Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 10, 2012

Location: DoubleTree Hotel by Hilton Washington D/C, Silver Spring, 8727 Colesville Road, Silver Spring, Maryland

Topic: The committee discussed the safety and efficacy of new drug application (NDA) 22 529, lorcaserin hydrochloride Tablets, sponsored by Arena Pharmaceuticals, Inc., as an adjunct to diet and exercise for weight management in patients with a body mass index (BMI) of equal to or greater than 30 kilograms (kg) per square meter, or a BMI equal to or greater than 27 kg per square meter if accompanied by weight-related co-morbidities.

These summary minutes for the May 10, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on _June 21, 2012___

I certify that I attended the May 10, 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/Signed/_____

Paul T. Tran, R.Ph
Designated Federal Officer, EMDAC

_____/Signed/_____

Abraham Thomas, M.D., M.P.H.
Chairperson, EMDAC

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 10, 2012

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on May 10, 2012. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the Food and Drug Administration (FDA) website at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/default.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA, Center for Drug Evaluation and Research, met on May 10, 2012 at the DoubleTree Hotel by Hilton Washington D/C, Silver Spring, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Arena Pharmaceuticals, Inc. The meeting was called to order by Abraham Thomas, M.D., M.P.H. (Chairperson), and the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Officer). There were approximately 150 people in attendance. There were sixteen Open Public Hearing speakers.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 22–529, lorcaserin hydrochloride Tablets, sponsored by Arena Pharmaceuticals, Inc., as an adjunct to diet and exercise for weight management in patients with a body mass index (BMI) of equal to or greater than 30 kilograms (kg) per square meter, or a BMI equal to or greater than 27 kg per square meter if accompanied by weight-related co-morbidities.

Attendance:
Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting): Vera Bittner, M.D., M.S.P.H.; Erica H. Brittain, Ph.D.; David M. Capuzzi, M.D., Ph.D., Eric I. Felner, M.D., MSCR; Edward W. Gregg, Ph.D.; Ida L. Spruill, Ph.D., R.N. (*Consumer Representative*); Abraham Thomas, M.D., M.P.H., FACP *(Chairperson)*; Lamont G. Weide, M.D., Ph.D., FACE

Endocrinologic and Metabolic Drugs Advisory Committee Members Not Present (Voting):
Ellen W. Seely, M.D.

Endocrinologic and Metabolic Drugs Advisory Committee Member Present (Non-Voting)
Mads F. Rasmussen, M.D., Ph.D. *(Industry Representative)*

Temporary Members (Voting):
Daniel H. Bessesen, M.D; Heidi M. Connolly, M.D.; Katherine M. Flegal, Ph.D.; Allison B. Goldfine, M.D; Peter A. Gross, M.D.; Ed J. Hendricks, M.D.; William R. Hiatt, M.D., FACP; Sanjay Kaul, M.D.; David E. Malarkey D.V.M., Ph.D., DACVP; Ernest E. McConnell, D.V.M.,

M.S.; Lewis S. Nelson, M.D.; Jeanmarie Perrone, M.D., FACMT; Robert J. Smith, M.D.; Angelica Walden (*Patient Representative*); Jack A. Yanovski, M.D., Ph.D.

FDA Participants (Non-Voting):
Fred Alavi, Ph.D.; Todd Bourcier, Ph.D.; Eric C. Colman,M.D.; Julie Golden, M.D.; Curtis J. Rosebraugh, M.D., M.P.H.

Designated Federal Officer: Paul T. Tran, R.Ph

Open Public Hearing Speakers:
Haluk Kaya Aydin, M.D; Kate Ryan, MPA - National Women's Health Network; Reza Ganjavi; Robert F. Kushner, M.D. – The Obesity Society; Joe Nadglowski - Obesity Action Coalition; Domenica Rubino, M.D. - Washington Center for Weight Management and Research; Janet H. Matope, MS - Men's Health Network; Denise Bruner, M.D., FASBP – American Society of Bariatric Physicians; Lisa Sutter; George Grunberger, M.D., FACP, FACE – American Association of Clinical Endocrinologists (AACE); Elizabeth Battaglino Cahill, R.N. - Healthy Women; Morgan Downey, J.D. – The Downey Obesity Report; Ted Kyle, RPh, MBA – ConscienHealth; Joseph Dedvukaj, Esq - The Joseph Dedvukaj Firm, P.C.; Sonia Nagda, M.D - National Research Center for Women & Families; Gary Deverman, CFRE – Building Healthier America.

