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APPLICATION NUMBER:

022529Orig1s000

OTHER ACTION LETTERS



NDA 022529

COMPLETE RESPONSE

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 acknowledge receipt of your amendments dated December 31, 2009, and January 11 and 13, February 9 and 25, March 3 and 10, April 2, 7, 20, and 27, May 4, 12, and 27, June 2 and 25, July 8, 16, 20, 26, 30 (2), August 3 (2), 9, 11, 26, and 27, and September 8, 2010.

We also acknowledge receipt of your amendment dated September 28, 2010, which was not reviewed for this action. You may incorporate applicable sections of that amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

NONCLINICAL

1. Diagnostic uncertainty in the classification of mammary masses in female rats

The incidence and proportion of female rats with adenocarcinoma was higher at all doses of lorcaserin at each update from week 55 to 96. Thereafter, and to submission of the final study report, the incidence of adenocarcinoma decreased in an imbalanced manner favorable to lorcaserin. Records documenting the reason and rationale for the change in each diagnosis are lacking. Additionally, at least two cases have been identified for high-dose females with apparent gross errors in the pathology reports. These issues are sufficiently concerning to warrant re-evaluation of relevant tissues from the rat carcinogenicity study to resolve the diagnostic uncertainty apparent in the study report and to permit re-assessment of clinical risk.

- a. Provide a detailed accounting of all slides prepared from female rats that contributed to mammary tumor incidence data in each update to the FDA and to the final study report. Include the identification of the slides examined, diagnoses made by the primary and subsequent pathologists, and documentation for any change in diagnosis from the interim updates to the final study report.
 - b. In consultation with the Agency, identify an independent pathologist or group of pathologists to re-adjudicate all mammary and lung tissues (neoplastic and non-neoplastic lesions) from all female rats. Assurance must be provided that all requested slides prepared and examined in the course of the rat study are included in the re-adjudication process. Furthermore, re-adjudication should be conducted in a blinded manner (i.e., reader should have no information about treatment group allocation).
2. Unresolved exposure-response relationship for lorcaserin-emergent mammary adenocarcinoma

There is evidence of decreased latency and increased aggressiveness of adenocarcinoma at all doses of lorcaserin in female rats. The incidence of adenocarcinoma was consistently higher in all dose groups from weeks 55 to 96 of the study, palpable nodules were detected earlier, and a greater number of mammary tumor-related deaths occurred at an earlier point in the study. Adenocarcinoma was also more prevalent at all doses of lorcaserin from the interim sacrifice of the toxicokinetic group females. Additionally, mammary adenocarcinoma metastasized to the lung in all groups administered lorcaserin but not in the control, with an incidence of 0, 2, 7, and 6 for the control, low, mid-, and high doses, respectively. Lastly, a concerning pattern is observed in the number of females found with multiple masses (as opposed to a single mass) of adenocarcinoma: 9, 21, 13, and 33 at the control, low, mid-, and high doses, respectively. The clinical relevance of this apparent decrease in latency and increase in aggressiveness of adenocarcinoma must be sufficiently addressed to permit adequate risk assessment.

Demonstrate that the apparent increase in aggressiveness of adenocarcinoma in rats administered lorcaserin is reasonably irrelevant to human risk assessment.

3. Unidentified mode of action and unclear safety margin for lorcaserin-emergent brain astrocytoma

The numerical and statistical increases in brain astrocytoma at the mid- and high doses in male rats are considered related to lorcaserin. Partitioning of lorcaserin to brain tissue differs between rats and monkeys, and variable estimates have been provided for partitioning within each species. Partitioning of lorcaserin to brain tissue in human subjects is unknown. The relationship between brain exposure in humans at the clinical dose of lorcaserin to the brain exposure in rats that results in astrocytoma is therefore uncertain. Demonstration of a substantial exposure margin based on comparative exposure to lorcaserin in the CNS of rats to human subjects would mitigate concern of long-term clinical risk.

- a. Provide additional data/information regarding the distribution of lorcaserin to the CNS in animals and human subjects that would clarify or provide a better estimate of exposure margins.
- b. Demonstration of a substantial margin to clinical exposure is unnecessary if key events in the tumorigenic mode of action are identified and reasonably shown to be irrelevant to human risk.

CLINICAL

4. The weight-loss efficacy of lorcaserin 10 mg twice a day relative to placebo in overweight and obese individuals without type 2 diabetes is marginal.
 - a. Submit the final study report for the trial of lorcaserin in overweight and obese individuals with type 2 diabetes (BLOOM-DM).
 - b. In the event that you cannot provide evidence to alleviate our concern regarding the clinical relevance of the breast and brain tumor findings in rats, additional clinical studies may be required to obtain a more robust assessment of lorcaserin's benefit-to-risk profile.

LABELING

5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated 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>.

In addition, we reference our advice letter dated September 7, 2010, in which we notified you that, based on our review of the materials submitted in your application, we would recommend placement of lorcaserin in Schedule IV of the Controlled Substances Act. Repeating these studies and submitting the data in your complete response to this letter may lead to a different recommendation.

- A. The rat study evaluating overt serotonin behaviors (Study #DBR09-011) 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} behaviors (wet dog shakes and back contractions) and 5HT_{2C} behaviors (decreased activity and increased penile grooming/penile erection). Thus, no conclusions can be drawn regarding the ability of lorcaserin to produce overt behaviors associated with either of these serotonin receptor subtypes. This study should be repeated to demonstrate that a 5HT_{2A} and 5HT_{2C} agonist produces both 5HT_{2A} and 5HT_{2C} behaviors, if the study is to be useful in assessing the abuse potential of lorcaserin. Instead of DOI as the positive control, we recommend 4-methyl-2,5-dimethoxy-amphetamine (DOM) or another 5HT_{2A} and 5HT_{2C} agonist that is listed in Schedule I.

- B. The rat drug discrimination study (Study # TOX08040) lacks validity because of numerous procedural discrepancies, including the inability of rats to maintain adequate recognition of the training drug, 4-methyl-2,5-dimethoxy-amphetamine (DOM), over the course of the study. Thus, no conclusions can be drawn regarding the ability of lorcaserin to generalize to DOM. This study should be repeated to demonstrate that rats can maintain discrimination of DOM at the 80% criterion over the course of the study, if the study is to be useful in assessing the abuse potential of lorcaserin.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry Formal Meetings Between the FDA and Sponsors or Applicants*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation Research

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

/s/

CURTIS J ROSEBRAUGH
10/22/2010