CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208524Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 14, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208524
Product Name and Strength:	Belviq XR (locaserin HCl) extended release tablet, 20 mg
Submission Date:	July 11, 2016
Applicant/Sponsor Name:	Arena Pharmaceuticals, Inc.
OSE RCM #:	2015-2143-1
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 PURPOSE OF MEMO

Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels for Belviq XR (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

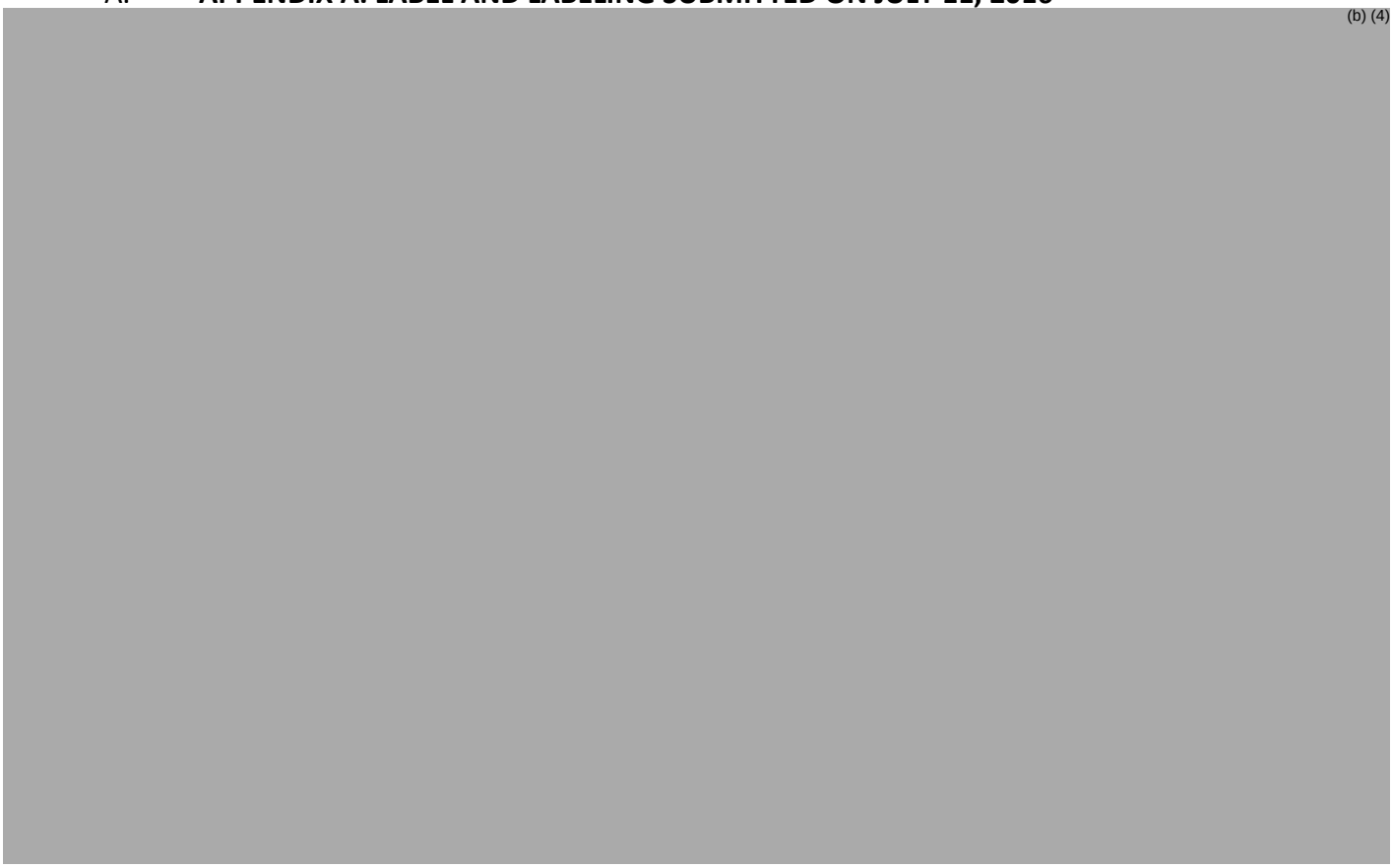
2 CONCLUSION

The revised container labels for Belviq XR is acceptable from a medication error perspective. We have no further recommendations at this time.

[1] Garrison, N. Label and Labeling Review for Belviq XR (NDA 208524). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Feb 29. 8 p. OSE RCM No.: 2015-2143.

A. APPENDIX A. LABEL AND LABELING SUBMITTED ON JULY 11, 2016

(b) (4)



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/s/

NICOLE B GARRISON
07/14/2016

HINA S MEHTA
07/14/2016

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: July 7, 2016

To: Jean-Marc Guettier, M.D., Director
Division of Metabolism and Endocrinology Products

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

From: Alan Trachtenberg, M.D., M.P.H., Medical Officer
Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: NDA 208524
Lorcaserin extended release (Belviq XR)
Indication: weight management
Dose: 20 mg/day
Sponsor: Arena Pharmaceuticals

Materials Reviewed NDA 208524; NDA 22-529; biomedical literature; October 21, 2015 response to FDA information request; Pre-NDA meeting package (6/16/2015)
Review of submitted epidemiologic analyses of Lorcaserin abuse, 2/22/2016, from the Office of Surveillance and Epidemiology Review (OSE)/Office of Pharmacovigilance and Epidemiology (OPE)

Table of Contents

Background:

The Division of Metabolic and Endocrine Products consulted CSS on October 19, 2015, regarding the new NDA 208524, for Belviq XR (lorcaserin HCl) 20 mg extended release tablets. In the CSS filing review of November 20, 2015, CSS noted that the application was missing case report data from post-marketing, and that only a summary was submitted in response to a previous FDA request during the pre-NDA phase. Additional case report data were submitted on October 21, 2015. A consultation was also requested from DMEP on the post-marketing surveillance of lorcaserin (IR) since its original marketing in 2013. This was submitted on February 22, 2016.

