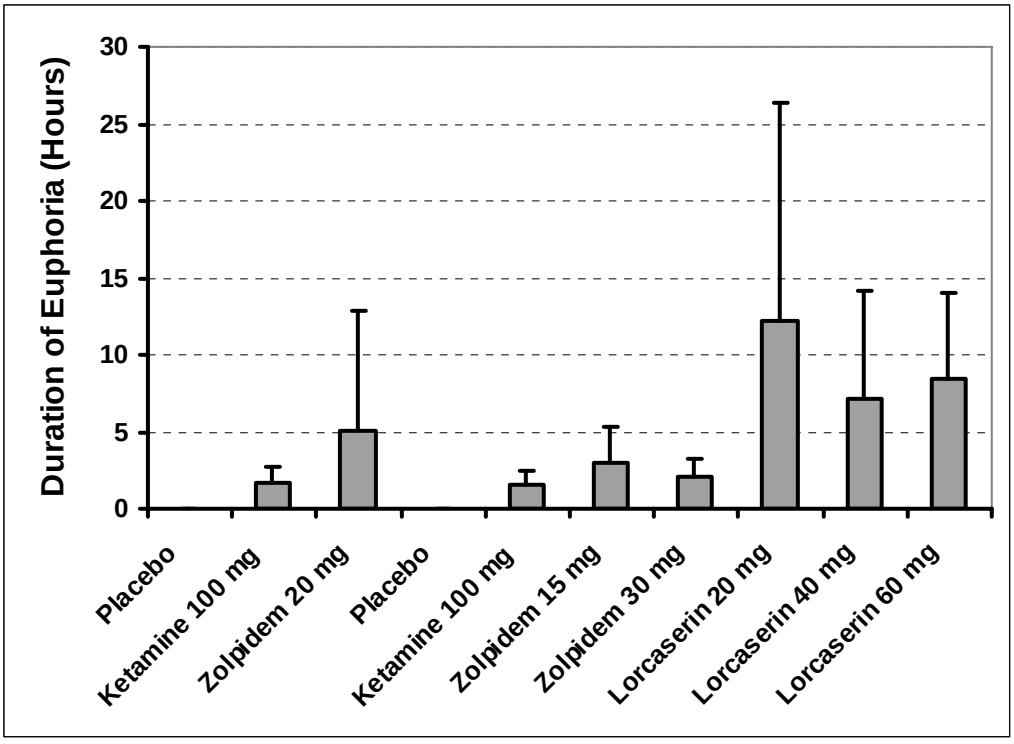


Duration of Euphoria

We generated the individual profile of euphoria duration in each treatment group of clinical study 013. It is obvious that several subjects in lorcaserin treatment groups had much longer duration of euphoria than what they had in both ketamine and zolpidem treatment groups.

The average time (hours) of euphoria in each treatment groups is shown in Figure 5. The duration of euphoria in lorcaserin treatment groups (12.2 hrs, 7.2 hrs, and 8.5 hrs for 20 mg, 40 mg, and 60 mg, respectively) was considerable longer than the durations of euphoria in the treatment groups for the two positive controls, ketamine (1.6 hrs) and zolpidem (3.0 hrs and 2.0 hrs for 15 mg and 30 mg, respectively).

Figure 5. Duration (Mean ± SD, hours) of euphoria in each treatment group of study 013.



5. Summary

The overall analysis of all available data for abuse related AEs indicated that lorcaserin produced an increased incidence of euphoria compared to placebo and the incidence of euphoria produced by lorcaserin was dose-dependent.

In clinical abuse potential study 013, the incidence of euphoria in lorcaserin treatment groups was less than that of ketamine treatment groups, but equal or slight higher than

zolpidem treatment groups. The duration of euphoria in lorcaserin treatment groups was much longer than that of two positive controls, ketamine and zolpidem.

The high incidence of abuse-related AEs in lorcaserin treatment group and dose dependent effects indicate that lorcaserin show drug abuse potential signals, especially at higher dosage. The longer duration of euphoria in lorcaserin treatment groups is a concern that is related to its abuse potential and safety.

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/s/

KATHERINE R BONSON
04/30/2012

Jianping P GONG
04/30/2012

MICHAEL KLEIN
04/30/2012

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 022529
Name of Drug: BELVIQ (lorcaserin HCl), 10 mg tablets
Applicant: Arena Pharmaceuticals

Labeling Reviewed

Submission Date: **December 23, 2011 and March 28, 2012 (email)**

Receipt Date: December 27, 2011 and March 28, 2012

Background and Summary Description

On December 18, 2010, Arena Pharmaceuticals submitted new drug application (NDA) 022529 for lorcaserin hydrochloride 10 mg tablets. Lorcaserin hydrochloride is a new molecular entity that targets activation of the serotonin 5HT2C receptor and is intended to promote weight loss in an obese population.

On October 22, 2010, the Agency issued a complete response letter, describing our concerns and the deficiencies in the data provided with the application. It also provided, where possible, our recommendations to address the issues.

The label format was not reviewed during the first review cycle. The applicant resubmitted NDA 022529 on December 23, 2011 (received 12/27/11). The label submitted on 12/27/11 was reviewed and an identical, unofficial WORD version was requested in order to make review of the PLR format somewhat easier. This was received on March 28, 2012.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

General

1. The symbols '<', '≤', '>', '≥' were utilized to represent "less than," "less than or equal too," "greater than," or "greater than or equal to," respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol. Symbols should be replaced with corresponding text.

2. The applicant numbered headings within subsections [e.g., (12.3.1 Metabolism)]. The company was told to use headings within a subsection without numbering [e.g., Metabolism]. (i.e. There should be no more than one decimal point.) For other labeling information (headings within subheadings), it was recommended that they use bold type sparingly. Italics or underline were suggested.

Highlights

3. Recommended referencing in Highlights with the numerical identifier in parentheses [e.g., (1)] following the summarized labeling information. It was pointed out the INDICATIONS AND USAGE section needed to be corrected.

4. Recommended including a concise statement of the drug's indications without the use of dashed lines. (INDICATIONS AND USAGE section requires correction.)

Full Prescribing Information (FPI)

5. The purpose of the required PATIENT COUNSELING INFORMATION section is to draw the prescriber's attention to the presence and content of a PPI, MG or Instructions for Use at the end of the labeling. It was recommended that the applicant include information for prescribers to convey to patients related to safe and effective use the drug (e.g., precautions concerning driving, concomitant use of other substances that may have harmful additive effects, adverse reactions reasonably associated with use of the drug, potential risks and benefits of use of the drug in pregnancy). This project manager recommended that the information, whether organized by subsection headings or bulleted items, should be listed in order of clinical importance. Also the company was reminded not to insert a PPI or MG under the Patient Counseling Information section in lieu of developing this section.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in an advice letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies within three weeks. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager Date

Chief, Project Management Staff Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

☒ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

☐ There is no redundancy of information.

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

☐ A horizontal line must separate the HL and Table of Contents (TOC).

☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

☒ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☒ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☒ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☒ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☒ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

  > "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

  ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

  > "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

  - "See FDA-approved patient labeling (Medication Guide)"
  - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information)"
  - "See FDA-approved patient labeling (Instructions for Use)"
  - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

PATRICIA J MADARA
04/06/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date:	March 21, 2012
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products
Through:	Michael Klein, Ph.D., Director Silvia Calderon, Ph.D., Team Leader Controlled Substance Staff
From:	Katherine Bonson, Ph.D., Pharmacologist J.P. Gong, M.D., Medical Officer Controlled Substance Staff
Subject:	Lorcaserin (b) (4), NDA 22-529 Indication: Weight Management Dose: 20 mg/day; 10 mg BID Sponsor: Arena Pharmaceuticals
Materials reviewed:	NDA 22-529; scientific and medical literature

Table of Contents

I. SUMMARY

A. Background:

CSS reviewed the abuse-related data submitted in NDA 22-529 for lorcaserin. This memorandum informs the Division and the Sponsor of the CSS recommendation to schedule lorcaserin in Schedule IV of the Controlled Substances Act. This conclusion is based on our assessment of nonclinical and clinical studies.

B. Conclusions:

1. The known pharmacology of lorcaserin predicts the abuse-related adverse events (AEs) of the drug in humans.
2. The rate of euphoria of lorcaserin is similar to that produced by the Schedule IV drug, zolpidem (13-16%).
3. Of greatest concern is that the psychiatric and neurological AEs are produced by lorcaserin at doses that are only 2-3 times that of the proposed therapeutic doses for the indication of weight loss.
4. The therapeutic index of lorcaserin is narrow relative to its abuse-related safety index.

C. Recommendation (to be conveyed to Sponsor):

CSS is recommending that lorcaserin be scheduled in Schedule IV of the Controlled Substances Act.

D. Discussion

Lorcaserin has a mechanism of action involving agonism at 5HT2 receptors that is similar to that of hallucinogens such as lysergic acid diethylamide (LSD) and 2,5-dimethoxy-4-methamphetamine (DOM). Animal studies confirmed that lorcaserin produces effects similar to those produced by DOM, as shown by full generalization between lorcaserin and the DOM cue in a drug discrimination test. Lorcaserin also produced overt behaviors associated with 5HT2 receptor activation, such as wet dog shakes, penile grooming, similar to DOM. In a human abuse potential study using individuals with histories of hallucinogen use, lorcaserin produced an increase in positive subjective measures such as “High”, “Good Drug Effects” and “Hallucinations”, similar to the Schedule IV drug, zolpidem. In clinical safety and efficacy studies, lorcaserin produced euphoria and hallucinations in 11 out of 70 patients (16%) at a dose that was only two times the highest proposed daily therapeutic dose. This rate of euphoria is similar to that produced by the Schedule IV drug, zolpidem (13-16%). Overall, these data suggest that lorcaserin has an abuse potential that is most similar to that produced by Schedule IV drugs.

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/s/

KATHERINE R BONSON
03/21/2012

Jianping P GONG
03/21/2012

SILVIA N CALDERON
03/21/2012

MICHAEL KLEIN
03/21/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****Pre-decisional Agency Information****

Memorandum

Date: November 8, 2010

To: Patricia Madara, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Kendra Jones, Regulatory Review Officer
Shefali Doshi, Acting Group Leader, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC

Subject: NDA 022529

DDMAC labeling comments for Lorqess (lorcaserin HCl) Tablets

We acknowledge receipt of your January 14, 2010, consult request for the proposed product labeling for Lorqess (lorcaserin HCl) Tablets, NDA 022529. Final labeling negotiations were not initiated during this review cycle and a Complete Response letter was issued on October 22, 2010. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions on the Prescribing Information, please contact Samuel Skariah at 301. 796.2774 or Sam.Skariah@fda.hhs.gov.

If you have any questions on Patient Labeling, please contact Kendra Jones at 301.796.3917 or Kendra.Jones@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
11/10/2010

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

REVIEW DEFERRAL MEMO

Date: November 1, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

From: Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management

Subject: Review Deferred: DRISK Review of Patient Labeling

Drug Name(s): Lorqess (lorcaserin hydrochloride) Tablet

Application Type/Number: NDA 22-529

Applicant/Sponsor: Arena Pharmaceuticals, Inc.

OSE RCM #: 2010-1228

This memorandum documents the deferral of our review of Lorqess (lorcaserin hydrochloride) Tablet. On June 1, 2010, the Division of Metabolism and Endocrinology Products (DMEP) requested that DRISK attend team meetings to become aware of safety concerns in the event that the Review Division needed to request a Medguide and communication plan. The Applicant did not submit any patient labeling.

On October 22, 2010 the Division of Metabolism and Endocrinology issued a Complete Response (CR) due to outstanding nonclinical and clinical deficiencies. DMEP does not plan to address labeling at this time. Therefore, DRISK defers comment on the sponsor's labeling at this time. A final review will be performed after the sponsor submits patient labeling to the Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

BARBARA A FULLER
11/01/2010
Consult Defer memo for Lorqess (lorcaserin hydrochloride) patient labeling.

LASHAWN M GRIFFITHS
11/01/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 28, 2010

TO: William Boyd, MD, Cross Discipline Team Leader
Division of Anti-Infective and Ophthalmology Products

FROM: Kassa Ayalew, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: NDA 22-529

APPLICANT: Arena Pharmaceuticals
6166 Nancy Ridge Drive
San Diego, CA 92121
Contact Information
Mark Brunswick, Ph.D.
Senior Director Regulatory Affairs
mbrunswick@arenapharm.com
Ph (858)-453-7200
Fax (858)-677-0222

DRUG: Lorqess (lorcaserin hydrochloride)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

PROPOSED INDICATION: 1) for weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet and a program of regular exercise

2) for obese patients with an initial body mass index ≥30 kg/m2, or overweight patients with a body mass index ≥27 kg/m2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea)

CONSULTATION REQUEST DATE: January 20, 2010

PDUFA: October 22, 2010

I. BACKGROUND: The sponsor, Arena Pharmaceuticals, Inc. submitted a New Drug Application (NDA) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lorquess (lorcaserin hydrochloride) tablets, 10 mg, on a letter dated December 18, 2009 to support a labeling claim indicated for the treatment of weight management, including weight loss and maintenance of weight loss in conjunction with a reduced-calorie diet and a program of regular exercise. The proposed indication is intended for obese subjects with an initial body mass index ≥30 kg/m^2, or overweight subjects with a body mass index ≥27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).

The product Lorquess (lorcaserin hydrochloride) has never been marketed in the United States. Lorcaserin hydrochloride (hereafter, lorcaserin) is designed to activate 5-HT2C receptors. It is a potent and selective agonist for the 5-HT2C receptor that has no serotonin-releasing properties. A common risk associated with serotonin 2C agonist therapy is Serotonin Syndrome. Serotonin syndrome requires immediate medical attention and may include one or more of the following symptoms: mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Valvular Heart Disease: Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, has been reported in otherwise healthy persons who took non-selective serotonergic drugs such as fenfluramine or dexfenfluramine for weight loss.

To support the approval, the Applicant provided data from 3 double blind, placebo controlled clinical trials (one phase 2, two phase 3) with study durations ranging from 12 to 104 weeks that included information about safety and efficacy of Lorqess for weight loss and/or maintenance of weight loss. The protocols inspected were Protocol APD356-009 and Protocol APD356-011. Brief descriptions of the studies inspected are provided below:

Protocol APD356-009

APD356-009 (Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) was a 104-week, randomized, placebo controlled, double blind, parallel arm study of the efficacy and safety of lorcaserin in 3182 obese and overweight adult subjects with at least 1 weight-related co-morbid condition. A dose of

10 mg BID was evaluated. All subjects underwent lifestyle modification counseling. Efficacy for weight loss was primarily assessed in the lorcaserin 10 mg BID group as compared to placebo at Week 52. Efficacy for weight maintenance was assessed during the second year of the trial: at Week 52, subjects assigned to lorcaserin were re-randomized 2:1 to remain on lorcaserin or to switch to placebo; all subjects on placebo remained on placebo. Subjects with pre-existing echocardiographic findings that met FDA valvulopathy criteria (mild or greater aortic regurgitation or moderate or greater mitral regurgitation) were excluded. Safety assessments included echocardiograms at screening, Week 24, Week 52, Week 76, and Week 104.