The agenda proceeded as follows:

Call to Order and Introduction of Committee	**Abraham Thomas, M.D., M.P.H., FACP** Chairperson, EMDAC
Conflict of Interest Statement	**Paul T. Tran, R.Ph** Designated Federal Officer, EMDAC
Introduction/Background	**Eric C. Colman, M.D.** Deputy Director Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
SPONSOR PRESENTATIONS	**Arena Pharmaceuticals, Inc.**
Introductory Remarks	**Craig M. Audet** VP, Global Regulatory Affairs Arena Pharmaceuticals
Clinical Study Designs and Patient Baseline Characteristics	**William Shanahan, M.D.** Sr. VP & CMO Arena Pharmaceuticals

Efficacy Results and Clinical Perspective	**Steven R. Smith, M.D.** Scientific Director, Translational Research Institute for Metabolism and Diabetes, Florida Hospital/Sanford Burnham Institute
Clinical Safety Results	**William Shanahan, M.D.** Sr. VP & CMO Arena Pharmaceuticals
Preclinical Studies	**Dominic Behan, Ph.D.** Sr. VP & CSO Arena Pharmaceuticals
Preclinical Safety: Relevance to Human Risk	**Samuel Cohen, M.D., Ph.D.** Professor of Pathology/Microbiology and Endowed Professor of Oncology, UNMC Fellow, American Toxicology Society
Concluding Remarks	**Dominic Behan, Ph.D.** Sr. VP & CSO Arena Pharmaceuticals
Clarifying Questions from Committee	

BREAK

FDA PRESENTATIONS

Lorcaserin: Receptor Pharmacology and Selectivity	**Todd Bourcier, Ph.D.** Supervisory Pharmacologist DMEP, ODE II, OND, CDER, FDA
Lorcaserin Carcinogenicity Assessment in Mice and Rats	**Fred K. Alavi, Ph.D.** Pharmacology/Toxicology Reviewer DMEP, ODE II, OND, CDER, FDA
Lorcaserin Hydrochloride: Clinical Efficacy and Safety Review	**Julie Golden, M.D.** Medical Officer DMEP, ODE II, OND, CDER, FDA
Clarifying Questions from the Committee	

LUNCH

Open Public Hearing

Questions to the Committee and

Committee Discussion

BREAK

Questions to the Committee and
Committee Discussion (cont.)

ADJOURNMENT

Questions to the Advisory Committee:

1) Discuss whether the sponsor has provided an adequate response regarding:

   a. Diagnostic uncertainty for mammary tumors – i.e., adenocarcinomas versus fibroadenomas - in rats treated with lorcaserin. **(DISCUSSION)**

      Committee Discussion: *The committee agreed that there was an increase in mammary tumors in both female and male rats in the data presented. Members commented that it can be appropriate to combine the incidence of both the adenocarcinomas with the fibroadenomas, depending on their sites of origin, but it would be preferable to keep them separate when there are no differences in the sites of origin.*

   b. The potential clinical risk associated with lorcaserin-induced mammary adenocarcinoma in rats (e.g., a sufficient safety margin). **(DISCUSSION)**

      Committee Discussion: *The committee felt that the relationship between potential clinical risk associated with locaserin-induced mammary adenocarcinomas and safety was inconclusive. However, the committee did express more concern with the incidence of mammary adenocarcinomas than of fibroadenomas that was seen in rats. Members felt that the data presented by both the sponsor and the FDA provided evidence of a reasonable safety margin well below the relative risk threshold. Furthermore, concerns were raised regarding the mechanism of action of the agent, but the committee was reassured that the molecule is not a genotoxic agent in the data presented. The committee agreed that additional studies are necessary to define a potentially vulnerable population who may be more likely to develop these types of tumor when taking locaserin.*

   c. The mechanism of action (e.g., prolactin increase) for the mammary tumors observed in rats. **(DISCUSSION)**

      Committee Discussion: *The committee agreed that the available data does not indicate prolactin is the possible mechanism for the mammary tumors observed in rats; however, there may be other mechanisms which will need to be explored further.*

      Please see the transcript for details of the committee's discussion.