The Division of Metabolic and Endocrine Products consulted CSS regarding a pre-NDA meeting package (6/16/15) submitted by Arena Pharmaceuticals for an extended release formulation of lorcaserin (Belviq XR) at 20 mg once a day. There were no abuse-related questions in the package, but CSS had a comment for the Sponsor about post-marketing case report data not being complete, and questioned whether it included any abuse related data.

In 2012, an immediate-release formulation of lorcaserin (10 mg BID) was approved for the treatment of obesity under NDA 22-529. Lorcaserin is a $5HT_{2C}$ and $5HT_{2A}$ agonist, which has the same basic pharmacodynamic mechanisms as Schedule I hallucinogens like LSD. Following review of that NDA, CSS concluded that lorcaserin had abuse potential and recommended Belviq for placement in Schedule IV of the Controlled Substances Act (CSA).

On December 19, 2012, the Drug Enforcement Administration (DEA) published a Notice of Proposed Rulemaking in the Federal Register proposing that lorcaserin be placed into Schedule IV of the CSA, based on recommendations from the Department of Health and Human Services. The drug was placed into Schedule IV of the CSA in 2013.

Conclusions:

1. The new extended release product for daily administration is equivalent to twice the amount (20 mg) of the API as in the original immediate release tablet (10 mg) for BID administration.

2. Safety reporting did not reveal alarming numbers of abuse related adverse events or epidemiologic reports for the immediate-release product since its approval in 2013. However, as noted by DMEP, the postmarketing data sources reviewed by the Sponsor, or otherwise available, are limited in their ability to capture cases of lorcaserin abuse, diversion, or overdose.

3. There is no evidence to indicate that this product will pose an abuse liability substantially greater than that of the original IR product.

Recommendation:

1. Lorcaserin, both the immediate-release and the new extended release product, should remain in Schedule IV of the CSA.

2. No changes are needed in section 9 of the new product's label.

3. Specific post-marketing surveillance for the non-medical use of lorcaserin and other diet medications might be considered, as current drug abuse surveys cannot be relied on to capture such information with adequate sensitivity.

4. Additionally, the sponsor could consider developing quantitative analyses of abuse-related adverse events from recently published clinical trials of lorcaserin in comparison with those of the other currently approved Schedule IV diet drugs. These trials previously showed medication-related adverse events, overall, to be significantly lower for lorcaserin and orlistat than for phentermine-topiramate, liraglutide, and naltrexone-bupropion (Khera et al, 2016). However, no comparisons by event type (abuse-related or not) have yet been published. These specific comparisons would be quite possible to quantitate, and might be of value to FDA and the general public.

Discussion:

The Sponsor reports that there were over 28 million patient days of exposure to lorcaserin since the June 27, 2012 approval of lorcaserin by the FDA. Additionally, there were 11,700 individual research subjects exposed to lorcaserin in clinical trials. In a search of their safety database, the Sponsor identified 117 reports meeting the broad search criteria for potential drug abuse signals generated from that exposure. The Sponsor believes that, given the large prevalence of exposure, that the rate of potential abuse related reports is very low.

The Sponsor's lorcaserin safety database was searched for reports received through September 30, 2015. These included all spontaneous reports of adverse events from lorcaserin patients, providers and the medical literature. These also included all serious adverse events reported from lorcaserin clinical trials, and any abuse-related adverse events from the clinical trial Protocol # APD356-G000-401: "A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Effect of Long-term Treatment with BELVIQ® (lorcaserin HCl) on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects with Cardiovascular Disease or Multiple Cardiovascular Risk Factors."

This search used the Version 18 MedDRA terms of "Euphoric mood; Elevated mood; Mood altered; Feeling drunk; Feeling abnormal; Hallucination, gustatory; Hallucination, olfactory; Somatic hallucination; Hypnagogic hallucination; Hallucination, auditory;

Hallucination, visual; Hallucinations, mixed; Hypnopompic hallucination; Hallucinations, tactile; Hallucinations; Hallucinations synaesthetic and Inappropriate affect." Ninety-eight of the 117 reports came from spontaneous reporting, 12 from lorcaserin clinical trials and 7 solicited reports, with 4 events that met serious criteria. Table 1 shows the number of each type of abuse-related adverse event reported:

Table 1: All Abuse related AE Reports

feeling abnormal	64
euphoric mood	19
feeling drunk	19
any hallucinations	12
auditory hallucinations	2
visual hallucinations	2
altered mood	5
elevated mood	1

The majority of the AE reports were cases of "feeling abnormal" (64 reports). In addition to these, there were 19 reports each of euphoric mood and feeling drunk, 12 reports of hallucinations, and 2 reports each of auditory hallucinations and visual hallucinations. There were 5 reports of altered mood and 1 report of elevated mood. This is consistent with the data in the original NDA. These AEs were predictable, based on the medication's serotonergic mechanism(s) of action.

The daily dosage, when reported (as in a small minority of cases) was generally described as 20 mg, except for a few that took 10 mg and one lone case of 30 mg/day. This case was reported from a 78 year old woman who took 10 mg 3 times/day for one week until
the onset of suicidal thoughts, headache, nausea, dizziness and hallucinations. These complaints lasted for a week off lorcaserin, after which she began a "heavy fast," which preceded a full resolution of her symptoms.

When gender was provided, as shown in Table 2, the reports came more frequently from females than from males.

Table 2: Sex of patients with AEs

male	17
female	95
unknown sex	5
total	117

The average age of patients who reported AEs was 54 years old with a range of 24 years to 78 years. Latency ranged from minutes to 307 days. Results of de-challenge are shown in Table 3.

Table 3: De-challenge Results

de-challenge (+)	51
de-challenge (-)	1
de-challenge - unknown	41
de-challenge - NA	24
Total	117

Of the 117 patients with AEs, only 16 had a prior psychiatric history. This included depression, anxiety, insomnia, alcohol abuse, anger, confusional state, panic disorders and substance abuse.