Protocol APD356-011

Prtocol APD356-011 (Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) was a 52-week, randomized, placebo controlled, double blind, parallel arm study of the efficacy and safety of lorcaserin in 4008 obese subjects and overweight subjects with at least 1 weight-related co-morbid condition. Doses of 10 mg QD and 10 mg BID were evaluated. All subjects underwent lifestyle modification counseling. Efficacy for weight loss was primarily assessed in the lorcaserin groups as compared to placebo at Week 52. Safety assessments included echocardiograms at baseline, Week 24 and Week 52.The primary efficacy parameter in these studies was weight loss at 1 year, which was assessed by percent of subjects achieving ≥5% weight loss at 1 year, mean weight loss at 1 year, and percent of subjects achieving ≥10% weight loss at 1 year. Protocol APD356-011 had no echocardiographic inclusion/exclusion criteria. Hence, the 4008 subjects enrolled in the study APD356-011 had a spectrum of echocardiographic findings that should be representative of the target subject population. In general the above two studies had similar eligibility criteria.

The primary efficacy endpoints for study were the mean weight change from baseline, proportion of subjects who lost 5% of baseline body weight and proportion of subjects who lost 10% of baseline body weight at 1 year.

Four domestic clinical investigators were selected for inspection, mainly due to high enrollment.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: Site #/ Subjects:	Inspection Date	Final Classification
Bruce Berwald, M.D Radiant Research, Inc. 675 Old Ballas Rd. St Louis, MO 63141	BLOOM (APD356-009)/ 107/ 260	03/24/2010 - 04/06/2010	*Pending (Interim classification: VAI)

Lydie Hazan, M.D 5800 Wilshire Blvd Los Angeles, CA 90036	BLOOM (APD356-009)/ 122/465	4/12/2010-4/26/2010	*Pending (Interim classification: VAI)
Leslie Moldauer, M.D Radiant Research 12015 E. 46th Avenue, Suite 500 Denver, CO 80239	BLOSSOM (APD356-011)/ 2145/127	4/19/2010-4/23/201	NAI
Martin Mollen, M.D Arizona Research Center 2525 W. Greenway Road, Suite 114 Phoenix AZ 85023	BLOSSOM (APD356-011)/ 202	3/24/2010-4/7/2010	*Pending (Interim classification: VAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and/or complete review of EIR is pending.

1. **Bruce Berwald, M.D**
   Radiant Research, Inc.
   675 Old Ballas Rd.
   St Louis, MO 63141
   Phone (314) 692-2100

   a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between 03/24/2010 - 04/06/2010.

      At this site a total of 261 subjects were screened of which 122 were enrolled in the study. Of the 122 enrolled, 42 subjects completed the study. The inspection included review of records for 122 subjects who were randomized. The following items were reviewed for verification: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequacy of adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

   b. **General observations/commentary**: The inspection of Dr. Bruce Berwald's site revealed deficiencies related to the conduct of the study. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

      1) Failure to adequately maintain investigational drug disposition records with respect to dates, quantity, and use by subjects. For example, there were occurrences of missing dates and initials for when and who dispensed and accepted return of

investigational product. In addition, the quantities dispensed, taken, returned, and lost cannot be reconciled for some subjects in isolated occasions during the course of the trial.

Table 1: Frequency of failure to maintain drug disposition records with respect to dates, quantity, and use by subjects during 22 visits

Frequency of Failure to maintain drug disposition records during 22 visits	# of subjects with missing dates	# of subjects with missing initials	# of subjects with drug reconciliation issues
1	16	20	21
≥2	7	19	9

DSI Reviewer Comment*: the clinical investigator failed to maintain investigational drug disposition records with respect to dates, initials, quantity, and use by subjects. The problem with drug accountability records appears more related to the mistakes in calculating the quantity of drugs dispensed, taken, lost and returned. In all of the 30 subjects with drug accountability issues, the problems were inaccurate calculation and documentation. In most of the instances, the numerical difference between the quantity dispensed and either taken, lost or returned was very small. There was source documentation to show that subjects received drugs to which they were assigned/randomized. This finding is therefore unlikely to significantly impact data evaluability.*

2) Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to drug administration and conducting study-related tests. Specifically, three female subjects (052/CSEZ, placebo), (095/CAD, placebo), and 238/DE (Lorcaserin, 63 years old women, completed 52 weeks), did not sign the Child Bearing Informed Consent prior to participation in study related activities. One subject, Subject 119 RMS (38 years old women receiving placebo) failed to put the date after signing the informed consent.

DSI Reviewer Comment: *Signed Informed Consent Documents (ICDs) could not be located in the source document files for the 3 subjects. Of the 3 subjects where informed consent could not be located, only one subject (63 years old women) was assigned to receive Lorcaserin. The other 2 were assigned to receive placebo. Although, the signed ICDs could not be located, there is documentation in the CRF which noted that informed consent was obtained, and participants were given copies of the informed consent. This violation denotes a failure to maintain records pertinent to the conduct of the study; however, given that there is other documentation to support that informed consent was obtained (even though the ICDs could not be located), the rights, safety, and welfare of subjects don't appear to have been compromised, and the nature of this specific finding is unlikely to impact, data reliability.*

3) Failure to ensure that study personnel performed only their designated responsibilities as required by the protocol and did not ensure that all employees assisting in the conduct of the study were trained prior to performing study related activities. Employee CR (a registered nurse) performed the role of Dietitian/Diet Counselor and was not authorized to do so by the Principal Investigator. In addition, employee (b) (6) and employee (b) (6) performed the study inclusion/exclusion, study screening visit, completed case report forms, and consented subjects. Both employees were not listed on the Delegation of Authority Form.

DSI Reviewer Comment: *the clinical investigator did not ensure that study personnel performed only their designated responsibilities as required by the protocol. Some performed multiple tasks outside their designated area. Although the clinical investigator failed to ensure that the study personnel perform only their designated responsibilities, the tasks the personnel involved were supported with sponsor provided interview guidance instructions or forms. Although the above protocol violations were noted, it is unlikely that they significantly affect overall reliability of efficacy and safety data from the site.*

4) Failure to ensure that study subjects were randomized and dosed within the 28 day window from the screening date. Sponsor exemption requested repeat labs for subject safety and the clinical investigator e failed to obtain lab results prior to dosing. Specifically, 22 subjects were randomized and dosed out of the 28 day window from the screening date.

DSI Reviewer Comment*: The clinical investigator failed to randomize and dose subjects within the 28 day window from the screening for 22 subjects. A total of 14 (63%) of the 22 subjects were randomized ≤ 2 weeks out from the window period. Although the clinical investigator failed to randomize and dose subjects within the 28 day window from the screening, the clinical investigator obtained lab tests on the day of randomization which were normal. The clinical investigator also requested waiver for 10 subjects after they started participating in the study. Although, the clinical investigator failed to ensure that study subjects were randomized and dosed within the 28 day window from the screening date according to investigational plan, the clinical investigator obtained lab tests on the day of randomization. The test results for all subjects were acceptable and can be used to provide the status of subjects at the time of screening. This finding is therefore unlikely to impact data reliability.*

5) Nine subjects failed to return the unused portion and empty blister packs of the investigational drugs that were dispensed to them at their previous study visit. Sponsor drug accountability training required that subjects bring back medication or be rescheduled for their visit or dropped from the study. Subjects who failed to return medication include 004 (b) (6), 017 (b) (6), 039 (b) (6), 062 (b) (6), 075 (b) (6), 084 (b) (6), 207 (b) (6), 216 (b) (6), and 258 (b) (6). These subjects were all dispensed additional investigational product and were allowed to continue in the study.

DSI Reviewer Comment: *The CI did not ensure that subjects return the unused portion and empty blister packs of the investigational drugs that were dispensed to them at their previous study visit. However, review of the drug accountability logs collected during the inspection and provided in the EIR shows that all subjects received drug to which they were randomized. Although the clinical investigator failed to ensure that subjects return the unused portion and empty blister packs of the investigational drugs, which is a regulatory violation, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

6) Failure to report promptly to the sponsor adverse affects that may reasonably be regarded as caused by, or probably caused by, an investigational drug. Specifically, the following serious adverse events (SAE) were not reported to the sponsor within 24 hours of notification as required by the protocol, although they were eventually reported:

   - SAE for subject 130/ (b) (6), "Worsening Incontinence/Bladder Sling Surgery", occurring (b) (6), reported to site 8/11/08, and reported to Sponsor 1/15/09.
   - SAE for subject 151/ (b) (6), "Rectal Prolapse/Surgery", occurring (b) (6), reported to site 7/1/08, reported to sponsor7/16/08.

DSI Reviewer Comment: *Although the clinical investigator failed to assure timeliness of reporting of serious adverse events to the sponsor, based on DSI's review of the EIR, all subjects with serious adverse events were reported to the sponsor. Although the clinical investigator failed to assure timeliness of reporting of serious adverse events according to the investigational plan, which is a regulatory violation, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

7) Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects. Specifically, the following serious adverse events (SAE) were not reported promptly to the IRB

   - SAE for subject 130/ (b) (6), "Worsening Incontinence/Bladder Sling Surgery", occurring (b) (6), reported to site 8/11/08, and reported to IRB1/15/09.
   - SAE for subject 144/ (b) (6), "Worsening of Rectocele/Surgery", reported to sponsor 11/19/07 and reported to the IRB 4/21/08.
   - SAE for subject 151/ (b) (6), "Rectal Prolapse/Surgery", occurring (b) (6) reported to site 7/1/08, reported to sponsor7/16/08, and reported to the IRB8/4/08

DSI Reviewer Comment: *Although the clinical investigator failed to assure timeliness of reporting of serious adverse events to the IRB, based on DSI's review of the EIR, all subjects with serious adverse events were reported to the IRB. This finding is unlikely*

to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

c. **Assessment of data integrity**: While the FDA inspection revealed several regulatory violations of clinical investigator obligations in the conduct of the study, overall data derived from Dr. Bruce Berwald,'s site appear reliable, as the findings were not considered pervasive and or the nature of the findings is unlikely to impact data reliability.

Note: A letter received from Radiant Research regarding the inspection conducted 3/24/2010-4/6/2010 for Arena Pharmaceuticals, Inc., protocol APD356-009 BLOOM, indicates that Dr Bruce Berwald, M.D has elected to discontinue his role as a clinical investigator as May 1, 201 and instead dedicate himself to his private practice of medicine full time.

2. **Lydie Hazan, M.D**
5800 Wilshire Blvd
Los Angeles, CA 90036

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between 4/12/2010-4/26/2010.

At this site, a total of 465 subjects were screened and 208 subjects were enrolled and 34 subjects completed the study. The inspection evaluated informed consent and included review of source documents and hard copy reporting for 106 subjects. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting, and 5) handling of pharmacokinetic samples. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**: In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued to this investigator for:

Failure to inform the IRB about changes in the length of study visit procedures. Specifically, the protocol allowable window for study visit procedures states that Echocardiograms for Week 104 visits (final study drug dose and visit) are to be performed within 14 days after the final dose of study drug. The sponsor requested this site implement "out of window" Week 104 Echocardiograms to be performed within 14 days of the ideal visit date, which was calculated using each subject's randomization date, instead of within 14 days after the final dose of the study drug. The IRB was not notified of these changes nor did the site receive IRB approval prior to changing the 14-day window for the Echocardiograms. Examples of subjects that received Echocardiograms outside

the 14 day window for Week 104 includes Subjects #'s 045, 192, 96,197,203,233,239,141,256,382,390, and 403. The IRB was not notified of these changes nor did the site receive IRB approval prior to changing the length of the Echocardiogram study.

DSI Reviewer Comments: *the clinical investigator followed the sponsor's request to perform "out of window" Week 104 Echocardiograms within 14 days of the ideal visit date, which was calculated using each subject's randomization date, instead of within 14 days after the final dose of the study drug as indicated in the approved informed consent by the IRB. The clinical investigator should have informed the IRB of the changes and obtained IRB approval prior to changing the length of the study. Although the clinical investigator failed to inform and obtain an IRB approval about changes in the length of study visit for Echocardiogram according to the investigational plan, which is a regulatory violation, the change in the time period to conduct the Echocardiogram appears unlikely to impact the clinical course, data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.*

c. Assessment of data integrity:

While the FDA inspection revealed regulatory violations in the conduct of the study, overall data derived from Dr. Lydie Hazan's site appear reliable, as the nature of the findings is unlikely to impact data reliability.

3 Leslie Moldauer, M.D
Radiant Research
12015 E. 46th Avenue,
Suite 500
Denver, CO 80239

a. **What was inspected**:

This inspection was conducted in accordance with Compliance Program 7348.811 between 4/19/2010-4/23/201.

At this site, a total of 126 subjects were screened and 81 subjects enrolled and 40 subjects completed the study. The informed consents for the 25 subjects enrolled were reviewed and verified to have been correctly completed. Additionally, an in-depth review of records for these 25 subjects was conducted during the inspection. Records for an additional 14 subjects that were either screen failures or that had terminated early from the study were also reviewed to ensure protocol compliance. The inspection evaluated informed consent and included review of source documents and hard copy reporting. Study subject files were reviewed for verification of: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, 4) adequate adverse experience reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. **General observations/commentary**:
In general, the study was conducted appropriately and no significant issues were identified. A Form FDA 483, Inspectional Observations, was not issued to this investigator.

d. **Assessment of data integrity**:
Based on the provided EIR for this site, data derived from Dr. Moldauer's site are considered acceptable.

4 Martin Mollen, M.D
Arizona Research Center
2525 W. Greenway
Road, Suite 114
Phoenix AZ 85023

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811 between 3/24/2010-4/7/2010.

At this site, 202 subjects were screened and 125 enrolled with 61 completing the study and 64 early terminations, consented, and randomized. An audit of 16 study subjects' records was conducted during the inspection. Review of records included, but was not limited to, verification of data line listings for efficacy endpoint data, adverse event reporting, and subject discontinuations; subject eligibility; informed consent documentation; test article accountability/disposition; Ethics Committee approvals; monitoring records; electric case report forms; concomitant medication usage, and adherence to protocol-specified procedures for blinding and randomization. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Mollen's site revealed that the study was not conducted in accordance with the investigational plan. A Form FDA 483, Inspectional Observations, was issued to this investigator because of the following regulatory violations observed during the inspection:

1) Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, subjects who met exclusion criteria were included in the study:

The study protocol required excluding subjects from the study if they tested positive for Hepatitis C. Two subjects (Subject 2146-046 and Subject 2146-S112 tested positive for Hepatitis C) who met exclusion criteria at screening were included in the study.

DSI Reviewer Comments*: the study protocol required excluding subjects from the study if tested positive for Hepatitis C. Although the clinical investigator failed to*

exclude the above subjects from the study according to the investigational plan, given the follow up hepatitis C RNA test and liver function tests were normal in both subjects, the observed violation may not have significant impact on the safety and welfare of the above subjects. They do not also appear to impact on data reliability or safety.

