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APPLICATION NUMBER:
022529Orig1s000

APPROVAL LETTER



NDA 022529

NDA APPROVAL

Arena Pharmaceuticals, Inc.
Attention: Craig M. Audet
Vice President, Global Regulatory Affairs
6166 Nancy Ridge Drive
San Diego, CA 92121

Dear Mr. Audet:

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 (FDCA) for Belviq (lorcaserin hydrochloride) Tablets, 10 mg.

We acknowledge receipt of your amendments dated October 28, November 12, and December 6, 2010, January 10 and 20, April 20, June 10, 14, and 17, July 12, August 25, September 7 and 29, October 4, and December 23, 2011, and January 16 and 27, February 1, 7(2), 20, 24, and 29, March 7 and 16, April 3, 10, 16, 19, 20, 23, and 25, May 18, 23, and 24, and June 5, 7(2), 18, and 25 (2), 2012. We also acknowledge receipt of your emails dated June 26 (10:35 PM EDT) and June 27, 2012 (10:10 AM, EDT), stating your agreement to the labeling revisions that we communicated to you by email on June 26 (10:05 PM, EDT) and June 27, 2012 (9:44 AM, EDT).

The December 23, 2011, submission constituted a complete response to our October 22, 2010, action letter.

This new drug application provides for the use of Belviq as an adjunct to reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a body mass index greater than or equal to 30 kg/m² (obese), or adult patients with a body mass index greater than or equal to 27 kg/m² (overweight) in the presence of at least one weight-related comorbid condition.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTROLLED SUBSTANCE SCHEDULING

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you that on December 18, 2009, and

again on December 22, 2011, you agreed not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert and the carton and immediate-container labels through supplementation of your NDA. This would include the statements detailing the scheduling of Belviq in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert. Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 022529.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA), 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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 6 years (inclusive) because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric

patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group. Weight maintenance, not weight loss is the clinical goal for obese children 2 to 6 years of age. Weight loss is not recommended in children less than 2 years of age because of the requirement for adequate growth and development and optimal deposition of lipids in the developing nervous system.

We are deferring submission of your pediatric studies for ages 7 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these required postmarketing studies (PMRs) must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1900-1 A clinical pharmacology study to assess pharmacokinetic parameters related to a Belviq dose of 10 mg in pediatric patients ages 12 to 17 years (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population.

Final Protocol Submission: March 31, 2013
Study Completion: December 31, 2013
Final Report Submission: March 30, 2014

1900-2 A clinical pharmacology study to assess pharmacokinetic parameters related to a Belviq dose of 10 mg in pediatric patients ages 7 to 11 years (inclusive). Data from this study should be considered when choosing dose(s) for the safety and efficacy study in this pediatric population.

Final Protocol Submission: September 30, 2014
Study Completion: June 30, 2015
Final Report Submission: September 30, 2015

1900-3 A 52-week, randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of Belviq for the treatment of obesity in pediatric patients ages 12 to 17 years (inclusive). You may not initiate this study until the results of your juvenile animal PMR study and the clinical pharmacology (pediatric patients ages 12 to 17 years) PMR study have been submitted and reviewed by the Agency.

Final Protocol Submission: June 30, 2015
Study Completion: September 30, 2017
Final Report Submission: March 30, 2018

1900-4 A 52-week, randomized, double-blind, placebo-controlled pediatric study to evaluate the safety and efficacy of Belviq for the treatment of obesity in pediatric patients ages 7 to 11 years (inclusive). You may not initiate this study until results from the Belviq adolescent safety and efficacy PMR study (ages 12 to 17 years) and the clinical pharmacology PMR study (pediatric patients ages 7 to 11 years) have been submitted and reviewed by the Agency.

Final Protocol Submission: June 30, 2018
Study Completion: October 31, 2020
Final Report Submission: April 30, 2021

Submit the protocols to your IND 069888, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess unexpected serious risks when available data indicate the potential for serious risks of impairment in learning, memory and motor development, physical development and sexual maturation in children exposed to Belviq (lorcaserin hydrochloride) due to the drug's activity in the central nervous system and due to elevated levels of prolactin associated with the use of Belviq (lorcaserin hydrochloride).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1900-5 A juvenile animal study with lorcaserin to assess effects on learning, memory, motor development, physical development and sexual maturation, mating and fertility. The study should include assessments of drug exposure and reversibility of any observed toxicity. The study should also include histological assessment of brain and endocrine tissues after dosing and recovery periods.

The timetable you submitted on June 18, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 30, 2013
Study Completion: September 30, 2014
Final Report Submission: December 31, 2014

Finally, there have been signals of a serious risk of major adverse cardiovascular events with some medications developed for the treatment of obesity, and available data have not definitively excluded the potential for this serious risk with Belviq (lorcaserin hydrochloride). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with anti-obesity medications, including Belviq (lorcaserin hydrochloride).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1900-6 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 and overweight subjects with cardiovascular disease or multiple cardiovascular risk factors. Serial echocardiographic assessments should also be included.

The timetable you submitted on June 18, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: March 31, 2013
Trial Completion: December 31, 2017
Final Report Submission: December 31, 2018

Submit the protocols to your IND 069888, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii)

provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instructions on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of two years, you submit 15-day alert reports on adverse events classified under the following MedDRA terms: Cardiac valve disorders (HLGT), Serotonin syndrome (PT), Neuroleptic malignant syndrome (PT), Euphoric mood (PT), Depression (PT), and Hallucinations (PT).

Additionally, we request that you provide analyses of clinical trial and post-marketing reports of adverse events of special interest classified under the following MedDRA terms: Cardiac valve disorders (HLGT), Serotonin syndrome (PT), Neuroleptic malignant syndrome (PT), Depressive disorders (HLT), Suicidal and self-injurious behavior (HLT), Cognitive and attention disorders and disturbances NEC (HLT), Dissociative States (HLT), Perception disturbances (HLT), Substance-related disorders (HLT), Mood disorders and disturbances NEC (HLGT), Disturbances in consciousness NEC (HLT), and Neoplasms benign, malignant, and unspecified (including cysts and polyps) (SOC) by reporting period and cumulatively, in your Periodic Adverse Drug Experience Reports (PADER).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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

Enclosures:

Content of Labeling
Carton and Container Labeling

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
06/27/2012