The Sponsor's weekly searches of PubMed revealed no articles suggesting abuse potential for lorcaserin, nor did searches performed by CSS staff at the time of the filing review.

The Sponsor reports that their search of the publicly available databases, as recommended in CSS guidance, did not reveal any reports of abuse, misuse, overdose or diversion of lorcaserin. The databases reportedly searched by the Sponsor included:

- SAMHSA's Drug Abuse Warning Network (DAWN),
- SAMHSA's National Survey on Drug Use and Health (NSDUH),
- The NIDA funded "Monitoring the Future" (MTF) study,
- SAMHSA's Treatment Episode Data Set (TEDS),
- SAMHSA's Substance Abuse and Mental Health Services Data Archive (SAMHDA), and
- SAMHSA's National Survey of Substance Abuse Treatment Services (N-SSATS).

The data reported from the Sponsor's post market experience and public data bases do not suggest an abuse liability of lorcaserin that is significantly greater than that assessed by CSS at the time of the original approval and scheduling of the API in Schedule IV. However, as noted by the Division of Epidemiology I's review, none of the epidemiologic data sources used in the Sponsor's post-marketing analysis are really capable of measuring abuse, misuse, diversion, or consequent morbidity or mortality with any great sensitivity relevant to lorcaserin use post-approval. Post-marketing data are very limited. None of the survey instruments asked specifically about lorcaserin, and data collection for DAWN ended in 2011, prior to approval of lorcaserin.

A meta-analysis recently published in JAMA (Khera et al, 2016) reviewed the 28 published randomized trials examining any of the 5 currently approved weight loss drugs, administered at their most effective recommended doses for at least 1 year. These trials had all compared the drugs with either placebo or each other and reported either the proportion of patients achieving at least 5% weight loss, or differences in mean weight

loss between different groups. This included 3 Trials of Lorcaserin, all vs. placebo, with a total enrollment of 6893 subjects.

The odds of discontinuation of drug due to medication-related adverse events (overall) were significantly lower for lorcaserin and orlistat than for phentermine-topiramate, liraglutide, and naltrexone-bupropion. This publication did not, however, further break these down into types, such as potentially abuse-related vs. other kinds of adverse events. However, there was not enough of a quantitative difference in any one category of events for lorcaserin to outweigh any of the 4 others, nor to prevent it from remaining lower, overall, than 3 out of the 4 others. Lorcaserin and orlistat were also associated with lower rates of achieving target weight loss outcomes.

Qualitative comparisons of potentially abuse-related adverse events listed in product prescribing information does also list euphoria and potential potentiation of CNS depressant drugs as warnings or adverse effects from post-marketing reports for the Schedule IV component (phentermine) of the diet medication combination of phentermine-topiramate, but not for the non-scheduled diet medication orlistat. While phentermine was associated with occasional reports of euphoria, it does not seem to have produced much of the hallucinatory effects reported rarely from lorcaserin. This may reflect lorcaserin's serotonergic mechanism of action, in contrast to the sympathomimetic properties of phentermine.

A listing of treatment-emergent adverse events from seven placebo-controlled clinical trials of orlistat did not include any that suggested abuse liability. The unscheduled combination diet product Naltrexone-Bupropion has associated reports of dissociation. The bupropion portion has also produced reports of "excitement," but these come from "experienced" drug abusers. A quantitative comparison of type-specific (abuse-related and otherwise) adverse effect data pooled from the trials reviewed in the Khera meta-analysis would be interesting and potentially quite relevant to bariatric physicians choosing from among these weight reduction drugs.

Reference

Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. *JAMA*. 2016:315(22):2424-2434.

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/s/

ALAN I TRACHTENBERG
07/07/2016

KATHERINE R BONSON
07/08/2016

MICHAEL KLEIN
07/08/2016

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

DATE: June 22, 2016

TO: Jean-Marc P. Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II (ODEII)
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance
Office of Translational Sciences

SUBJECT: Review of EIR covering NDA 208524, Lorcaserin hydrochloride Extended Release Tablets, sponsored by Arena Pharmaceuticals, Inc., USA

Summary: Based on inspectional findings, these reviewers recommend that the analytical portion of Study APD356XR-101 submitted to NDA 208524 be accepted for further Agency review

Inspection:
At the request of the Division of Metabolism and Endocrinology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion of the following study submitted to NDA 208524 at [redacted] (b) (4)

Study Number: APD356XR-101
Study Title: "A Two-way, Two-sequence, Randomized, Crossover Study to Determine the Pharmacokinetics and Bioequivalence of Single and Multiple Doses of

Reference ID: 3963811

Lorcaserin hydrochloride Extended Release (XR) and Lorcaserin hydrochloride Immediate Release (IR) to Fasted Subjects"

Analytical Site: [redacted] (b) (4)

Analytical study dates: [redacted] (b) (4)

The inspection of the analytical portion of Study APD356XR-101 was conducted by Drs. Melkamu Getie-Kebtie (DGDBE/OSIS) and Yiyue Zhang (DNDBE/OSIS) from [redacted] (b) (4) The audit covered the bioanalytical method validation and study sample analysis of lorcaserin. The audit also included a thorough examination of facilities and equipment, review of study records and correspondence, records of subject sample receipt and storage, notebooks and electronic records, and interviews and discussions with [redacted] (b) (4) management and staff. For surveillance assessment of the firm's bioanalytical operations, several key components from ongoing BE study [redacted] (b) (4) [redacted] (b) (4) were selected for audit.

No major deficiencies were observed and no Form FDA 483 was issued at the conclusion of the inspection.

Recommendations:

Following review of the inspectional findings, the analytical data from study APD356XR-101 conducted at [redacted] (b) (4) were found to be reliable. Therefore, we recommend that data for the analytical portion of the study be accepted for further Agency review.