2) **An abnormal ECG at screening was an exclusion criterion in the protocol. A subject (Subject 2146-S161) was enrolled in the study despite having an abnormal ECG (QTc prolongation) at screening. This subject was early terminated by the sponsor's request.**

DSI Reviewer Comments: *The study protocol required excluding subjects from the study if they had abnormal ECG at screening. The clinical investigator excluded the subject from the study for QTc elevation per sponsor request. Given the fact that Valvular Heart Disease is a common risk associated with serotonergic drugs such as fenfluramine or dexfenfluramine for weight loss, the subject should have been excluded from the study at the time of screening. Although the clinical investigator failed to follow protocol requirements for excluding subjects from the study, based on DSI's review of the EIR the observed violation was an isolated occurrence and does not appear to impact on data reliability or safety.*

3) A subject (Subject 2146-S107) was screened and randomized into the study while using opiates for dally treatment and received concomitant lipid lowering agent for treatment of dyslipidemia

DSI Reviewer Comments*: The study protocol required excluding subjects from the study if using opiates and concomitant lipid lowering agent for treatment of dyslipidemia. The CI failed to exclude Subject 2146-S107 who was using opiates and lipid lowering agent during the study. Although the clinical investigator failed to follow protocol requirements for excluding subjects from the study, based on DSI's review of the EIR the observed violation was an isolated occurrence and does not appear to affect data reliability.*

4) The screening laboratory procedures (hematology and urine analysis) for inclusion/exclusion criteria were not complete (Subject 2146-8023).

DSI Reviewer Comments: *The study protocol required that the CI obtain and review clinical laboratory tests such as serum chemistry, hematology, urinalysis, virology screens, drugs of abuse screens, and urine pregnancy testing for inclusion and exclusion criteria at screening. The clinical investigator performed laboratory tests that were required for inclusion and exclusion at screening. Although, the CI obtained the specimens, hematology (Complete Blood Count) and urinalysis, these tests were not performed by the laboratory due to the age of the specimens. Those tests should have been repeated and reviewed at the time of screening. Based on DSI's review of the EIR, the observed violations were isolated occurrences and do not appear to affect data reliability, safety and welfare of subjects in the study.*

5) Failure to report to the sponsor adverse events from 3 subjects that may reasonably be regarded as caused by, or probably caused by, an investigational drug. Those adverse events include Tricuspid regurgitation and arrhythmia (Subject # 2146-S112, on Lorcaserin 10 mg BID), insomnia (Subject # 2146-S024, Placebo) and cold (Subject # 2146-S023, Lorcaserin 10 mg QD).

DSI Reviewer Comments*: The clinical investigator failed to report adverse events in 3 subjects as required by the protocol. In particular, adverse events, Tricuspid regurgitation and arrhythmia (Subject # 2146-S112, Lorcaserin 10 mg BID) should have been reported to the sponsor. Although, the CI failed to report the above adverse events to the sponsor, those events were isolated and we do not think they significantly affect overall reliability of efficacy and safety data from the site. However the review division may choose to consider including the adverse events in the safety analysis.*

6) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent.

- Specifically, source documents do not always match electronic case report form for some parameters including weight (Subject # 2146-S023 at week 2, Subject # 2146-S001 at week 20), hip circumference (Subject # 2146-S0184 at week 52), blood pressure (Subject # 2146-S090 at week 20) and heart rate (Subject # 2146-S184 at week 36).

- There was no adequate documentation of vital signs for one subject at one of the 22 visits (Subject 2146-S024)

- There was no reconciliation between quantities of study drug dispensed and quantities of study drug returned for one subject at one of the visits (Subject 2146-S122)

- Informed consent was signed in the wrong place for one subject (Subject # 2146-050)

- Subject dietary and behavioral diaries were not properly maintained for one subject (Subject # 2146-0158)

DSI Reviewer Comment: *Although, the CI failed to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent, which is a regulatory violation, the violations were isolated and rare. Therefore, we do not think the observed regulatory violations would impact data integrity or reliability.*

6) Failure to obtain approval by Institutional Review Board before increasing the number of subjects for enrollment. Specifically, the protocol allows for a maxim of 50 subjects per site unless otherwise approved by the sponsor. The sponsor approved this site for

125 subjects in 25 increments (75, 100, and 125 subjects, respectively) throughout the course of the study. The changes in the enrollment number of subjects have not been updated in the protocol and the CI never received an IRB approval for the increase in enrollment. This should have been conducted according to the protocol (1.3 Ethics and Regulatory Considerations, page 22).

DSI Reviewer Comment*: The clinical investigator failed to obtain IRB approval prior to making changes in the maxim number of subjects for enrollment at his site. An IRB approval and changes in the protocol should have been done before increasing the number of subjects for enrollment. Although, the CI failed to obtain the IRB before changing the number of subjects for enrollment, he obtained an approval by the sponsor. The observed regulatory violation do not appear to significantly affect data reliability or integrity from Dr. Mollen's site.*

c. Assessment of data integrity:

Although the above regulatory violations were noted, it is unlikely that these findings would affect subject data reliability or integrity. In general, based on the provided Establishment Inspection Report (EIR) for this site, data derived from Dr. Mollen's site is considered a reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the studies appear to have been conducted adequately and the data in support of the NDA appear reliable.

The preliminary classification of Clinical Investigator inspections of Dr. Bruce Berwald, Dr Lydie Hazan and Dr. Martin Mollen, are Voluntary Action Indicated (VAI). The final classification of the Clinical Investigator inspections of Dr. Leslie Moldauer is No Action Indicated (NAI). Although regulatory violations were noted at the sites of Drs. Berwald, Hazan, and Mollen, these are considered isolated or the nature of the findings are unlikely to significantly impact reliability of the data. The data are considered reliable in support of the application.

Note: Final classification for Drs. Berwald, Hazan, and Mollen are pending and will be determined when the final EIR and associated exhibits are received and/or reviewed. Should the final classification for Clinical Investigators be different from the current preliminary classification, the Division will be notified and an inspection summary addendum will be generated.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASSA AYALEW
10/01/2010

TEJASHRI S PUROHIT-SHETH
10/01/2010

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date:	September 3, 2010
To:	Mary Parks, M.D., Director Division of Metabolism and Endocrinology Products
Through:	Michael Klein, Ph.D., Director Controlled Substance Staff
From:	Katherine Bonson, Ph.D., Pharmacologist J.P. Gong, M.D., Medical Officer Controlled Substance Staff
Subject:	Lorcaserin (Lorquess), NDA 22-529 Indication: Weight Management Dose: 20 mg/day; 10 mg BID Sponsor: Arena Pharmaceuticals
Materials reviewed:	NDA 22-529; scientific and medical literature

Table of Contents

I. SUMMARY

A. Background

This memorandum summarizes our findings related to the abuse potential assessment of lorcaserin (Lorquess, NDA 22-529), as requested by the Division of Metabolism and Endocrinology Products, to help determine appropriate labeling and scheduling of the drug. The PDUFA date for the NDA is October 22, 2010. Lorcaserin is not marketed in any country.

The proposed indication for lorcaserin is weight management, including weight loss and maintenance of weight loss, in conjunction with reduced-calorie diet and regular exercise. The proposed dose range is 20 mg/day (10 mg BID). The Sponsor asserts that lorcaserin has no abuse potential and should not be controlled under the CSA.

Lorcaserin is a new molecular entity that has high affinity for $5HT_{2C}$ and $5HT_{2A}$ receptors in human brain tissue. As a $5HT_{2C}$ and $5HT_{2A}$ agonist, lorcaserin has an identical mechanism of action as that of Schedule I hallucinogens such as lysergic acid diethylamide (LSD), psilocybin and 2,5-dimethoxy-4-methamphetamine (DOM). The Sponsor asserts that because the affinity of lorcaserin at human $5HT_{2C}$ receptors (13 nM) is several-fold lower than its affinity at human $5HT_{2A}$ receptors (92 nM), the $5HT_{2A}$ contribution is negligible. However, the binding affinity of lorcaserin for the $5HT_{2A}$ site is still relatively high and likely to contribute to the psychoactivity and behavioral responses resulting from administration of the drug. Previous research demonstrates that stimulation of both $5HT_{2A}$ and $5HT_{2C}$ receptors may be required for hallucinogenic activity (Burris et al., 1991; Sanders-Bush, 1994) and that known hallucinogens are potent $5HT_{2C}$ agonists (Burris et al., 1991; Sanders-Bush & Breeding, 1991). Research has also shown that many novel hallucinogens are agonists at both $5HT_{2C}$ and $5HT_{2A}$ serotonin receptors (Nichols, 2006) and often are more selective for the $5HT_{2C}$ receptor (Chambers et al., 2001).

The $5HT_{2C}$ and $5HT_{2A}$ agonist mechanism of action of lorcaserin presented difficulties in the selection of a positive control drug for the human abuse potential study. As noted above, $5HT_{2C}$ and $5HT_{2A}$ agonists are Schedule I hallucinogens and are not readily available for use in clinical studies and present serious safety concerns. Therefore, in assessing whether lorcaserin produces hallucinogenic-like subjective responses, the Sponsor proposed that the prescription drugs ketamine (a Schedule III NMDA antagonist) and zolpidem (Schedule IV agonist at BZ-1 GABA sites) serve as the positive controls, since both drugs are known to produce hallucinogenic-like adverse events. Although we agreed that these two drugs are the best available comparators for use in a human abuse potential pharmacology study with lorcaserin, we also recognized and stated the limitations of using positive controls with different mechanisms of action from that of lorcaserin. These limitations are critical in evaluating the results of the human abuse potential study.

B. Conclusions

The review of abuse-related clinical and preclinical data in the NDA shows that:

1. Lorcaserin is a high-affinity agonist at $5HT_{2A}$ and $5HT_{2C}$ receptors. This mechanism of action is identical to that of Schedule I hallucinogenic drugs. Lorcaserin does not have high affinity for other binding sites in the brain.

2. A rat study evaluating overt serotonin behaviors lacks validity because the positive control in the study, 2,5-dimethoxy-4-iodoamphetamine (DOI; a $5HT_{2A}$ and $5HT_{2C}$ agonist) failed to produce both $5HT_{2A}$ and $5HT_{2C}$ behaviors. Thus, no conclusions can be drawn regarding the ability of lorcaserin to produce overt behaviors associated with either of these serotonin receptor subtypes.

3. A rat drug discrimination study conducted in rats lacks validity because of numerous procedural discrepancies, including the inability of rats to maintain adequate recognition of the training drug, 2,5-dimethoxy-4-methamphetamine (DOM), over the course of the study. Thus, no conclusions can be drawn regarding the ability of lorcaserin to generalize to DOM.

4. Phase 1 clinical pharmacokinetic studies show that the major metabolite of lorcaserin in humans is lorcaserin sulfamate (M1). The M1 metabolite is pharmacodynamically inactive, based on binding studies. The Tmax of lorcaserin is approximately 2 hours, with a half-life of 11 hours.

5. The overall incidence of euphoria in Phase 1 and Phase 2/3 clinical efficacy and safety studies following administration of lorcaserin (0.7%) is more than 10 times higher than that reported following administration of placebo (0.06%). The ability of lorcaserin to produce euphoria is dose-dependent, with supratherapeutic doses producing the highest incidence of the AE. Individuals treated with lorcaserin showed a higher incidence of other prominent safety or abuse-related AEs (such as feeling jittery, psychomotor hyperactivity, paresthesia, abnormal dreams, and confusional state) than subjects treated with placebo.

6. Although the overall incidence of the AE euphoria in Phase 1, 2 and 3 studies is relatively low, lorcaserin produces a high rate of the AE euphoria (6-19%) in a human abuse potential study with drug abusers. The incidence of euphoria in this study resulting from lorcaserin administration is similar to that reported following zolpidem administration (13-16%), lower than that reported following ketamine administration (50%), and higher than that reported following placebo administration (0%). Lorcaserin also produced a high rate of headache (61-84%), nausea (21-45%) and dizziness (13-19%), abdominal discomfort (9-26%), hot flush (3-19%), decreased appetite (3-19%), paresthesia (3-16%), anxiety (3-10%) and depressed mood (3-9%).

7. In the human abuse potential study in recreational abusers of psychedelic drugs and CNS depressants (n = 28), lorcaserin (20-60 mg, p.o.) and the positive control drugs, zolpidem and ketamine, produced statistically significant increases on certain positive subjective measures ("High", "Good Drug Effects" (unipolar scale) and "Good Drug Effects" (bipolar scale)), as well as a numerical increase in "Hallucinations" compared to placebo. Lorcaserin, as well as zolpidem and ketamine, produced statistically significant increases in "Sedation" compared to placebo. The subjective response data suggest that lorcaserin produces effects that are similar to those of ketamine and zolpidem, drugs with hallucinogenic and euphorigenic properties. However, lorcaserin did not produce statistically significant increases in ratings on other positive control drugs compared to placebo ("Drug Liking", "Overall Drug Liking", "Euphoria", "Take Drug Again"), although zolpidem and ketamine did. Additionally, lorcaserin produced statistically significant increases in certain negative subjective effects ("Overall Dislike Drug", "Bad Effects"). On the VAS-Drug Similarity scale, subjects identified the two highest doses of lorcaserin as similar to "LSD" and "MDMA," while subjects identified ketamine as "ketamine" and zolpidem as "benzodiazepine." However, since zolpidem and ketamine have different mechanisms of action from that of lorcaserin, they are not ideal comparators for determining the hallucinogenic profile of lorcaserin.

8. The ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses, in healthy individuals and in obese patients, at doses greater than the proposed therapeutic dose of 20 mg suggests that lorcaserin can produce psychic dependence similar to that of other 5HT2 agonist hallucinogens.

9. After a review of all abuse-related data submitted in the NDA, CSS concludes that lorcaserin is a drug with hallucinogenic properties, that it has abuse potential and that it can produce psychic dependence. These conclusions are different than those drawn by the Sponsor (see below under **Discussion**).

C. Recommendations (to be conveyed to Sponsor):

Following our review of the NDA, we conclude that lorcaserin has abuse potential and recommend lorcaserin for placement in Schedule IV of the Controlled Substances Act.

We recommend that:

1. You report to FDA all cases of abuse, misuse, overdose and addiction associated with lorcaserin after its introduction on the market.

2. You provide draft text for the label for Sections 9.2 and 9.3 of the Drug Abuse and Dependence section (Section 9.0), with language that captures the specific safety risks associated with lorcaserin abuse.

D. Discussion

The Sponsor states in the NDA that lorcaserin does not have abuse potential and proposes that the drug not be scheduled under the CSA, based on the following assertions:

Lorcaserin has 7-fold higher affinity for $5HT_{2C}$ receptors than $5HT_{2A}$ receptors; lorcaserin produces $5HT_{2c}$-associated overt behaviors in rats, but does not produce $5HT_{2A}$-associated overt behaviors; lorcaserin does not produce generalization to the $5HT_{2A}/5HT_{2C}$ Schedule I hallucinogen 4-methyl-2,5-dimethoxyamphetamine (DOM) in the drug discrimination study with rats; the subjective responses in the human abuse potential study following lorcaserin administration are not similar to those produced by the positive controls, zolpidem (a GABA agonist) and ketamine (an NMDA antagonist); the incidence of euphoria and other abuse-related AEs in the clinical studies is small; and, lorcaserin does not produce dependence.

We disagree with the Sponsor that lorcaserin does not have abuse potential and should not be scheduled. These conclusions are based on the following data:

- Although the binding of lorcaserin is numerically greater at $5HT_{2C}$ receptors than at $5HT_{2A}$ receptors, the affinity of lorcaserin is still relatively high for both receptor subtypes. As discussed below in the review section, the receptor binding profile of lorcaserin is identical to that of Schedule I hallucinogens (Nichols, 2006).