2) Discuss whether the sponsor has provided an adequate response regarding the potential clinical risk associated with lorcaserin-induced astrocytoma in rats (e.g., a sufficient safety margin). **(DISCUSSION)**

   Committee Discussion: *There was a general consensus from the committee that the sponsor has provided an adequate response regarding the potential clinical risk associated with lorcaserin-induced astrocytoma in rats. Several members indicated that it was reassuring to only see this issue with one species and in one gender. The incidence of astrocytomas in female rats was significantly less and they were more likely to die from other causes such as adenocarcinoma of the breast. The committee was also reassured from the data that the cerebral spinal fluid level of drug exposure and the receptor concentration were lower than expected, although we do not have human modeling data.*

   Please see the transcript for details of the committee's discussion.

3) Taking into account the new in-vitro 5HT2 receptor potency data, discuss whether the phase 3 echocardiography data are sufficient to rule out a clinically meaningful increase in the risk for valvular heart disease in patients treated with lorcaserin. **(DISCUSSION)**

   Committee Discussion: *The committee agreed that there is not sufficient data at this time to rule out a meaningful increase of risk of valvular heart disease. There is a concern that the upper bound to rule out an increase is around 1.5 and some of the analyses indicated that it's higher than 1.5 and we would need further data to access this issue. The committee noted the need to conduct large studies to rule out valvular heart disease and assessment of other cardiac functions, such as cardiac remodeling, as part of the post-marketing requirement. There is a concern that in the real world when lorcaserin is taken in combination with other agents and the possibility of drug-drug interactions arises that this could lead to an increase in the risk of valvular heart disease. Therefore, the potential for drug-drug interactions; should be studied further. Several panel members indicated that an echocardiogram has do be done at the initiation of therapy and possibly during yearly physical check while the patient is on therapy. Some panel members were concerned that patients who lose the most weight will probably be taking the agent the longest and will be exposed to the agent longer leading to a possible increase in risk for valvular heart disease, which will need to be studied further.*

   Please see the transcript for details of the committee's discussion.

4) Taking into account the March 28 and 29, 2012 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting on cardiovascular risk assessment of obesity drugs, discuss the available data to assess for excess risk for major adverse cardiovascular events in patients treated with lorcaserin. **(DISCUSSION)**

   Committee Discussion: *The committee noted that based on the current data available, they could not make a full assessment of the excessive risk for major adverse cardiovascular events at this time. One panel member indicated that it's not fair to*

change the requirement at this time since the previous guidance does not have this requirement and the new guidance has not been finalized. However, a change in the guidance has been done in the past with diabetes drugs and drugs already on the market as well as pending new drug applications were required to comply with the change in requirements. The committee expressed reassurance with the data on blood pressure and heart rate, which did not increase in most patients treated with lorcaserin. There was a general consensus from the committee that a cardiovascular outcome trial should be conducted but as part of the post approval requirements.

Please see the transcript for details of the committee's discussion.

5) Do the available data demonstrate that the potential benefits of lorcaserin outweigh the potential risks when used long-term in a population of overweight and obese individuals? **(VOTING)**

Yes: 18 No: 4 Abstain: 1

a) If you voted 'Yes' to question #5, please provide your rationale and comment on the need for and approach to patient monitoring and risk management.

Committee Discussion: *Many panel members indicated that it was a very difficult vote and they reluctantly voted "Yes" that the benefits outweigh the risk for treatment of obesity patients since the magnitude of weight loss was moderate. Several panel members indicated that valvulopathy should be included in the Risk Evaluation and Mitigation Strategies (REMS) requirements and as part of the warning in the labeling and major adverse cardiovascular events (MACE) should be addressed as part of the phase 4 post-marketing cardiovascular trials requirements. Additional studies should be conducted to explore the issue of prolactin, tumor development, psychiatric effects and possible drug-drug interaction since this drug will probably be used in combination with other drugs. Echocardiogram should be required at the initiation of therapy and possibly at yearly physical check up.*

Please see the transcript for details of the committee's discussion.

b) If you voted 'No' to question #5, please provide your rationale and comment on what additional preclinical or clinical information should be required to potentially support approval.

Committee Discussion: *The committee members who voted "No" suggested that the sponsor should conduct similar studies as those seen in diabetes trials to include a higher risk population. The population should be composed of two-thirds hypertensive patients and one-third to one-half diabetics and dyslipidemic patients. In addition, the valvulopathy study should be extended. Further studies may be needed for the potential drug-drug interactions with other psychiatric drugs and selective serotonin reuptake inhibitors (SSRIs). Other suggestions included a REMS requirement, a warning in the labeling for the potential of valvulopathy, and prescriber training and patient education*

regarding the safe and proper use of lorcaserin. Please see the transcript for details of the committee's discussion.

The meeting was adjourned at approximately 5:00 p.m.