Final Classification:

NAI
FEI: [redacted] (b) (4)

DARRTS cc:
OTS/OSIS/Kassim/Taylor/Haidar/Kadavil/Fenty-Stewart/Nkah/Kadavil
OTS/OSIS/DGDBE/Cho/Skelly/Choi/Au/Getie-Kebtie
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OND/ODEII/DMEP/Guettier/Madara

Draft: MG 6/16/2016; YZ 6/16/2016

Edits: MFS 6/21/2016

BE file [redacted] (b) (4)
FACTS:

_____
Melkamu Getie-Kebtie, Ph.D., R.Ph.

_____
Yiyue Zhang, Ph.D.

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/s/

MELKAMU GETIE KEBTIE
06/23/2016

YIYUE ZHANG
06/23/2016

MICHAEL F SKELLY
06/23/2016
Skelly signing on behalf of Dr. Cho

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: June 20, 2016

To: Patricia Madara, Regulatory Project Manager
Division of Metabolism & Endocrine Products (DMEP)

From: Charuni Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 208524
OPDP labeling comments for BELVIQ XR® (lorcaserin hydrochloride) extended release tablets for oral use, CIV

On November 2, 2015, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Package Insert (PPI), and carton/container labeling for BELVIQ XR® (lorcaserin hydrochloride) extended release tablets for oral use, CIV. OPDP's comments on the proposed draft labeling are based on the version sent by Patricia Madara via email on June 13, 2016, and are marked on the version provided directly below.

OPDP does not have any comments on the proposed carton/container labeling at this time.

Comments on the PPI are provided in a collaborative review between DMPP and OPDP under a separate cover.

Thank you for the opportunity to comment on this material.

If you have any questions, please contact Charuni Shah at 240-402-4997 or Charuni.Shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
06/20/2016

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

PATIENT LABELING REVIEW

Date:	June 16, 2016
To:	Jean-Marc Guettier, MD Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Charuni Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	BELVIQ XR (lorcaserin hydrochloride)
Dosage Form and Route:	extended release tablets, for oral use, CIV
Application Type/Number:	NDA 208524
Applicant:	Arena Pharmaceuticals, Inc.

1 INTRODUCTION

On September 18, 2015, Arena Pharmaceuticals, Inc. submitted for the Agency's review a New Drug Application for BELVIQ XR (lorcaserin hydrochloride) extended release tablets, for oral use, CIV. The purpose of the submission is to seek approval for the extended release form for BELVIQ (lorcaserin hydrochloride) tablets, for oral use, CIV which are currently approved.

BELVIQ XR (locaserin hydrochloride) extended release tablets, for oral use, CIV are used as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition, (e.g., hypertension, dyslipidemia, type 2 diabetes)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on November 2, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BELVIQ XR (lorcaserin hydrochloride) extended release tablets, for oral use, CIV.

2 MATERIAL REVIEWED

- Draft BELVIQ XR (lorcaserin hydrochloride) extended release tablets, for oral use, CIV, PPI received on November 2, 2015, and received by DMPP and OPDP on June 13, 2016.
- Draft, BELVIQ XR (lorcaserin hydrochloride) extended release tablets, for oral use, CIV, Prescribing Information (PI) received on November 2, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 13, 2016.
- Approved BELVIQ (lorcaserin hydrochloride) tablets, for oral use, CIV labeling dated December 9, 2014.

3 REVIEW METHODS

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

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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- 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 and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP 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
06/16/2016

CHARUNI P SHAH
06/16/2016

SHAWNA L HUTCHINS
06/16/2016

LASHAWN M GRIFFITHS
06/16/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
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Division of Pediatric and Maternal Health Memorandum

Date: May 26, 2016 **Date consulted:** November 2, 2015

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Director
Division of Pediatric and Maternal Health

To: Division of Metabolic and Endocrine Products

Drug: Belviq XR (lorcaserin hydrochloride extended-release) tablets, 20mg

NDA: 208524

Applicant: Arena Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: An adjunct to diet and exercise for chronic weight management in obese or overweight adults

Materials Reviewed:

- DPMH consult request dated November 2, 2015, DARRTS Reference ID 3841939.
- Sponsor's submitted background package for Belviq XR (lorcaserin hydrochloride extended release) tablets, NDA 208524.
- DPMH review of lorcaserin HCl, NDA 22529. Jeanine Best, MSN, RN, PNP. May 30, 2012. DARRTS Reference ID 3137879.
- DPMH review of lorcaserin HCl, NDA 22529/S-005. Miriam Dinatale, D.O. January 5, 2016. DARRTS Reference ID 3868431.

Consult Question:
DMEP requests DPMH assistance "to determine if the PLLR format in the proposed PI is acceptable."

INTRODUCTION

On September 18, 2015, Arena Pharmaceuticals, Inc., submitted a 505 (b)(1) new drug application (NDA) for Belviq XR (lorcaserin hydrochloride extended-release) tablets, NDA 208524, for the proposed indication of weight management. The immediate-release formulation of Belviq was approved on June 27, 2012.

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) on November, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Belviq XR labeling to comply with Pregnancy and Lactation Labeling Rule format.

BACKGROUND

Pregnancy and Obesity[1,2]

The incidence of obesity (BMI greater than 30 kg/m^2) has increased over the past 20 years with 50% of women between the ages of 15-49 meeting the definition of obese or overweight (BMI greater than 25.9). Obesity may result in the following complications: coronary artery disease, type 2 diabetes, hypertension, and hyperlipidemia. When an obese woman becomes pregnant, she is at an increased risk for several pregnancy complications, including gestational diabetes, preeclampsia, spontaneous abortion, stillbirths, macrosomia and fetal malformations (neural tube defects, cardiac anomalies, orofacial clefts).