- The overt behavioral study shows that lorcaserin induces a predominance of $5HT_{2C}$-associated behaviors over $5HT_{2A}$-associated behaviors. However, the positive control, DOI (a $5HT_{2A}/5HT_{2C}$ agonist) produces only $5HT_{2A}$-associated behaviors, but not $5HT_{2C}$-associated behaviors, revealing limitations of this behavioral method. Additionally, the study lacked a positive control that produces $5HT_{2C}$–associated behaviors.

- The drug discrimination study is invalid because of methodological issues, as discussed below in the review section.

- Lorcaserin produces some, but not all, of the positive subjective responses in the human abuse potential study produced by zolpidem and ketamine. However, given that lorcaserin is a $5HT_2$ receptor agonist, while zolpidem is a GABA agonist and ketamine is an NMDA antagonist, it is not unexpected that these three drugs produce different behavioral responses in humans.

- The incidence of the AE euphoria following administration of supratherapeutic doses (40 and 60 mg) of lorcaserin ranged from 15-19%.

- The ability of lorcaserin to produce hallucinations, euphoria, and positive subjective responses at therapeutic and supratherapeutic doses in healthy

individuals and in obese patients suggests that lorcaserin can produce psychic dependence similar to that of other 5HT2 agonist hallucinogens.

Given that lorcaserin has a mechanism of action identical to that of 5HT2 hallucinogens, it was specifically of interest to determine whether lorcaserin produces hallucinogenic-like effects. After a review of the adverse events produced by lorcaserin in clinical studies (euphoria, hallucinations, paresthesias, nausea, abdominal discomfort, hot flush, dizziness, anxiety and decreased appetite) and the subjective responses observed in the human abuse potential study ("High," "Good Drug Effects," "Hallucinations"), we conclude that lorcaserin has hallucinogenic properties.

Lorcaserin produces modest weight reduction but a serious degree of psychiatric adverse events (including euphoria and hallucinations), demonstrating that the risk-benefit calculation for lorcaserin is fairly small. Of particular concern is that the euphoria and hallucinations emerged at only two times the proposed therapeutic dose. This suggests that patients risk exposing themselves to serious psychiatric AEs if they double their lorcaserin dose, by choosing to ignore the recommended dose (because they desired a greater weight loss response), by inadvertent mistakes in dosing (forgetting a dose and then taking twice as much subsequently) or by deliberate misuse for abuse purposes (taking higher doses for euphoric or hallucinatory responses). Thus, lorcaserin appears to have a narrow therapeutic window that may lead to considerable risks in the intended clinical population. Additionally, given that drugs with hallucinogenic-like properties have known abuse potential, diversion of lorcaserin may occur from a patient population or a drug abusing population.

II. REVIEW

A. Chemistry of Lorcaserin

Lorcaserin hydrochloride ((*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate) is a new molecular entity with a molecular formula of $C_{11}H_{15}Cl_2N \cdot 0.5H_2O$ and a molecular weight of lorcaserin of 241.16 g/mol. Lorcaserin HCl is very soluble in water, but no further information is available regarding other solvents. With heat, lorcaserin HCl dehydrates between 80°C and 120°C to anhydrous (b) (4) which melts at onset 199°C.

B. Pharmacology of Lorcaserin

1. Receptor Binding and Second Messenger System Studies

a. Receptor Binding Studies (Study # DBR09-004, -005, -006, -007, -008)

Lorcaserin has high affinity in human brain tissue for $5HT_{2C}$ (13 nM) and $5HT_{2A}$ (92 nM) receptors. The $5HT_{2A}$ receptor is known to be the main pharmacological site of action of Schedule I hallucinogens.

Lorcaserin does not have significant affinity for other CNS sites, including: glutamate (NMDA, PCP), GABA (benzodiazepine, GABA, GABA channel), sigma, acetylcholine (muscarinic and nicotinic subtypes), norepinephrine ($alpha_1$, $alpha_2$, $beta_1$, $beta_2$), cannabinoid (CB-1, CB-2), histamine (H1 and H2 subtypes), dopamine (D1-D5 subtypes), non-$5HT_2$ serotonin sites (11 receptor subtypes), opioid receptors (mu and delta subtypes) and monoamine transporters (dopamine, serotonin and norepinephrine). Additionally, lorcaserin does not have significant affinity for the calcium channel or the potassium channel.

b. Second Messenger System Studies (Study # DBR09-004, -005, -006, -007, -008)

Lorcaserin produces second messenger system activation at both $5HT_{2A}$ and $5HT_{2C}$ receptors. For inositol phosphate accumulation, the mean EC50 value for the $5HT_{2A}$ receptor ranged from 14-133 nM in humans, 31-649 nM in rats and 23 nM in monkeys, while the EC50 value for the $5HT_{2C}$ receptor ranged from 2-9 nM in humans, 5-192 nM in rats and 2 nM in monkeys. For calcium release, the EC50 value is 52 nM at the $5HT_{2A}$ receptor and 6 nM at the $5HT_{2C}$ receptor.

2. Preclinical Behavioral Studies

a. General Behavioral Responses to Lorcaserin (Study #TOX-8015)

In rats, lorcaserin is generally well-tolerated at doses ranging from 30 to 500 mg/kg (the designated maximum tolerated dose). Behaviors observed following lorcaserin administration include salivation, penile erections and ejaculation, piloerection, and tremors, all of which are reversible over time. Lorcaserin also produces a decrease in body weight and food consumption. Mortality occurs at 1000 mg/kg.

b. Locomotor Activity Study (Study #DBR04-013)

Acute administration of lorcaserin reduces locomotion in rats. However, after 21 days of lorcaserin administration, the drug no longer produced the change in locomotor behavior. Given that $5HT_2$ receptors are known to down-regulate rapidly following administration of $5HT_2$ receptor agonists (Buckholtz et al., 1988), the inability of lorcaserin to alter locomotor behavior over time demonstrates the development of tolerance.

c. Overt Behavioral Response to Lorcaserin (Study #DBR09-011)

The overt behavioral response study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail.

Study Design

Rats (n = 6/group) received lorcaserin (4.5, 9.0 and 18 mg/kg; p.o.), DOI (a hallucinogen and a $5HT_{2A}$ and $5HT_{2C}$ agonist; 1.0 mg/kg; s.c.) or vehicle (either p.o. or s.c.). Observations were made for 60 minutes for signs of $5HT_{2A}$ activation (back muscle contractions, wet dog shakes) and $5HT_{2C}$ activation (decreased activity and penile grooming).

Results

As shown in Table 1 (below), lorcaserin increases $5HT_{2C}$-associated behaviors (decreased activity and increased penile grooming/penile erection) but did not increase $5HT_{2A}$ associate behaviors (wet dog shakes and back contractions). In contrast, DOI increased $5HT_{2A}$-associated behaviors but did not alter $5HT_{2C}$-associated behaviors. Both lorcaserin and DOI significantly reduced sleep time.

Table 1: Rat Behaviors Following Administration of Lorcaserin, DOI and Vehicle

Behavior	Vehicle (p.o.)	Vehicle (s.c.)	Lorcaserin 4.5 mg/kg (p.o.)	Lorcaserin 9.0 mg/kg (p.o.)	Lorcaserin 18 mg/kg (p.o.)	DOI 1.0 mg/kg (s.c.)
Active	7.8 + 1.1	6.7 + 0.9	8.5 + 0.6	5.7 + 0.5 *	4.8 + 0.5 *	8.8 + 0.5
Resting	0.8 ± 0.3	1.7 ± 0.2	3.0 ± 0.5**	5.8 ± 0.5**	7.2 ± 0.5**	2.8 ± 0.5
Sleeping	3.3 ± 1.1	3.5 ± 1.2	0.5 ± 0.3**	0.5 ± 0.3**	0.0 ± 0.0**	0.3 ± 0.3**
Penile Grooming	0.8 ± 0.8	0.7 ± 0.3	7.8 ± 1.2**	6.8 ± 1.5**	4.8 ± 0.5**	0.8 ± 0.3
Wet Dog Shakes	0.7 ± 0.3	1.0 ± 0.7	0.7 ± 0.5	1.8 ± 0.7	1.0 ± 0.5	32.8 ± 2.3**
Back Contractions	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	36.5 ± 6.7**

** $p < 0.01$ compared to placebo

Conclusions

The positive control drug, DOI, is a $5HT_{2A}$ and $5HT_{2C}$ agonist. However, in the present study, DOI produces only $5HT_{2A}$-associated behaviors, but no $5HT_{2C}$-associated behaviors. The inability of DOI to produce both behavioral profiles suggests that the study is not valid for distinguishing between activation of the two serotonin receptor subtypes. Thus, the inability of lorcaserin to produce $5HT_{2A}$-associated behaviors, despite its ability to produce $5HT_{2C}$-associated behaviors, does not suggest that lorcaserin is selective in activating one receptor subtype over another.

Other methodological issues exist in this study. Administration of the two drugs occurred via different routes of administration (subcutaneous for DOI, intraperitoneal for lorcaserin), so a direct comparison is not valid. Additionally, a positive control that produces $5HT_{2C}$-associated behaviors is not used in the study. Finally, the Tmax of the two drugs and the duration of the observation period are not provided, so it is not possible to determine if observations occurred at Cmax.

d. Drug Discrimination Study in Rats (Study # TOX08040)

The drug discrimination study in rats is a pivotal animal behavioral study for abuse potential assessment and is reviewed in detail.

Study Design

Rats (n = 8) were trained to discriminate DOM ($5HT_{2A}$ and $5HT_{2C}$ receptor agonist and Schedule I hallucinogen; 0.56 mg/kg, i.p., 30 minutes pretreatment time) from saline. The schedule of reinforcement began at a fixed ratio (FR) of 1 and increased to FR10 over the course of training. Drug training sessions occurred daily. The training proceeded with DOM and saline being administered on alternate days, followed by

"double alternation" in which DOM was given for two consecutive days and saline was given for two consecutive days.

Once animals responded with 80% accuracy on the appropriate training drug or saline lever, challenge sessions began. Rats received challenge doses of lorcaserin (0.1, 0.3, 1.0, 3.0, 5.0 mg/kg, i.p., 30 minutes pretreatment time), interspersed on separate days with challenge doses of saline and DOM (0.56 mg/kg, i.p.).

Results

In drug discrimination studies, animals must select the training drug-appropriate lever at least 80% in order for the test drug to be considered to have full generalization to the training drug. Although rats treated with DOM responded with 99.5% accuracy on the DOM lever at the beginning of the study, this accuracy fell to 75% at the end of the study. As a contrast, rats treated with saline responded with 86% accuracy on the saline lever at the beginning of the study and 87% accuracy at the end of the study.

Administration of lorcaserin produces generalization to the DOM cue that is less than 20% for the 0.1, 3.0 and 5.0 mg/kg doses. At the 0.3 and 1.0 mg/kg doses of lorcaserin, there is partial generalization to the DOM cue, at 25% and 38%, respectively.

As shown in Table 2 (below), an evaluation of the individual response data, however, reveals that lorcaserin produces full generalization to the DOM in certain individual rats at each of the doses tested. Notably, the highest doses (3.0 and 5.0 mg/kg) eliminated behavioral responding on either the DOM-associated or the saline-associated levers in many rats.

Table 2: Responding on DOM-Associated Lever by Saline, DOM and Lorcaserin

Rat	Saline	DOM 0.56 mg/kg	Lorcaserin 0.1 mg/kg	Lorcaserin 0.3 mg/kg	Lorcaserin 1.0 mg/kg	Lorcaserin 3.0 mg/kg	Lorcaserin 5.0 mg/kg
(b) (4)							
Mean			13%	25%	38%	4%	--

(--) = animals failed to respond on either lever

Conclusions

In a test of drug discrimination in rats trained to recognize DOM (a $5HT_{2A}$ and $5HT_{2C}$ receptor agonist), mean data show that lorcaserin did not generalize to the DOM cue. However, there are numerous methodological deficits in this study that invalidate the study:

- In DOM-trained rats, the rate of generalization to the DOM cue following administration of DOM fell from 99% at the beginning of the study to 75% at the end of the study. Given that 80% generalization to the training drug cue is the criteria for "full generalization", these data demonstrate that this group of rats did not maintain recognition of a $5HT_2$-associated cue over time. When individual rat responses to DOM and saline are analyzed, the data show that 4 of 8 rats had at least one trial in which more than 95% of their responses are on the incorrect lever.

- The instability of the DOM behavioral data may be related to the "double alternation" drug administration design in which DOM is given on consecutive days, before and after saline (saline-DOM-DOM-saline). Since $5HT_{2A}$ and $5HT_{2C}$ receptors are known to down-regulate rapidly in response to repeated administration of $5HT_2$ agonists (Buckholtz et al., 1988), the unstable responding to DOM may reflect the development of tolerance.

- The 30-minute pretreatment time for DOM is inappropriate. As noted in a published drug discrimination study (Fiorella et al., 1995), a short (15-minute) pretreatment time for DOM (0.56 mg/kg, i.p.) produces unstable responding on the DOM-associated lever. This published study also showed that DOM did not produce full generalization to the cue for LSD (another $5HT_{2A}$ and $5HT_{2C}$ agonist with hallucinogenic properties) until the pretreatment time for DOM increases to 75 minutes. Given that the purpose of the present drug discrimination study is to evaluate whether lorcaserin produces $5HT_{2A}$ and $5HT_{2C}$ agonist responses, it is likely that the short pretreatment time used for DOM during the training phase did not produce a full $5HT_2$ agonist response. Thus, the overall lack of generalization between lorcaserin and DOM is not meaningful.

- The pretreatment time for lorcaserin may not be appropriate. According to pharmacokinetic data submitted in the NDA, the Tmax of lorcaserin is 4-18 hours in rats after oral administration. Although Tmax data were not provided for intraperitoneal administration, it is likely longer than the 30 minute pretreatment time used in this study.

- When individual responses to lorcaserin are analyzed, 5 of 8 rats (63%) showed full generalization to the DOM cue following administration of at least one dose of lorcaserin. Thus, even though a full lorcaserin response may not have had

sufficient time to develop given the pretreatment time used, the lorcaserin interoceptive cue was similar to some aspects of the DOM cue. Alternatively, it is possible that full generalization between lorcaserin and DOM in individual animals reflects poor stimulus control, based on the instability of the response to DOM itself.

- Administration of each dose of lorcaserin occurred on only one occasion. Given the variability in response for DOM, saline and lorcaserin, additional exposures to each dose of lorcaserin would have increased the reliability of the data.