Pregnancy and Weight Gain Guidelines

A minimum weight gain and no weight loss is recommended during pregnancy for all women, including those who are already overweight or obese. Excessive weight gain and weight loss during pregnancy have been associated with adverse maternal and fetal outcomes. Excessive weight gain during pregnancy can lead to gestational diabetes, macrosomia, an increased risk for cesarean section, spontaneous preterm delivery and infant hyperglycemia with infants being at higher risk for childhood obesity. Poor weight gain during pregnancy can result in fetal growth restriction and having a low birth weight infant. The reader is referred to the DPMH review of Belviq by Jeanine Best, MSN, RN, PNP and Miriam Dinatale, D.O. for further details related to pregnancy and weight gain.[3,4]

Lorcaserin and Drug Characteristics

Lorcaserin is serotonin receptor subtype 2C (5-HT2C) agonist that is thought to decrease food consumption and promote satiety by selectively activating 5-HT2C receptors on

[1] www.cdc.gov. Reproductive Health: Maternal and Infant Health and Pregnancy Complications. Accessed 12/18/2015.
[2] Racusin, et al. Obesity and the Risk and Detection of Fetal Malformations. Seminars in Perinatology. 2012; 36(3): 213-221.
[3] DPMH review of lorcaserin HCl, NDA 22529. Jeanine Best, MSN, RN, PNP. May 30, 2012. DARRTS Reference ID 3137879
[4] DPMH review of lorcaserin HCl, NDA 22529/S-005. Miriam Dinatale, D.O. January 5, 2016. DARRTS Reference ID 3868431

anorexigenic pro-opiomelanocortin neurons located in the hypothalamus. The exact mechanism of action is not known. Lorcaserin has a molecular weight of 241.16 g/mol, is 70% protein bound in human plasma, and has a half-life of 11 hours.[5]

Common adverse events seen in adults who took lorcaserin in clinical trials include: nausea, vomiting, constipation, fatigue, headache, dizziness. Serious adverse events included: serotonin syndrome, valvular heart disease (mitral and aortic valves), cognitive impairment (confusion, somnolence), psychiatric disorders (euphoria, hallucinations, dissociation), hypoglycemia in patients with type 2 diabetes mellitus, priapism, bradycardia, pulmonary hypertension, hematologic changes (leukopenia, lymphopenia, neutropenia) and elevated prolactin.

Pregnancy and Nursing Mothers Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[6] also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[7] format to include information about the risks and benefits of using these products during pregnancy and lactation.

PREGNANCY

Nonclinical Experience

Belviq XR labeling proposed by the applicant includes data from animal reproduction studies that were conducted for the initial approval of Belviq in 2012; no additional animal reproduction studies were submitted with the current NDA. In animal reproduction studies, oral administration of lorcaserin to pregnant rats and rabbits during the period of organogenesis at doses 44 and 19 times the (b) (4) dose, respectively, did not result in embryofetal toxicity. In a pre- and postnatal development study, maternal rats were dosed from gestation through post-natal day 21. The highest dose (44 times the (b) (4) dose) resulted in still (b) (4) and lower pup viability. All doses resulted in a decrease in pup body weight that persisted to adulthood; however, no developmental abnormalities were observed.

In rat carcinogenicity studies, there was an increase in mammary adenocarcinoma and fibroadenomas in female rats at dose 87-time the daily human clinical dose. In male rats, neoplastic changes were seen in the subcutis (fibroadenoma, Schwannoma), the skin (squamous cell carcinoma), mammary gland (adenocarcinoma and fibroadenoma) and the

[5] Applicant proposed Belviq (lorcaserin) labeling. Section 12 Clinical Pharmacology.
[6] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[7] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

brain (astrocytoma) at doses 17-times the human clinical dose. The relevance of these findings to humans is unknown.[8] The reader is referred to the Nonclinical review by Fred Alavi, Ph.D. for further details.[9]

Review of Literature

There are no controlled studies that have evaluated the use of lorcaserin in pregnant women. However, there have been reported pregnancies in clinical trials with immediate-release lorcaserin. The reader is referred to the DPMH review of lorcaserin by Miriam Dinatale, D.O. for further details of the clinical trials.[10] DPMH conducted a review of published literature in PubMed and Embase, and no publications were found evaluating the use of lorcaserin in pregnant women.

Summary

Limited data on the use of lorcaserin during pregnancy do not demonstrate an increased risk of fetal malformations or miscarriage. In addition, animal reproduction studies do not show an increase in teratogenicity or embryofetal toxicity. Therefore, since there is no evidence of embryofetal toxicity, formal pregnancy testing and contraception are not necessary for lorcaserin labeling. However, since minimum weight gain, and not weight loss, is currently recommended for all pregnant women, there is no benefit for a weight-loss medication during pregnancy. Therefore, the "Contraindication" for pregnancy will remain. In addition, a "Clinical Considerations" section, which describes the importance of appropriate weight gain based on pre-pregnancy weight, will remain in current labeling.

LACTATION

There are no (b) (4) human data on the use of lorcaserin during lactation. The Drugs and Lactation Database (LactMed), [11] *Medications and Mother's Milk*,[12] PubMed and Embase were searched for available data on the use of lorcaserin during breastfeeding, and no information was found.

Summary

(b) (4)

Lorcaserin has a protein-binding of 70% (medications with protein-binding less than 90% are more likely to be excreted into breastmilk) and a molecular weight of 241.16 g/mol (b) (4)

(b) (4)

[8] Applicant proposed Belviq (lorcaserin) labeling. Section 13 Nonclinical Toxicology.

[9] Pharmacology/Toxicology Review. Lorcaserin HCl, NDA 22529. May 30, 2012. Fred Alavi, Ph.D. DARRTS Reference ID 3137062.

[10] DPMH review of lorcaserin HCl, NDA 22529 (b) (4)

[11] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[12] Hale, Thomas. Medications and Mothers' Milk, 15th edition. Hale Publishing, L.P. 2012

compartment).[13] (b) (4) (b) (4) (b) (4) DPMH recommends that patients taking lorcaserin should not breastfeed while taking the drug.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

In animal fertility studies with rats, lorcaserin did not result in reproductive toxicity at exposures up to 29-times the human clinical dose.[14] The reader is referred to the full Nonclinical review by Fred Alavi, Ph.D. for further details.[15]

Review of Literature

DPMH performed a search of PubMed and Embase using search terms "lorcaserin and fertility," "lorcaserin and reproduction," and "lorcaserin and sperm." There are no published studies that evaluate the effects of lorcaserin on reproductive potential.

Summary

Since there is no information about fertility, section 8.3 (Females and Males of Reproductive Potential) will not be included in Belviq XR labeling.

CONCLUSIONS

Belviq XR labeling has been updated to comply with the PLLR. A review of published literature revealed no data with lorcaserin use in pregnant or lactating women. DPMH has the following recommendations for Belviq XR labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of Belviq XR labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections[16].
- **Lactation, Section 8.2**
  - The "Lactation" section of Belviq XR labeling was formatted in the PLLR format to include the "Risk Summary" section[17].

RECOMMENDATIONS

DPMH revised sections 4, 8.1, 8.2 and 17 of Belviq labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. See Appendix A for the applicant's proposed pregnancy and lactation labeling.

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[13] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

[14] Applicant proposed Belviq (lorcaserin) labeling. Section 13 Nonclinical Toxicology.

[15] Pharmacology/Toxicology Review. Lorcaserin HCl, NDA 22529. May 30, 2012. Fred Alavi, Ph.D. DARRTS Reference ID 3137062.

[16] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[17] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

DPMH Proposed Belviq XR (lorcaserin hydrochloride extended-release) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------CONTRAINDICATIONS----------

- Pregnancy (4)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Breastfeeding not recommended (8.2)

FULL PRESCRIBING INFORMATION
4 CONTRAINDICATIONS

- Pregnancy: weight loss in a pregnant woman offers no benefit and may result in fetal harm *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
BELVIQ XR is contraindicated during pregnancy, because weight loss offers no benefit to a pregnant woman and may result in fetal harm *[see Clinical Considerations]*. Limited data on (b) (4) use in pregnant women are not sufficient to determine a drug-associated risk of major congenital malformations or miscarriage (b) (4), no adverse developmental effects were observed when lorcaserin was administered to pregnant rats and rabbits during organogenesis at exposures up to 44 and 19-times the 20mg/day clinical dose, respectively. In rats, maternal exposure to lorcaserin in late pregnancy resulted in lower body weight in offspring which persisted to adulthood *[see Data]*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data
Animal Data
Reproduction studies were performed in pregnant rats and rabbits that were administered lorcaserin hydrochloride during the period of embryofetal organogenesis. Plasma exposures up to 44 and 19 times human exposure in rats and rabbits, respectively, did not reveal evidence of teratogenicity or embryolethality with lorcaserin hydrochloride.

In a pre- and postnatal development study, maternal rats were dosed from gestation through post-natal day 21 at 5, 15, and 50mg/kg lorcaserin hydrochloride; pups were indirectly exposed *in utero* and throughout lactation. The highest dose (~44 times human exposure) resulted in stillborns and lower pup viability. All doses lowered pup body weight similarly at birth which persisted to adulthood; however, no developmental abnormalities were observed and reproductive performance was not affected at any dose.

8.2 Lactation

Risk Summary

There are no data on the presence of lorcaserin in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of BELVIQ XR is not recommended while breastfeeding.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider with a known or suspected pregnancy *[see Contraindications (4), Use in Specific Populations (8.1)]*.

Lactation

Advise women to avoid use of BELVIQ XR while breastfeeding *[see Use in Specific Populations (8.2)]*.

PATIENT INFORMATION

Do not take BELVIQ if you:

- are pregnant or planning to become pregnant. BELVIQ XR may harm your unborn baby.

Before you take BELVIQ, tell your doctor if you:

- are pregnant or plan to become pregnant.
- are breast feeding or plan to breastfeed. It is not known if BELVIQ XR passes into your breastmilk. You and your doctor should decide if you will take BELVIQ XR or breastfeed. You should not do both.

APPENDIX A – Applicant's Proposed Belviq XR (lorcaserin hydrochloride extended-release) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------CONTRAINDICATIONS----------

- Pregnancy (4)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: (b) (4)

FULL PRESCRIBING INFORMATION
4 CONTRAINDICATIONS

- Pregnancy *[see Use in Specific Populations (8.1)]*

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary

BELVIQ XR is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. (b) (4)

(b) (4)

(b) (4)

The background risk of major birth defects and miscarriage for the indicated populations are unknown. (b) (4) the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. (b) (4)

(b) (4)

[see Data]. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations

A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

Reproduction studies were performed in pregnant rats and rabbits that were administered lorcaserin during the period of embryofetal organogenesis. Plasma exposures up to 44 and 19 times (b) (4) in rats and rabbits, respectively, did not reveal evidence of teratogenicity or embryolethality with lorcaserin hydrochloride.

In a pre- and postnatal development study, maternal rats were dosed from gestation through post-natal day 21 at 5, 15, and 50mg/kg lorcaserin; pups were indirectly exposed *in utero* and throughout lactation. [redacted] stillborns and lower pup viability. All doses lowered pup body weight similarly at birth which persisted to adulthood; however, no developmental abnormalities were observed and reproductive performance was not affected [redacted]

8.2 Lactation

Risk Summary

[redacted] the presence of lorcaserin in human milk, the effects of lorcaserin on the breastfed infant, or the effects of lorcaserin on milk production. [redacted]

17 PATIENT COUNSELING INFORMATION

- [redacted]

PATIENT INFORMATION

Do not take BELVIQ XR if you:

- are pregnant or planning to become pregnant. BELVIQ XR may harm your unborn baby.

Before you take BELVIQ XR, tell your [redacted] if you:

- are pregnant or plan to become pregnant.
- are breast feeding or plan to breastfeed. It is not known if BELVIQ XR passes into your breastmilk. You and your doctor should decide if you will take BELVIQ XR or breastfeed. You should not do both.