3. Physical Dependence Studies in Animals (Study # DBR-04-009, TOX05004, TOX04038, TOX05003)

Four physical dependence studies were conducted in which animals treated with lorcaserin for varying durations were evaluated following drug discontinuation for behavioral changes.

a. 30-Day Rat Study (#DBR-04-009):

Rats treated with lorcaserin (18, 36, 72 mg/kg/day, p.o.), the Schedule IV anorectic, sibutramine (6 mg/kg/day, p.o.), or placebo for 30 days, were abruptly discontinued from the drug and observed for 28 days. The only behavioral responses monitored were feeding and changes in body weight. Discontinuation of lorcaserin led to a rapid and statistically significant increase in feeding and body weight compared to placebo-treated animals that was above control levels. These behavioral responses returned to control levels within 7-10 days of lorcaserin discontinuation.

b. 13-Week Mouse Study (#TOX05004)

Mice treated with lorcaserin (25, 50, 250, 350 mg/kg/day, p.o.) and placebo for 13 weeks, were abruptly discontinued and observed for 4 additional weeks. During the discontinuation phase, changes in feeding and body weight, as well as general behaviors (salivation, activity level, prostration, righting reflex, tremors, reactivity to handling and bizarre behavior), were monitored. Both feeding and body weight increased in lorcaserin-treated mice above that of placebo-treated animals during the withdrawal period (no statistical analysis conducted). No other behavioral changes were exhibited following drug discontinuation.

c. 13-Week Monkey Study (#TOX04038)

Cynomolgus monkeys were treated with lorcaserin (2, 10, 75, 125 mg/kg/day, p.o.) and placebo for 13 weeks, followed by abrupt discontinuation and observation for 4 additional weeks. During the discontinuation phase, changes in feeding and body weight as well as general behaviors (salivation, activity level, prostration, righting reflex, tremors,

reactivity to handling and bizarre behavior) were monitored. Both feeding and body weight increased in lorcaserin-treated mice at the two highest doses above that of placebo-treated animals (no statistical analysis conducted). No other behavioral changes were exhibited following drug discontinuation.

d. 6-Month Rat Study (#TOX05003)

Rats treated with lorcaserin (1, 5, 50 mg/kg/day, p.o.) and placebo for 6 months were abruptly discontinued from the drug and observed for 4 additional weeks. During the discontinuation phase, changes in feeding and body weight as well as general behaviors (salivation, activity level, prostration, righting reflex, tremors, reactivity to handling and bizarre behavior) were monitored. Although feeding increased compared to placebo in females treated with the highest dose of lorcaserin, there were no changes in males. There were also no changes in body weight in either sex at any dose of lorcaserin compared to placebo (no statistical analysis conducted). No other behavioral changes were exhibited following drug discontinuation.

Overall Conclusions for Animal Physical Dependence Studies

Discontinuation of lorcaserin following chronic administration did not produce behavioral changes typically associated with withdrawal. This suggests that lorcaserin may not produce physical dependence. However, during the drug discontinuation period, there was an increase in feeding and body weight, which diminished over time. Given that lorcaserin produces a decrease in feeding and body weight during active drug administration, the reversal of these effects following drug discontinuation are difficult to interpret.

One explanation is that these signs represent a withdrawal syndrome, since they are opposite to the behavior and outcome induced by the drug treatment. The rebound nature of the discontinuation response, in which the feeding and weight gain increase initially but then subsided support this interpretation. This would also be consistent with the down-regulation and re-emergence of the 5HT2 receptor following (respectively) chronic administration and discontinuation of $5HT_2$ agonists such as lorcaserin. If this were the case, these data indicate that lorcaserin induces physical dependence.

Alternately, these signs could represent a return to normal feeding behavior and weight gain following cessation of a drug treatment that pharmacologically blocks this behavior and outcome. In this case, the signs observed following lorcaserin discontinuation are not indicative of either withdrawal or physical dependence.

C. Clinical Pharmacology

1. Absorption

Lorcaserin is absorbed rapidly (Tmax ≤ 2.0 hr) from the gastrointestinal tract after oral administration. The plasma half-life of lorcaserin is approximately 11 hr with steady state achieved within 3 days. Plasma AUC and Cmax increase dose-proportionately following oral administration up to 40 mg in humans. After 24 weeks of lorcaserin administration at 10 mg (BID), Cmax is 43 ng/ml and AUC_{24hr} is 1038 ng*hr/ml. Systemic accumulation of lorcaserin under steady-state conditions is two-fold or less across gender and dose, with similar exposure between genders in humans. Food does not affect exposure to lorcaserin (Cmax and AUC), although it does delay Tmax by 1 hr.

2. Metabolism and Elimination

Lorcaserin is extensively metabolized in the liver to lorcaserin sulfamate (M1), the major circulating metabolite. M1 exposure exceeds exposure to lorcaserin by several-fold in humans, as well as in animals. M1 does not bind with significant affinity to serotonin or monoamine transporters and is considered inactive. M1 is not found in appreciable quantities in the CNS. Renal excretion is the primary route of elimination in humans. In male human subjects, urine recovery is 92.3%.

D. Clinical Studies

1. Human Abuse Potential Study (Study # APD356-013)

Study Design

A human abuse potential study with a randomized, double-blind, placebo- and active comparator-controlled single dose crossover design was conducted in individuals with a history of using "psychedelic drugs (drugs that are associated with perceptual changes, e.g., LSD, marijuana/cannabis (tetrahydrocannabinol; THC), ketamine, phencyclidine (PCP), dextromethorphan, 3,4 methylenedioxymethamphetamine (MDMA), mescaline, psilocybin, zolpidem)" and "CNS depressants (benzodiazepines, barbiturates, gamma hydroxybutyrate (GHB), zolpidem, zopiclone)" (n = 28 study completers). The study had three phases: 1) Qualifying Phase (oral administration of 100 mg ketamine, 20 mg zolpidem and placebo), 2) Treatment Phase (lorcaserin (20, 40, 60 mg), ketamine (100 mg), zolpidem (15 and 30 mg), and placebo), and 3) Post-treatment Follow-up Phase 5-10 days after study termination.

The proposed therapeutic daily dose of lorcaserin is 20 mg/day (10 mg BID). Thus, the doses of lorcaserin selected for the present study represent single, double and triple the proposed daily therapeutic dose. Since the 60 mg dose of lorcaserin had not been previously administered to humans, subjects only received this high dose if they were able to adequately tolerate the 40 mg dose of lorcaserin.

Based on an AE profile showing that lorcaserin can produce euphoria and hallucinations, the Sponsor chose zolpidem and ketamine as positive control drugs. Although zolpidem and ketamine act by different mechanisms (GABA agonist and NMDA antagonist, respectively) than lorcaserin, both are known to produce euphoria and hallucinations at higher doses. The doses of these drugs are selected on the basis of their previous use in human abuse potential studies.

Subjective and Cognitive Measures Outcome Data and Discussion

The Sponsor identified VAS-Drug Liking as the primary measures. Other subjective measures were considered secondary: VAS for Good Effects, Bad Effects, Good and Bad Effects (bifurcated scale), Overall Drug Liking, Take Drug Again, High, Feel Sick, Dizziness, Alertness/Drowsiness, Spaced Out, Floating, Detached, Hallucinations, Sounds Louder, Vision Crisp/Clear, Drug Similarity and Any Effects and the Addiction Research Center Inventory subscales for Morphine-Benzedrine Group (MBG; measure of euphoria), LSD (measure of dysphoria), Pentobarbital Chlorpromazine Alcohol Group (PCAG; measure of sedation). The Choice Reaction Time Test (CRT; a cognitive measure) are also given during each drug session.

Table 3 (below) depicts peak responses (Emax over the first 8 hours after drug administration) for these measures following administration of placebo, zolpidem (15 and 30 mg; Z15, Z30), ketamine (100 mg; K100), lorcaserin (20, 40, 60 mg; L20, L40, L60).

The data in Table 3 show that both zolpidem and ketamine produced statistically significant increases on the primary measure (Drug Liking) compared to placebo, which validates the study. Lorcaserin (40 and 60 mg) produced responses that are greater than placebo, though smaller than responses from ketamine and zolpidem. Secondary positive measures showed a variable response, depending on specific measure (Table 3). There is a statistically significant increase in response on the measures of "Good Effects" (bipolar scale), "Good Effects" (unipolar scale) and "High" following administration of the two highest doses of lorcaserin compared to placebo. There is also a statistically significant increase in response on the measure of "Euphoria" following administration of the 60 mg dose of lorcaserin. The two highest doses of lorcaserin also produced a numerical increase in "Hallucinations" compared to placebo (only descriptive statistics are conducted for this measure). In contrast, there is also a statistically significant decrease in response on the measures of "Overall Drug Liking" and "Take Drug Again" following administration of the two highest doses of lorcaserin compared to placebo. Additionally, the 60 mg dose of lorcaserin produced responses that are statistically indistinguishable from the 15 and/or 30 mg doses of zolpidem on "High" and "Euphoria" scales, as well as responses that are numerically similar to those produced by ketamine on the "Hallucinations" scale.

Table 3: Human Abuse Potential Study (#APD356-013) Primary and Secondary Positive Endpoints: Mean Emax (+ S.E.) VAS and ARCI Scores

Scale (Value Range)	Placebo	Z 15	Z 30	K 100	L 20	L 40	L 60
VAS – Drug Liking (0-100; *bipolar scale,neutral =50*)	56 ± 3	74 ± 3 *	77 ± 3 *	84 ± 3 *	54 ± 3 ! # ^	63 ± 3 ! # ^	67 ± 3 ! # ^
VAS – Overall Drug Liking ***(Emax** of Drug Liking Disliking* (0-100; *bipolar scale,neutral =50*)	49 ± 5	63 ± 4	68 ± 4 *	72 ± 4 *	43 ± 4 ! # ^	33 ± 6 * ! # ^	35 ± 6 * ! # ^
VAS – Good Effects ***(Emax** of VAS Good/Bad)*(0-100; ***bipolar** scale, neutral = 50*)	54 ± 2	77 ± 4 *	77 ± 3 *	84 ± 3 *	53 ± 1 ^ ! #	63 ± 3 * ^ ! #	69 ± 4 * ^ #
VAS – Good Effects (0-100; *unipolar scale, neutral = 0*)	28 ± 6	77 ± 4 *	83 ± 3 *	86 ± 4 *	24 ± 6 ^ ! #	46 ± 7 * ^ ! #	58 ± 6 * ^ ! #
VAS – High (0-100; *unipolar scale, neutral = 0*)	20 ± 6	70 ± 5 *	79 ± 5 *	92 ± 4 *	21 ± 7 ! # ^	56 ± 8 * ! # ^	75 ± 7 * ^
ARCI – MGB (Euphoria) (0-17; *unipolar scale, neutral = 0*)	1.2 ± 1	3.7 ± 1 *	5.3 ± 1 *	5.2 ± 1 *	1.2± 1 ! # ^	2.4 ± 1 # ^	3.0 ± 1 * # ^
VAS – Take Drug Again (0-100; *unipolar scale, neutral = 0*)	43 ± 5	64 ± 5 *	69 ± 5 *	75± 5 *	30 ± 5 ! # ^	29 ± 5 * ! # ^	22 ± 6 * ! # ^
VAS – Hallucinations (0-100; u*nipolar scale, neutral = 0*)	3 ± 6	25 ± 5	48 ± 5	21 ± 5	9 ± 5	17 ± 6	20 ± 6

VAS = visual analog scale, ARCI = Addiction Research Center Inventory, Values are Emax mean (± s.d.)
* = $p < 0.05$ compared to placebo; ! compared to Z 15; # compared to Z 30, ^ compared to K 100
(Source: DARRTS, NDA 22-529, Biometrics Review, Dr. Ling Chen, July 13, 2010)

Table 4 (below) depicts peak responses for secondary measures that assess the negative and sedating subjective properties of drugs during the human drug abuse study following administration of placebo, zolpidem (15 and 30 mg; Z 15, Z 30), ketamine (100 mg; K 100), lorcaserin (20, 40, 60 mg; L 20, L40, L60). PCAG ("Sedation") is the only measure that showed a statistically significant increase following administration of the positive

controls, zolpidem and ketamine, compared to placebo. The two highest doses of lorcaserin also produced a statistically significant increase in "Sedation" compared to placebo.

In contrast, the only drug treatment that produced a statistically significant increase in ratings for "Disliking" (bipolar scale) and "Bad Effects" (bipolar scale) compared to placebo was lorcaserin at the two highest doses. Additionally, lorcaserin at the two highest doses produced numerical increases in "Bad Effects" (unipolar scale), LSD ("Dysphoria") and "Feeling Sick" compared to both placebo and to zolpidem and ketamine (only descriptive statistics are conducted for these measures).

Table 4: Human Abuse Potential Study (#APD356-013) Secondary Negative Endpoints: Mean Emax (+ S.E.) VAS and ARCI Scores

Scale (Value Range)	Placebo	Z 15	Z 30	K 100	L 20	L 40	L 60
VAS – Overall Drug Disliking *(**Emin** of VAS Drug Liking/ Disliking)* (0-100; *bipolar scale,neutral =50*)	56 ± 3	73 ± 3	77 ± 3	84 ± 3	54 ± 3 * ^	63 ± 3 * ^ ! #	67 ± 3 * ^ ! #
VAS – Bad Effects *(**Emin** of VAS Good/Bad)*(0-100; ***bipolar** scale, neutral = 50*)	46 ± 2	42 ± 3	40 ± 4	47 ± 2	33 ± 4 * ^	22 ± 4 * ^	13 ± 3 * ^
ARCI – PCAG (sedation) (0-15; *unipolar scale, neutral = 0*)	1.8 ± 1	5.5 ± 1 *	6.9 ± 1 *	3.3 ± 1 *	1.6 ± 1 ! # ^	3.9 ± 1 * ! #	4.1 ± 1 * #
VAS – Bad Effects (0-100; ***unipolar** scale, neutral = 0*)	30± 6	34 ± 6	53 ± 6	25 ± 6	36 ± 7	75 ± 6	89 ± 3
ARCI – LSD (dysphoria) (0-13; *unipolar scale, neutral = 0*)	0.5 ± 0	2.0 ± 0	3.0 ± 0	3.4 ± 0	1.5 ± 0	3.5 ± 0	4.7 ± 0
VAS – Feeling Sick (0-100; *unipolar scale, neutral = 0*)	19 ± 5	16 ± 6	35 ± 6	10 ± 5	25 ± 6	62 ± 7	74 ± 6

VAS = visual analog scale, ARCI = Addiction Research Center Inventory, Values are Emax mean (± s.d.)
* = $p < 0.05$ compared to placebo; ! compared to Z 15; # compared to Z 30, ^ compared to K 100
(Source: DARRTS, NDA 22-529, Biometrics Review, Dr. Ling Chen, July 13, 2010)

On the VAS-Drug Similarity scale, placebo produced the highest rating for "placebo" (59), zolpidem (15 and 30 mg) produced the highest rating for "benzodiazepine" (66 and

75, respectively) and ketamine produced the highest rating for "ketamine" (81). The 20 mg dose of lorcaserin produced the highest rating for "placebo" (50), while the 40 and 60 mg doses produced highest ratings for "MDMA" (31 and 38, respectively) and "LSD" (26 and 40). The ratings of drug similarity for lorcaserin are low compared to those for other treatments.

Finally, lorcaserin did not produce impairment on reaction time or accuracy on the Choice Reaction Time (CRT) test at the two lowest doses. At the highest dose, there is some interference with performance, but this occurred after peak drug concentrations when adverse events (such as nausea, headache and abdominal discomfort) are reported. In contrast, zolpidem produced statistically significant impairment CRT, while ketamine did not.

Conclusions

The subjective response data suggest that lorcaserin produces effects that are similar to those of ketamine and zolpidem, drugs with hallucinogenic and euphorigenic properties.

2. Abuse-Related and Negative AEs in Clinical Efficacy and Safety Studies

a. Adverse Events in Phase 1 and Phase 2/3 Clinical Trials

During lorcaserin development, the Sponsor conducted 13 Phase 1 clinical safety studies in healthy volunteers (n = 493) and 7 Phase 2/3 clinical safety and efficacy studies in obese patients (n = 8683). An analysis of euphoria-related AEs, as well as other abuse-related AEs, indicates that lorcaserin has abuse potential.