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/s/

MIRIAM C DINATALE
05/26/2016

TAMARA N JOHNSON
05/26/2016

LYNNE P YAO
05/26/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Memorandum

Date:	February 22, 2016
From:	Jana McAninch, MD, MPH, MS, Medical Epidemiologist, Prescription Drug Abuse Team Justin Mathew, Pharm D, Drug Use Analyst Division of Epidemiology II
To:	Julie Golden, MD, Medical Officer Division of Metabolism and Endocrinology Products Alan Trachtenberg, MD, MPH, Medical Officer Katherine Bonson, PhD, Pharmacologist Controlled Substances Staff
Through:	Cynthia Kornegay, PhD, Prescription Drug Abuse Team Lead Rajdeep Gill, Pharm D, Drug Use Team Lead Judy Staffa, PhD, RPh, Division Director Division of Epidemiology II
Drug Name(s):	Lorcaserin HCL (Belviq XR)
NDA Number:	208524
Subject	Review of submitted epidemiologic analyses of Lorcaserin abuse
OSE RCM #:	2015-2583

1 BACKGROUND

Lorcaserin HCL (Belviq) is a serotonin 2C receptor agonist approved for treatment of obesity. The immediate-release version of this product was approved in June 2012. Following review of abuse liability data submitted by the Sponsor, the Controlled Substances Staff (CSS) concluded that lorcaserin had abuse potential and recommended lorcaserin for placement in Schedule IV of the Controlled Substances Act. Since approval, the market uptake of lorcaserin has been modest but steadily increasing, with an estimated (b) (4) patients receiving a dispensed prescription from an outpatient retail pharmacy in 2015 (see Appendix A for full Belviq Drug Utilization review).

The Sponsor has now submitted NDA #208524 for an extended-release formulation of lorcaserin (Belviq XR). In response to an information request (IR), the Sponsor has submitted some information related to postmarketing adverse events possibly related to abuse of immediate-release lorcaserin. In addition, the Sponsor stated in their IR response that they conducted a search of multiple publically-available databases for postmarketing epidemiologic data on lorcaserin abuse.

The Division of Metabolism and Endocrinology Products (DMEP) consulted the Division of Epidemiology II (DEPI) Prescription Drug Abuse Team, requesting that we review the Sponsor's epidemiologic analyses and to determine whether additional information is needed. The submitted postmarketing spontaneous adverse event reporting data and case report information are being reviewed separately by the Division of Pharmacovigilance (DPV).

2 REVIEW OF SUBMITTED EPIDEMIOLOGIC ABUSE DATA ANALYSES

The Sponsor reported that they conducted a search of the following databases for information on lorcaserin abuse:

- Drug Abuse Warning Network (DAWN),
- National Survey on Drug Use and Health (NSDUH),
- Treatment Episode Data Set (TEDS),
- Monitoring the Future (MTF),
- National Survey of Substance Abuse Treatment Services (NSSATS), and
- Substance Abuse and Mental Services Administration/Data Archive (SAMHSA/SAMHDA),

stating that "*no information relating to lorcaserin or BELVIQ has appeared in any of the searches, indicating that lorcaserin is not the subject of reports of abuse, misuse, overdose, or diversion.*" While this statement may be technically correct, it implies that these databases would be capable of capturing such events, were they to occur. Unfortunately, for the following

reasons, none of these publically-available databases are currently capable of detecting cases of abuse, misuse, diversion, or overdose related to lorcaserin use in post-approval settings:

- DAWN— Was a public health information system that tracked the impact of drug use, misuse, and abuse in the U.S. by monitoring drug-related hospital ED visits. Data collection ended in 2011, prior to approval of lorcaserin.

- NSDUH— This survey is the federal government's primary source of information on the nature and extent of substance use and abuse in the United States. NSDUH collects data by administering questionnaires to a representative sample of persons aged 12 or older at their places of residence. The survey questionnaire asks about nonmedical use of certain classes of prescription drugs, including pain relievers, tranquilizers, sedatives, and stimulants. Although NSDUH does ask about lifetime nonmedical use of "diet pills," it does not include questions specifically about lorcaserin.

- TEDS— This data resource is a compilation of data detailing the demographic and substance use characteristics of admissions to and discharges from publically-funded substance use treatment facilities. TEDS collects information on primary, secondary, and tertiary problem substances at the time of admission, including information on problem use of the most common prescription drug classes, including pain relievers, sedatives, and stimulants. TEDS does not collect information on problem use of lorcaserin or other specific drugs approved for treatment of obesity.

- MTF— MTF is an annual national survey that tracks drug use trends among 8^{th}, 10^{th}, and 12^{th}-graders in the U.S. Like NSDUH, the MTF survey assesses nonmedical use of certain prescription drugs, including pain relievers, sedative-hypnotics, and stimulants, but does not ask students about nonmedical use of lorcaserin.

- N-SSATS—-This survey provides information at the facility level about characteristics of treatment facilities and does not collect individual-level data on substances abused.

- SAMHSA/SAMHDA— SAMHDA provides public-use data files, file documentation, and access to restricted-use data files to facilitate access to and use of data resources managed by SAMHSA, specifically DAWN, NSDUH, TEDS, and N-SSATS (described above).

The currently available postmarketing data on abuse, misuse, diversion, and overdose related to prescription drugs are extremely limited. DEPI is aware of few existing population-based data sources that would be capable of measuring community levels of abuse of lorcaserin or other approved weight loss products, although work is ongoing to expand the population data resources available to evaluate abuse signals and adverse events associated with misuse and abuse of pharmaceuticals.

Spontaneous adverse event reports (e.g. FAERS) can sometimes be helpful in identifying and characterizing new abuse signals in post-approval settings. However, the inherent limitations of these data preclude estimation of population rates of abuse or abuse-related adverse events, and therefore these data are less useful when one is interested in evaluating the scope or trends in abuse of a drug with known abuse potential or comparing the level of abuse with other drug products.