Euphoric Mood

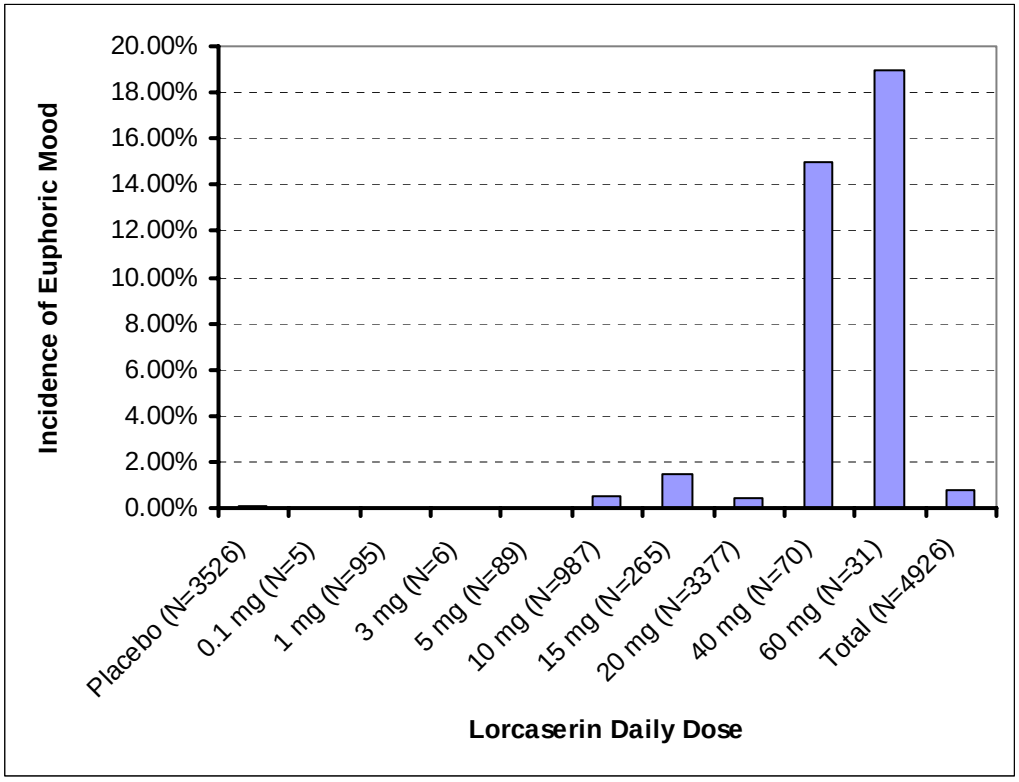
The Sponsor conducted a search in the safety database for lorcaserin using a list of abuse-related treatment-emergent AEs (TEAEs). From the data provided, euphoric mood was evaluated as a primary AE indicative of abuse potential. These data show that lorcaserin-treated individuals have a higher incidence of euphoric mood than placebo-treated individuals. Table 5 (below) presents a summary of euphoric mood reported in single and multiple dose studies conducted with lorcaserin in healthy volunteers (including one study with polydrug abusers) and obese patients. Summed data from Phase 1 and Phase 2/3 studies show that the incidence of euphoric mood in the lorcaserin-treated group at doses ranging from 0.1 to 60 mg/day (<1.0%; n = 38 of 4926 subjects) was greater than 10 times higher than that reported in placebo-treated group (< 0.1%; n = 2 of 3526 subjects).

Table 5: Incidence of Euphoric Mood in Phase 1 and Phase 2/3 Clinical Studies with Lorcaserin (0.1-60 mg) Compared to Placebo (NDA 22-529)

Study	Dose	Placebo	Lorcaserin Daily Dose (mg)									
			0.1	1	3	5	10	15	20	40	60	Total
Phase I	Single	0 of 20 (0%)	0 of 5 (0%)	0 of 5 (0%)			0 of 35 (0%)		0 of 12 (0%)	4 of 6 (67%)	6 of 31 (19%)	
Phase I	Multiple	0 of 117 (0%)			0 of 6 (0%)		1 of 34 (2.9%)	4 of 60 (6.7%)	6 of 54 (11%)	7 of 64 (11%)		
Phase II & III	Multiple	1 of 3389 (0.03%)		0 of 90 (0%)		0 of 89 (0%)	4 of 918 (0.4%)	0 of 205 (0%)	6 of 3311 (0.18%)			
Total		2 of 3526 (0.06%)	0 of 5 (0%)	0 of 95 (0%)	0 of 6 (0%)	0 of 89 (0%)	5 of 987 (0.5%)	4 of 265 (1.5%)	12 of 3377 (0.4%)	11 of 70 (16%)	6 of 31 (19%)	38 of 4926 (0.8%)

Figure 1 (below) demonstrates that the incidence of euphoric mood was dose-dependent. Individuals who received 40 mg lorcaserin (twice the proposed daily therapeutic dose and four times the proposed single therapeutic dose) reported a 16% incidence of euphoria (n = 11 of 70 subjects). When 60 mg lorcaserin (three times the proposed daily therapeutic dose and 6 times the proposed single therapeutic dose) was administered, there was a 19% incidence of euphoria (n = 6 of 31 subjects). Incidences of euphoria at the 40 and 60 mg doses are (respectively) more than 250 and 300 times greater than that reported following placebo administration

Figure 1: Incidence of Euphoria Mood in Phase 1 And Phase 2/3 Clinical Studies with Lorcaserin (0.1-60 mg) in Healthy Volunteers and Obese Patients Compared to Placebo (NDA 22-529)



The most critical AE case report related to abuse potential occurred in a female obese patient who received 40 mg lorcaserin in Study 001A (Subject #25). On Day 1 of lorcaserin treatment, this woman experienced numerous abuse-related AEs, including euphoria, disorientation, and hallucination. The moderate euphoria began ~40 minutes after her morning dose of lorcaserin and persisted for ~30 minutes. She concurrently experienced severe disorientation that persisted for 140 minutes. Approximately 90 minutes after lorcaserin administration, she experienced severe hallucinations (loss of arm awareness) that persisted for 10 minutes. These AEs resulting from lorcaserin administration are of particular note because they are consistent with the behavioral profile of other $5HT_2$ agonists such as the hallucinogens, LSD, psilocybin, and DOM. It

is noteworthy that these AEs occurred on the first day of lorcaserin administration, before $5HT_2$ receptor down-regulation and subsequent tolerance develops to lorcaserin. These data suggest that a motivated individual would be able to use lorcaserin for abuse purposes on an acute basis.

Table 6 (below) shows data from Study 001A (as presented in the Sponsor's "Adverse Event Listing by Treatment" of Study #APD356-001 in NDA 22-529). The Sponsor reported an incidence of euphoric mood in 4 of 6 healthy individuals (67%) who were treated with 40 mg/day lorcaserin. Two additional individuals experienced mood alteration and paresthesia. These data show that the 40 mg dose of lorcaserin produced abuse-related AEs in all subjects in this study.

Table 6: Abuse-Related AEs in Patients Receiving 40 mg/day Lorcaserin (Study 001A)

Subject #	Euphoric Mood	Mood Altered	Disorientation	Feeling Drunk	Hallucination	Paresthesia
19	+					
21	+					
23	+					
24		+				
25	+		+	+	+	
27						+

Other Abuse-Related Adverse Events

Drug addiction is a complex disorder characterized by compulsive drug use with multiple symptoms. Besides euphoric mood, there are some other AEs which can also be indicative of drug abuse potential.

In lorcaserin clinical trials with healthy volunteer population, dizziness was the most common TEAE, with 31.5% of lorcaserin-treated subjects reporting this effect compared to 3.3% of placebo-treated subjects in APD356-007 study. The incidence of dizziness increased with lorcaserin dose; subjects receiving 40 mg lorcaserin reported the highest incidence (45.3%) in this study (Table 7), indicating the dose-dependent effects with lorcaserin treatment. Since the blood pressure didn't change dramatically after lorcaserin treatment, dizziness in those subjects is likely associated with the CNS effects of lorcaserin.

Some serotonergic agents such as selective 5-HT reuptake inhibitors (SSRIs) are known to have dizziness side effects. For example, 7.1% and 10% of patients reported dizziness in clinical trials with therapeutic doses of paroxetine and fluoxetine, respectively. The higher incidence of dizziness can be an indication of the strong effects of lorcaserin on CNS serotonin system, which is a potential pathway involved in drug addiction.

Furthermore, the incidence of mood altered and paresthesia in study APD356-007 were significantly higher in the lorcaserin treatment group than in placebo group (Table 7). There is a significant difference between the placebo group and the 40 mg/day lorcaserin group. The overall incidence of various abuse-related AEs also showed dose-dependent effects. High dosage groups of 15 and 40 mg in Study 007 were associated with higher incidence of various abuse-related AEs than low dosage groups of 3 and 10 mg in Study 002 (Table 7) (as represented in the Sponsor's "Incidence of Potential Abuse-Related AEs in Multiple Dose Trials of Lorcaserin in Healthy Volunteers" of Study #APD356-001 in NDA 22-529).

Similarly, the incidence of abuse-related AEs was higher in lorcaserin-treated obese patients than in placebo-treated obesity patients (Table 8). The most commonly reported TEAEs occurring at greater than placebo levels were dizziness (8.0% vs. 3.8% in placebo-treated patients) and fatigue (7.1% vs. 3.6%). Relative to patients who received placebo, those who were treated with lorcaserin showed a much higher incidence of feeling jittery, psychomotor hyperactivity, paresthesia, abnormal dreams, and confusion state. Those symptoms are not due to a general medical condition and are not better accounted for by another mental or psychological disorder.

The high incidence of abuse-related AEs in lorcaserin treatment group and dose dependent effects indicate that lorcaserin had drug abuse potential, especially at supratherapeutic dosing.

Table 7. Reported Abuse-Related and Prominent Safety AEs in Multiple-Dose Trials of Lorcaserin in Healthy Volunteers Compared to Placebo (NDA 22-529)

Preferred Term (PT)	APD356-007				
	Placebo	Placebo / Moxifloxacin	Lorcaserin daily dose (mg)		All Lorcaserin
			15	40	
	N=60	N=60	N=60	N=64	N=124
Euphoric mood	1 (1.7)	0 (0.0)	5 (8.3)	6 (9.4)	11 (8.9)
Feeling abnormal	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	1 (0.8)
Mood altered	0 (0.0)	0 (0.0)	1 (1.7)	5 (7.8)	6 (4.8)
Abnormal dreams	1 (1.7)	0 (0.0)	2 (3.3)	2 (3.1)	4 (3.2)
Paresthesia	0 (0.0)	0 (0.0)	9 (15.0)	12 (18.8)	21 (16.9)
Dizziness	2 (3.3)	7 (11.7)	10 (16.7)	29 (45.3)	39 (31.5)
Dizziness postural	0 (0.0)	1 (1.7)	0 (0.0)	2 (3.1)	2 (1.6)

Table 8. Reported Abuse-Related and Prominent Safety AEs in Multiple-Dose Trials of Lorcaserin in Obese Patients Compared to Placebo (NDA 22-529)

Preferred Term (PT)	APD356-009 and APD356-011			
	Pooled Placebo	Lorcaserin daily dose (mg)		All Lorcaserin
		10 BID	10 QD	
	N=3185	N=3195	N=801	N=3996
Euphoric mood	1 (0.03)	6 (0.2)	3 (0.4)	9 (0.2)
Feeling abnormal	3 (0.1)	7 (0.2)	2 (0.2)	9 (0.2)
Feeling drunk	0	2 (0.1)	0	2 (0.1)
Anxiety	47 (1.5)	49 (1.5)	15 (1.9)	64 (1.6)
Feeling jittery	3 (0.1)	12 (0.4)	1 (0.1)	13 (0.3)
Restlessness	3 (0.1)	7 (0.2)	0	7 (0.2)
Paresthesia	15 (0.5)	37 (1.2)	12 (1.5)	49 (1.2)
Hypoaesthesia	19 (0.6)	13 (0.4)	7 (0.9)	20 (0.5)
Abnormal dreams	6 (0.2)	16 (0.5)	2 (0.2)	18 (0.5)
Confusional state	1 (0.03)	6 (0.2)	2 (0.2)	8 (0.2)
Dizziness	122 (3.8)	270 (8.5)	50 (6.2)	320 (8.0)
Dizziness postural	1 (0.03)	4 (0.1)	0	4 (0.1)

b. Adverse Events in Human Abuse Potential Study

In the human abuse potential study (Study # APD356-013), spontaneously-reported AEs related to abuse potential were monitored following administration of placebo, zolpidem (15 and 30 mg; Z 15, Z 30), ketamine (100 mg; K 100), lorcaserin (20, 40, 60 mg; L 20, L40, L60) [see full description of study design below, in Section B.i.b.].

As seen in Table 9 (below), lorcaserin administration produced a relatively high incidence of the abuse-related AE of euphoria (6-19%) compared to 0% from placebo. The rate for euphoria from lorcaserin is similar to that reported following zolpidem administration (13-16%), but less than that reported for ketamine (50%). Euphoria is the only abuse-related AE reported for any of the drug treatments at a rate greater than placebo.

Table 9: Comparative Incidence of Adverse Events in Human Abuse Potential Study with Lorcaserin (Study #APD356-013)

Adverse Event	Placebo (n = 31)	Z 15 (n = 32)	Z 30 (n = 31)	K 100 (n = 32)	L 20 (n = 33)	L 40 (n = 34)	L 60 (n = 31)
Euphoria	0 (0%)	4 (13%)	5 (16%)	16 (50%)	2 (6%)	6 (18%)	6 (19%)
Headache	8 (26%)	2 (6%)	3 (10%)	4 (13%)	20 (61%)	29 (85%)	26 (84%)
Nausea	0 (0%)	0 (0%)	0 (0%)	1 (3%)	7 (21%)	17 (50%)	14 (45%)
Dizziness	0 (0%)	4 (13%)	5 (16%)	4 (13%)	1 (3%)	5 (15%)	6 (19%)
Abdominal Discomfort	1 (3%)	0 (0%)	0 (0%)	0 (0%)	3 (9%)	6 (18%)	8 (26%)
Hot Flush	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)	6 (19%)
Decreased Appetite	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	4 (12%)	6 (19%)
Paresthesia	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	5 (15%)	5 (16%)
Anxiety	1 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	1 (3%)	3 (10%)
Depressed Mood	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	3 (9%)	2 (7%)

The adverse events most frequently reported with all three doses of lorcaserin are headache (61-84%) and nausea (21-45%). Headache is also prevalent following administration of placebo (26%), zolpidem (6-10%) and ketamine (13%) while nausea is only present following these treatments in a single subject in the ketamine group (3%).

The rate of dizziness is comparable between the two control drugs and the highest doses of lorcaserin (13-19%) and much greater than placebo (0%).

In contrast, the other AEs reported for lorcaserin are either not observed following zolpidem and ketamine administration or are not seen at a rate greater than that of placebo. These AEs following lorcaserin administration included abdominal discomfort (9-26%), hot flush (3-19%), decreased appetite (3-19%), paresthesia (3-16%), anxiety (3-10%) and depressed mood (3-9%).

3. Human Physical Dependence Studies

Two clinical studies are conducted to evaluate whether chronic administration of lorcaserin produces physical dependence in humans.

a. 4 Week Physical Dependence Study (#APD356-003)

Obese patients received lorcaserin (1, 5, 10 mg/kg, p.o.) for 4 weeks, followed by abrupt discontinuation and observation for 2 additional weeks. During the discontinuation period, patients returned on Days 4, 7 and 14 after final lorcaserin administration to assess any psychological, behavioral, or mood changes as measured by body weight and waist/hip measurements, Bond and Lader Mood VAS (scales for Alertness, Calmness, and Contentment), Subjective Sensations Questionnaire (SSQ) Hunger/Appetite VAS (scales for Relaxed, Hunger, Sleepiness, Happiness, Desire to Eat, Fullness, Nausea, Dizziness, Indigestion, Prospective Food Consumption, Gastric Emptiness, and Headache), assessment of any AEs, and physical and neurological examination.

During the discontinuation phase, there are no statistically significant changes in body weight, in waist/hip measurements, or on the Bond and Lader Mood VAS between lorcaserin and placebo treatment groups. On the SSQ VAS, the only measure that showed a statistically significant change from placebo is the Headache scale, in which lorcaserin reduced the incidence during the discontinuation period. AEs are not delineated for the discontinuation period, so it is not possible to ascertain their frequency following drug withdrawal.

b. 12 Week Physical Dependence Study (#APD356-004)

Obese patients received lorcaserin (5, 10, 20 mg/kg, p.o.) for 12 weeks, followed by abrupt discontinuation and observation for 2 additional weeks. During the discontinuation period, patients returned on Days 7 and 14 after final lorcaserin administration to assess any psychological, behavioral, or mood changes as measured by body weight and waist/hip measurements, Bond and Lader Mood VAS (scales for Alertness, Calmness, and Contentment), Subjective Sensations Questionnaire (SSQ) Hunger/Appetite VAS (scales for Relaxed, Hunger, Sleepiness, Happiness, Desire to Eat, Fullness, Nausea, Dizziness, Indigestion, Prospective Food Consumption, Gastric

Emptiness, and Headache), assessment of any AEs, and physical and neurological examination.

During the discontinuation phase, there are no statistically significant changes in body weight, in waist/hip measurements, on the Bond and Lader Mood VAS and on the SSQ VAS between lorcaserin and placebo treatment groups. AEs are not delineated for the discontinuation period, so it is not possible to ascertain their frequency following drug withdrawal.

Overall Conclusions from Human Physical Dependence Studies

Discontinuation of lorcaserin following chronic administration did not produce behavioral changes in measures of mood, interest in food or weight. The Sponsor interprets this as indicating that lorcaserin does not produce withdrawal or physical dependence.

However, during the two studies, the Sponsor did not utilize instruments that measure classic signs or symptoms associated with drug withdrawal. Additionally, as noted above for both studies, data submitted on AEs occurring during the discontinuation period were not adequate for evaluation, so it is not possible to determine whether these responses indicate a withdrawal syndrome.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

KATHERINE R BONSON
09/03/2010

Jianping P GONG
09/03/2010

MICHAEL KLEIN
09/03/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	August 27, 2010
To:	Mary Parks, Division Director Division of Metabolism and Endocrinology Products
Application Type/Number:	NDA 022529
Through:	Melina Griffis, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Lubna Najam, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Lorqess (Lorcaserin) Tablets, 10 mg
Applicant/sponsor:	Arena Pharmaceuticals
OSE RCM #:	2010-142

1. INTRODUCTION

This review responds to a request from the Division of Metabolism and Endocrinology Products for a review of the revised Lorqess labels and labeling submitted on August 9, 2010, in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant. DMEPA reviewed the initial proposed label and labeling under OSE #2010-142 dated March 18, 2010.

2. METHODS AND MATERIALS REVIEWED

The Applicant provided revised label and labeling on August 9, 2010. We also evaluated the recommendations pertaining to the previous revision in OSE review #2010-142.

3. CONCLUSION AND RECOMMENDATIONS

Our review of the revised labels and labeling note that the majority of the revisions are satisfactory with respect to DMEPA's recommendations under OSE review #2010-142, however, we note that the lot number and expiration date is not displayed on the sample blister card label. Please ensure that the sample blister card labels incorporate the expiration date and lot number.

If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Margarita Tossa at 301-796-4053.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

LUBNA NAJAM
08/27/2010

MELINA N GRIFFIS
08/27/2010

DENISE P TOYER
08/27/2010

Executive CAC
Date of Meeting: August 10, 2010

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Haleh Saber, Ph.D., DHP, Alternate Member
Todd Bourcier, Ph.D., Team Leader
Fred Alavi, Ph.D., Presenting Reviewer

NDA 22-529
Drug Name: Lorcaserin HCl
Sponsor: Arena Pharmaceuticals

Background:

Lorcaserin is a first-in-class serotonin 5HT2C receptor agonist. The sponsor is seeking an indication for the treatment of obesity.

Mouse Carcinogenicity Study
Carcinogenic assessment in CD1 mice was initiated at doses of 25, 50, and 100mg/kg, in accordance with the Committee's dosing recommendations. High mortality within two weeks of dosing initiation prompted a reduction in doses to 5, 25, and 50mg/kg, and the addition of 10 mice/sex to the control and 50mg/kg groups on day 19. The survival rate across the dose groups was similar to control for the remainder of the study. Drug exposure at the 5, 25, and 50mg/kg dose groups provided multiples of 0.5x, 4x, and 7x in males and 0.3x, 1x, and 4x in females relative to the clinical dose of 10mg bid.

Rat Carcinogenicity Study
Carcinogenic assessment in Sprague Dawley rats was initiated at doses of 10, 30, and 100mg/kg, in accordance with the Committee's dosing recommendations. Survival declined significantly at all doses in females due to the emergence of drug-related mammary tumors. Survival also declined significantly in high dose males, due to the emergence of drug-related tumors in the brain, skin, mammary tissue, and nerve sheaths (schwannoma). Drug exposure at the 10, 30, and 100mg/kg dose groups provided multiples of 5x, 17x, and 55x in males and 7x, 24x, and 82x in females relative to the clinical dose of 10mg bid.

Because excess mortality was due to drug-induced tumors rather than dose-limiting toxicity, the high dose of 100mg/kg is not considered to have exceeded the MTD.

Mechanistic studies were presented showing, at most, a small and non-sustained increase in serum prolactin in rats administered lorcaserin. Immunohistochemical staining of pituitary and mammary tissue failed to establish a correlation between prolactin and mammary tumors. Conversely, the anti-dopaminergic compound haloperidol readily

increased prolactin in these studies, and is associated with rodent mammary tumors via this mechanism.

Immunohistochemical staining of astrocytoma in thirteen sections showed a lack of staining with GFAP, and occasional staining with MHCII and an anti-CD68 marker, suggesting that the cellular lineage of the astrocytomas was not astrocytic but rather monocytic. The literature reports an absence of GFAP staining in rat astrocytoma, but this lack of staining is not necessarily evidence of a non-astrocytic origin of the tumor (Nagatani M et al; Toxicol Path, 2009). Regardless of cell lineage, the mechanism of tumor induction was not assessed and the relevance to human risk cannot be dismissed.

The incidence of mammary adenocarcinoma and fibroadenoma was reported on a quarterly basis in response to the Division's request starting at week 55. The Division expressed concern that the number of adenocarcinoma in the mid- and high-dose groups decreased from week 96 to the final study report, whereas the incidence in the control and low dose groups either increased (control) or stayed the same (low dose) over the same time period. Additionally, the Division identified 2 cases of high dose females suspected of having a mammary tumor that were not counted as such in the study report.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed that the study was acceptable, as mortality was encountered at doses higher than 50mg/kg.

- The Committee concluded that the study was negative for any statistically significant drug-related tumor findings.

Rat:

- The Committee expressed some concern about the conduct and evaluation of the study. Specifically, concern was expressed about a large number of diagnostic changes of mammary tumor type in the evaluation for the mid and high dose group.

- The Committee noted that because high-dose animals died due to drug-induced tumors, the MTD was not exceeded in this study.

- The Committee was not persuaded by the sponsor's argument that mammary tumors were caused by increased prolactin levels. Specifically, the sponsor's data failed to demonstrate an increase in prolactin in repeat-dose mechanistic studies and in the 2 year carcinogenicity study.

- A mechanism for the induction of astrocytomas was not identified. Drug-induced astrocytomas were observed at exposures equal to 17x the clinical exposure, with a NOAEL that provides a 5x multiple to the clinical dose.

The Committee concluded that the following tumors were drug-related:

Males
Brain: Astrocytoma at HD. Numerical, non-statistically significant increase in astrocytoma at mid-dose also considered drug-related.

Liver: Hepatocellular adenoma and carcinoma combined, at HD.

Mammary: Adenocarcinoma and fibroadenoma combined, at MD & HD.

Skin, subcutis: Fibroma at MD & HD

Skin: Squamous Carcinoma at HD. Numerical, non-statistically significant increase in squamous carcinoma at MD also considered drug-related.

Schwannoma (all sites) at HD. Numerical, non-statistically significant increase at the MD also considered drug-related.

Thyroid: Follicular cell adenoma at HD.

Females
Mammary: Adenocarcinoma + fibroadenoma at LD, MD, HD

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DMEP
/Todd Bourcier, DMEP
/Fred Alavi, DMEP
/Pat Madara, DMEP
/ASeifried, OND IO

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

ADELE S SEIFRIED
08/13/2010

DAVID JACOBSON KRAM
08/13/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	March 18, 2010
To:	Mary Parks, MD, Division Director Division of Metabolism and Endocrinology Products
Through:	Melina Griffis, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Najam, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Lorqess (Lorcaserin HCL) Tablets 10 mg
Application Type/Number:	NDA 022529
Applicant/sponsor:	Arena Pharmaceuticals
OSE RCM #:	2010-142

CONTENTS

EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis evaluated the proposed labels and labeling for Lorqess (NDA 022529) and identified areas of vulnerabilities that could lead to medication errors. We provide recommendations in Section 2 with the aim of reducing the risk of medication errors with regards to the proposed product label and labeling.

1 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, blister sample pack label, and insert labeling submitted as part of the December 18, 2009 original NDA submission. See Appendix A -D for images of proposed container labels and blister pack labels.

2 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. We request the recommendations for the container label and blister sample pack label, in Section 2.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Margarita Tossa at 301-796-4053.

2.1 COMMENTS TO THE APPLICANT

A. Container Label (10 mg 100 tablets)

1. The proprietary name and established name are separated by intervening graphics. In accordance with 21CFR 201.10(a), the proprietary name and established name should appear together without any intervening written, printed or graphic matter. Revise this label to remove the green graphic separating the proprietary name and the established name.
2. The product strength and net quantity are located next to each other on the principal display panel and are of equal prominence. The size of the product strength should be increased to appear more prominently on the label. In addition the net quantity statement should be relocated to a less prominent area of the label to minimize the potential for confusion with the product strength.
3. The Principal display panel (PDP) appears crowded as it contains the "each tablet contains" statement in addition to the "made in", manufactured and distributed by information. Relocate the "each tablet contains." statement to the side panel to minimize the clutter and allow for more important information to be provided on the PDP.

B. Sample Pack Carton Labeling (10 mg 10 tablets)

1. See comment A1.
2. The product strength and net quantity are located next to each other on the principal display panel and are of equal prominence. The size of the product strength should be increased to appear more prominently on the label. In addition the net quantity statement should be relocated to a less prominent area of the label.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

C. Blister Sample Pack Label (10 mg 10 tablets)

The proprietary name, established name and strength are present only on the back panel. Thus when tablets are removed this information may be destroyed and unreadable. This label should be revised so that the proprietary name, established name and strength presentation are also located on the front panel or at a minimum ensure that the information remains on the blister pack label after each tablet is removed.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

LUBNA NAJAM
03/19/2010

MELINA N GRIFFIS
03/22/2010

DENISE P TOYER
03/24/2010

DENISE P TOYER on behalf of CAROL A HOLQUIST
03/24/2010

DSI CONSULT
Request for Nonclinical Site Inspections

DATE: March 3, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

Attn: Jacqueline A. O'Shaughnessy, Ph.D.
Acting GLP Team Leader

FROM: Pat Madara, Regulatory Project Manager, Division of Metabolism and Endocrinology Products, HFD-510

SUBJECT: **Request for Nonclinical Site Inspections**
NDA 22529
Lorqess (lorcaserin HCl) Tablets, 10 mg
Arena Pharmaceutical, Inc
6166 Nancy Ridge Drive
San Diego, California 92121

Study monitor (b) (6)
(b) (6) Drug Safety Evaluation
Arena Pharmaceuticals, Inc.
Telephone: 858.453.7200, (b) (6)
Fax: 858.677.0222
Email: (b) (6)

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	
(b) (4) study # 900-062 (Arena study # TX05070)	(b) (4) .(2-Year mouse carcinogenicity study) (b) (4)	
(b) (4) study # 900-063 (Arena study# TX05071)	(b) (4) (2-Year rat carcinogenicity study) (b) (4)	

Sierra Study # (b) (4) 00016 (Arena study # TX04039)	(b) (4) (52 week monkey toxicology study) (b) (4)	
(b) (4) study # 900-062 (Arena study # TX05070) and (b) (4) study # 900-063 (Arena study# TX05071)	(b) (4)	
(b) (4) study # 900-062 (Arena study # TX05070) and (b) (4) study # 900-063 (Arena study# TX05071)	(b) (4)	
(b) (4) Study # (b) (4) 00016 (Arena study # TX04039) (52 week monkey tox study)	(b) (4)	
The two external pathologists were hired by Arena to examine monkey renal tissues (they dismissed the study pathologists and peer review pathologists findings).	**2 External pathologists enlisted by Arena** (b) (4)	

Comments:

Primary nonclinical reviewer is Dr. Fred Alavi. He states:

"In the mouse study, we are interested in looking at the study in general. In rat study, we would like DSI to examine nearly everything, from brain and breast tumor incidence to how the drug levels were measured. In the monkey study, we would like DSI to see if the slides were blinded and why there was such a discrepancy and how often the external pathologists examined monkey kidney slides. I am still expanding my list of what needs to be examined."

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.) N/A

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **September 1, 2010 (Lorqess will be discussed at an advisory committee meeting in September 2010, and we are requesting that all site inspections be completed prior to the AC**. We intend to issue an action letter on this application by **October 22, 2010**.

Should you require any additional information, please contact Pat Madara, project manager (61249) or Dr. Fred Alavi, Nonclinical Reviewer (61167).

Concurrence:
Todd Bourcier, Ph.D., Nonclinical Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
03/04/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22529 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Lorqess Established/Proper Name: lorcaserin HCl Dosage Form: tablet Strengths: 10 mg		
Applicant: Arena Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: December 18, 2009 Date of Receipt: December 22, 2009 Date clock started after UN:		
PDUFA Goal Date: October 22, 2010	Action Goal Date (if different):	
Filing Date: February 19, 2010	Date of Filing Meeting: February 10, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s): for weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet and a program of regular exercise. Indicated for obese patients with an initial body mass index ≥30 kg/m^2, or overweight patients with a body mass index ≥27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		**X** 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		**X** Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR	

☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 69888

Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	XX			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	XX			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	XX			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		XX		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	XX			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: **X** Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: **X** Not in arrears ☐ In arrears

Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		**XX**		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		**XX**		

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		**XX**		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) **X** All electronic ☐ Mixed (paper/electronic) **X** CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: X legible X English (or translated into English) X pagination X navigable hyperlinks (electronic submissions only) **If no**, explain.				
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:* **12/30/09**	**XX** **XX**			
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	**XX**			
Are all establishments and their registration numbers listed on the form/attached to the form?	**XX**			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	**XX**			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	**XX**			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	**X**			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	**XX**			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			**XX**	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	**XX** **XX**			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	**XX**			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	**XX**			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		**XX**		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***	**XX**			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	**XX** Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) **XX** Carton labels **XX** Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	**XXX**			
Is the PI submitted in PLR format?	**XXX**			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	**XX**			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Not submitted**				
REMS consulted to OSE/DRISK? **not submitted**				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	**XXX**			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	**XX**			

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	**XX**			

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s): May 1, 2006** ***If yes, distribute minutes before filing meeting***	**XX**			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s): August 12, 2009** ***If yes, distribute minutes before filing meeting***	**XX**			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***				

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 10, 2010

NDA #: 22529

PROPRIETARY NAME: Lorqess

ESTABLISHED/PROPER NAME: lorcaserin HCl

DOSAGE FORM/STRENGTH: 10 mg tablet

APPLICANT: Arena Pharmaceuticals

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): for weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet and a program of regular exercise. Indicated for obese patients with an initial body mass index ≥30 kg/m^2, or overweight patients with a body mass index ≥27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pat Madara	Y
	CPMS/TL:	Lina Aljuburi	N
Cross-Discipline Team Leader (CDTL)	Eric Colman		Y
Clinical	Reviewer:	Julie Golden	Y
	TL:	Eric Colman	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Immo Zdrojewski	Y
	TL:	Sally Choe	Y
Biostatistics	Reviewer:	Janice Derr	Y
	TL:	Todd Sahlroot	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fred Alavi	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	TBD	N
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Olen Stephens	N
	TL:	Su Tran	Y
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:	N/A	
	TL:		
Facility Review/Inspection	Reviewer:	TBD	
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Melina Griffis	N
	TL:	Anne Crandall	N
OSE/DRISK (REMS)	Reviewer:	Barbara Fuller	Y
	TL:		N
Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalwe	Y
	TL:	Tejashri Purohit-Sheth	N

Other reviewers	Katherine Bonson, CSS Xiao Ding, DBVII	Y
Other attendees	Lori Love, TL, CSS	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	X Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	X YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	X YES Date if known: 9/16/10 ☐ NO ☐ To be determined Reason:

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES X NO
BIOSTATISTICS **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE X Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	X Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Curtis Rosebraugh, ODE II Director **21st Century Review Milestones (see attached)** (optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> X Standard Review ☐ Priority Review
ACTIONS ITEMS	
X	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
N/A	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). N/A
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74 – see attached 74-day letter
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22529

FILING COMMUNICATION

Arena Pharmaceuticals, Inc.
Attention: Mark Brunswick, Ph.D.
Senior Director, Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Dr. Brunswick;

Please refer to your new drug application (NDA) dated December 18, 2009, received December 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lorqess (lorcaserin HCl) Tablets, 10 mg.

We also refer to your submissions dated December 30, 2009, and January 12 and 13, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 22, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 1, 2010.

During our filing review of your application, we have identified the following deficiencies and request submission of the information described below. Please submit the requested materials as rapidly as possible so that we may continue our review of your NDA.

Clinical: Please respond to the request in bold font (1.h.) within one week. Provide an estimated timeline for your responses to the other requests.

1. Adverse Events of Special Interest
    a. In the note under table S09.1, you state that AESI categories were defined by the Sponsor using existing SMQs or a customized list. Please clarify whether those AESIs that used existing SMQs were customized. For those AESIs that were generated by Arena (e.g., Cardiac Valve Disorder), describe the process used to select the MedDRA preferred terms.
    b. All AESIs as presented in section 6.1.2 of the ISS statistical report should be also conducted for the two phase 2 studies, and BLOOM (through year 2) and BLOSSOM studies, separately.
    c. An analysis using PTs related to male and female priapism should be conducted (as asked for at the preNDA meeting); see suggested search terms, below. These data should be presented as with other AESIs in Table S09.1, for phase 2 and phase 3 studies separately and phase 3 studies pooled.

MedDRA Search Terms for Priapism

LLT	PT	HLT	SOC
Priapism	Priapism	Erection and ejaculation disorders	Reproductive system and breast disorders
Priapism aggravated			
Clitoral engorgement	Clitoral engorgement	Vulvovaginal signs and symptoms	
Clitorimegaly	Enlarged clitoris	Female gonadal function disorders	Endocrine disorders
Clitoris engorgement			
Clitoris enlarged			
Hypertrophy of clitoris			
Vulvodynia	Vulvovaginal pain		
Erection increased	Erection increased	Sexual arousal disorders	Psychiatric disorders
Penile edema	Penile oedema	Penile disorders NEC	
Penile vascular disorder	Penile vascular disorder		
Penile pain	Penile pain		
Spontaneous penile erection	Spontaneous penile erection		

    d. 'Hyperprolactinemia', 'blood prolactin abnormal', and 'blood prolactin increased' were not included in the PTs searched for the AEs related to prolactin and should be added to the analysis. These data should be presented as with other AESIs in Table S09.1, for phase 2 and phase 3 studies separately and phase 3 studies pooled.
    e. 'Serotonin syndrome' was not included in the PTs searched for AEs related to serotonin syndrome and should be added to the analysis. These data should be

presented as with other AESIs in Table S09.1, for phase 2 and phase 3 studies separately and phase 3 studies pooled. Additionally, please perform analyses using the *neuroleptic malignant syndrome SMQ* and *dystonia SMQ*. Narrow and broad SMQs should be presented.

f. Update Table 60 in ISS (breast cancers) to include any baseline or on-study prolactin concentrations that are available for these patients.
g. An additional AESI analysis that we are requesting is: *acute renal failure SMQ*. Please present this analysis for phase 2 and phase 3 studies separately and phase 3 studies pooled.
h. Suicidality analysis: detail how your implementation of C-CASA was different from the Posner 2007 publication and justify the rationale for those modifications.
i. Provide the literature references (actual articles) that describe the validation of the BDI-II and the procedure for scoring, or describe their location in the NDA.

2. Laboratory and vital sign data
   a. All laboratory data as presented in Table S14 of the ISS statistical report should be also be presented through year 2 of the BLOOM study (i.e., present the BLOOM study separately).
   b. Please conduct similar outlier analyses for all safety laboratory values (not just selected).
   c. Provide the criteria used to identify safety laboratory outliers.
   d. Present a similar analysis as in Table S14 for vital signs and ECG parameters, with a separate presentation for BLOOM (through year 2) and justification for outlier cutoffs.
   e. Identify the prolactin assay that was used in your program, or state where in the NDA this information is located.

3. Echocardiograms
   a. Please provide the 90% CI for the proportion of patients who developed FDA valvulopathy for each study individually.
   b. Additional information/analyses related to echocardiogram inter- and intrareader variability not included in the 6-month EDSMB report were supposed to be included in the final study reports. Please state the location of these analyses in the NDA, or provide them.
   c. As discussed in the preNDA meeting, source documents (written interpretations) were supposed to be provided for all cases of FDA-defined valvulopathy and in those situations that required third reader adjudication for AR and MR readings with ≥ 2 grades discordance. Please describe their location in the NDA or provide them.

4. Concomitant medications
   a. In BLOSSOM, Tables 32 and 33 (patients who changed or initiated selected medications) are helpful. Similar analyses were conducted in BLOOM, although only in the PP1 population (see request (b)). Please generate these tables for the Safety population for BLOOM (through year 2) and for the phase 3 studies, pooled.

b. In BLOOM, please clarify why the numerators in Table 14.2.140 add up to the denominator and yet there are still patients counted as "yes" in the respective medication category for Table 14.2.141. These groups should be mutually exclusive.
c. Similar tables to those in request (a) should be generated for concomitant psychiatric medications, and then further separated by antidepressants, anxiolytics, and antipsychotics.
d. In the preNDA meeting, you alluded to approximately 50 – 100 patients who had broken protocol and been exposed to SSRIs for up to six months during the clinical trials. Please present a treatment exposure and safety analysis (SAEs, withdrawals, AESIs, and common AEs) by treatment group for these patients (phase 3 studies individually and pooled).

5. Comorbid conditions
    a. Provide an analysis of efficacy (weight loss) and safety (common AEs) by the presence or absence of comorbid condition: hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, and sleep apnea.

6. CRFs and investigators
    a. Please describe how eCRFs were filled out, or where in the application this is described (i.e., were they entered electronically by the investigator or filled out by hand and entered electronically by the CRO).
    b. Please describe where on the CRF the investigator made narrative comments about a particular adverse event.
    e. It appears that there are CRFs included for patients who did not experience death, SAEs, or AEs leading to dropout. Describe the selection process for the inclusion of additional CRFs in the NDA.
    f. In study 003, it appears that there was a patient who was discontinued for pregnancy, but that CRF was not located.
    g. In study 004, there are links to CRFs for subjects 08-012 and 40-031, but the links do not work and the CRFs are not included in the separate listings.
    h. Please clarify:
        1. whether Larry Dee Stonesifer (site 173, BLOOM) enrolled any patients.
        2. why, in the BLOSSOM trial, there were a number of sites with an investigator formerly another investigator (e.g., Douglas Denham, formerly Mark Kipnes).
        3. the name and address for site 2165 in the BLOSSOM trial.

7. Miscellaneous
    a. Provide a table of overall drug exposure by days of treatment including year 2 of BLOOM (i.e., extend Table 7 in the ISS), or, enumerate how many patients have been exposed to lorcaserin for 18 months and 2 years.
    b. Please provide an analysis of lorcaserin overdose experience in the clinical trials (intentional or accidental), and a discussion of any theoretical or observed risk from lorcaserin overdose.

Biometrics

1. At the pre-NDA meeting on August 12, 2009, we requested additional statistical analyses of certain efficacy endpoints from Study 009 and Study 011. While we did locate the results of the completers analysis for the two studies combined, we did not locate results of the other analyses that we requested. For this reason, we request that you conduct the following analyses separately for Study 009 and Study 011: a) for the co-primary endpoints, use the completers population and the primary efficacy analysis models; and b) for the percent change in body weight from baseline, use the MITT1 and PP1 populations and a mixed-model-repeated measures (MMRM) analysis model. If you have already conducted and reported these analyses, please indicate their location in the submitted materials.

Clinical Pharmacology

1. Submit the bioanalytical method validation for study APD-356-001C.
2. Submit individual subject concentration data including their renal impairment and hepatic impairment classification information from the studies APD-356-016 and APD-356-017, respectively.
3. Submit the actual names of the analytes that are reported in individual subject concentration datasets for studies APD-356-012 and APD-356-002.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Metabolism and Endocrinology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a partial waiver of pediatric studies (b) (4) for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies (b) (4) (b) (4) for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at 301-796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

ERIC C COLMAN
02/24/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
04/01/2010

DSI CONSULT: Request for Clinical Inspections

Date: January 20, 2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Kassa Ayalew, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Julie Golden, M.D./Medical Officer/Division of Metabolism and Endocrinology Products (DMEP) and

Eric Colman, M.D., Deputy Director, DMEP

From: Patricia Madara; Project Manager, DMEP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: **NDA-22529**
Applicant/ Applicant contact information (to include phone/email):
Mark Brunswick, Ph.D.
Senior Director Regulatory Affairs
Arena Pharmaceuticals
6166 Nancy Ridge Drive
San Diego, CA 92121
Ph (858)-453-7200
Fax (858)-677-0222
mbrunswick@arenapharm.com

Drug Proprietary Name (proposed): **Lorqess**
NME or Original BLA (Yes/No): **Yes**
Review Priority (Standard or Priority): **Standard**

Study Population includes < 17 years of age (Yes/No): **No**
Is this for Pediatric Exclusivity (Yes/No): **No**

Proposed New Indication(s): **for weight management, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced-calorie diet and a program of regular exercise. Indicated for obese patients with an initial body mass index ≥30 kg/m^2, or overweight patients with a body mass index ≥27 kg/m^2 in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, cardiovascular disease, glucose intolerance, sleep apnea).**

PDUFA:
Action Goal Date: **October 22, 2010**
Inspection Summary Goal Date: TBD with input from DSI

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
107 - Bruce Berwald Radiant Research, Inc. 675 Old Ballas Rd. St Louis MO 63141 Phone (314) 692-2100 Fax (314) 692-2122 info@radiant reseach.com	BLOOM (APD356-009)	260 subjects screened 122 subjects randomized	See proposed indication above
122 - Lydie Hazan, MD 5800 Wilshire Blvd Los Angeles, CA 90036 Office - (310) 289-8242 Fax - (310) 289-8248 drhazan@impactla.org	BLOOM (APD356-009)	465 subjects screened 208 subjects randomized	See proposed indication above
2145 - Leslie Moldauer; Radiant Research 12015 E. 46th Avenue, Suite 500 Denver CO 80239 Phone (303).477.1880 Fax (303).480.1086	BLOSSOM (APD356-011)	127 subjects screened 81 subjects randomized	See proposed indication above
2146 - Martin Mollen; Arizona Research Center 2525 W. Greenway Road, Suite 114 Phoenix AZ 85023 Phone: (602)863-6363 Fax: (602)863-6611	BLOSSOM (APD356-011)	202 subjects screened 125 subjects randomized	See proposed indication above

III. Site Selection/Rationale

Lorcaserin is an NME. It will be presented before an FDA advisory committee meeting later this year. Concerns have been raised regarding the conduct of the nonclinical program, which places the entire development program under heightened scrutiny. With the exception of Ivan Goldsmith (site 189, BLOOM study), who already underwent a for-cause inspection by DSI, there are no specific concerns with any particular investigative site, although it is unclear why one investigator signed off on another investigator's eCRFs (L. Hazan (site 122, BLOOM) signed off on eCRFs for I. Goldsmith (site 189, BLOOM)). An inspection of the CRO (b) (4) (b) (4) might be informative. Finally, it should be noted that a safety endpoint (cardiac valvulopathy as assessed by echocardiogram) was a prespecified endpoint, and therefore, inspection of the core echocardiography laboratory (b) (4) might be useful.

The sites selected took into account enrollment size and early discontinuations (see attached). Individual sites have not yet been evaluated for site-specific efficacy or safety. Study APD356-009 had 98 sites. A total of 3182 subjects were randomized. Study APD356-011 had 97 sites. A total of 4008 subjects were randomized. It is unlikely that any one site drove the efficacy or safety results.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- x Enrollment of large numbers of study subjects
- ____ High treatment responders (specify):
- x Significant primary efficacy results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- x Other (specify): Significant primary safety results pertinent to decision-making

International Inspections:

Reasons for inspections (please check all that apply):

- ____ There are insufficient domestic data
- ____ Only foreign data are submitted to support an application
- ____ Domestic and foreign data show conflicting results pertinent to decision-making
- ____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

Not applicable.

Should you require any additional information, please contact Pat Madara, project manager at 301-796-1249 *or* Medical Officer, Julie Golden at 301-796-1216.

Concurrence: (as needed)

_____**X**_____ Medical Team Leader
_____**X**_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Please note investigator site summaries attached to this consult, submitted after the original NDA, in response to a request from DMEP.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICALS INC	LORQESS (lorcaserin hydrochloride) Tablets

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/s/

PATRICIA J MADARA
02/26/2010