One proprietary data source that could potentially have some value in examining misuse and abuse of lorcaserin in post-approval settings is poison control center call data (e.g. the National Poison Data System). These data could be analyzed to examine the number of exposure calls in which misuse or abuse of lorcaserin was reported. FDA does not have access to these data, but sponsors have submitted these types of analyses in the past for FDA review. The inherent limitations of using poison center call data to estimate the incidence of abuse of a drug need to be considered, as many factors may influence whether an abuse event generates a call to a poison center. If a sufficient number of calls has accumulated, however, comparisons could potentially be made to other CSA scheduled substances or other products with a similar indication to better characterize the scope of lorcaserin abuse and misuse in the community.

Although DEPI does not consider data from social media or internet forums to be an appropriate source for generating quantitative abuse estimates, a descriptive analysis of online peer-to-peer discussions can sometimes be useful for exploring an abuse signal and identifying the context and manner of abuse being discussed, for example whether the drug is being taken in combination with other drugs to enhance euphoria or if alternate routes of administration are described.

Otherwise, examining abuse of lorcaserin in the community would likely involve collection of novel data, for example through a confidential survey of patients dispensed the drug or a survey of visitors to drug abuse forum websites or other high-risk groups.

3 CONCLUSION

None of the epidemiologic data sources in which the Sponsor reports conducting searches are currently capable of measuring abuse, misuse, diversion, or overdose related to lorcaserin use in post-approval settings. The available postmarketing data are extremely limited, although work is ongoing to expand data resources in this area. Spontaneous reports, social media and peer-to-peer online discussion forums may be useful for qualitative exploration of lorcaserin abuse in the community. With sufficient prescription volume, poison control center call data could potentially be useful in characterizing patterns of lorcaserin abuse in the community and conducting quantitative comparisons with other controlled substances or drugs with similar indications. Otherwise, estimating lorcaserin abuse rates in the community would likely involve collection of novel data, for example through surveys of users or high-risk groups. However,

since abuse potential for lorcaserin has already been identified in pre-market abuse liability studies and the product has been placed in Schedule IV under the Controlled Substances Act, it is not clear what the regulatory objective of such epidemiologic abuse investigations would be at this time.

4 APPENDIX A: BELVIQ DRUG UTILIZATION REVIEW

4.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspective™ was used to determine the various retail and non-retail channels of distribution for Belviq®. The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches[1], extended units[2], and share of market. These data are based on national projections. Outlets within the overall retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Sales distribution of Belviq® bottles for 2015 showed that it is primarily distributed to the outpatient retail pharmacy setting ((b) (4)%), while non-retail pharmacies and mail-order/specialty pharmacies accounted for (b) (4)% each.[3] As a result, outpatient retail utilization patterns were examined in this review. Outpatient retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. Inpatient and mail-order/specialty pharmacies data were not included in this analysis.

4.2 DATA SOURCES USED

Proprietary drug utilization databases available to the Agency were used to conduct this analysis (see Section 3.4 for full database description).

The IMS Health, National Prescription Audit™ (NPA™) database was used to obtain nationally estimated number of prescriptions dispensed for Belviq® from U.S. outpatient retail setting from the product's market launch in June 2013 through December 2015, annually. The NPA™ measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA™ measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over (b) (4) prescription claims per year, captured from a

[1] This measure represents the number of single items (such as vials, syringes, bottles, or packet of pills) contained in a unit or shipping package and purchased by providers in a specific time period. An eaches is not a single pill or dosage of medicine (unless one package consists of a single dose).

[2] Extended units are the number of tablets, capsules, milliliters, ounces, etc. of a product shipped in each unit. This number is calculated by multiplying the number of eaches by the product size.

[3] Source: IMS Health, National Sales Perspectives (NSP), DATA 2016-31 Belviq Drug Abuse.xlsx

sample of the universe of approximately (b) (4) pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly (b) (4) % of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72- rolling months with a lag of 1 month

The IMS Health, Total Patient Tracker (TPT) database was used to provide the nationally estimated number of patients who were dispensed prescriptions for Belviq® from the product's market launch in June 2013 through December 2015, annually. The TPT is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over (b) (4) prescription claims per year, representing over (b) (4) unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over (b) (4) unique patients.

4.3 RESULTS

Table 1 below provides the nationally estimated number of prescriptions dispensed for Belviq® from U.S. outpatient retail pharmacies from June 2013 through December 2015, annually. The total number of prescriptions dispensed has increased to (b) (4) prescriptions for year 2015.

Table 1.

NATIONALLY ESTIMATED NUMBER OF PRESCRIPTIONS DISPENSED FOR BELVIQ® FROM U.S. OUTPATIENT RETAIL PHARMACIES, 2013-2015, ANNUALLY

	2013*	2014	2015
	TRx	TRx	TRx
BELVIQ® TOTAL			(b) (4)

**Year 2013 data is from June 2013-December 2013*

IMS Health: Vector One® Total Patient Tracker (TPT). Extracted January 2016. File: DATA 2016-31 Belviq Drug Abuse.xslx

Table 2 below provides the nationally estimated number of patients who received a dispensed prescription dispensed for Belviq® from U.S. outpatient retail pharmacies from June 2013 through December 2015, annually. The number of unique patients has increased to (b) (4) in year 2015.

Table 2.

NATIONALLY ESTIMATED NUMBER OF PATIENTS WHO RECEIVED A DISPENSED PRESCRIPTION FOR BELVIQ® FROM U.S. OUTPATIENT RETAIL PHARMACIES, 2013-2015, ANNUALLY

	2013*	2014	2015
	Patient (n)	Patient (n)	Patient (n)
BELVIQ® TOTAL			(b) (4)

**Year 2013 data is from June 2013-December 2013*

***'Please note due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across time periods.*

IMS Health: Vector One® Total Patient Tracker (TPT). Extracted January 2016. File: DATA 2016-31 Belviq Drug Abuse.xslx

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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

DATE: 3/7/2016

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208524

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials Early Phase Services, LLC	2455 N.E. Loop 410, Suite 150 San Antonio, TX

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SHILA S NKAH
03/07/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 29, 2016
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208524
Product Name and Strength:	Belviq XR (lorcaserin HCl) extended release tablet, 20 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Arena Pharmaceuticals, Inc.
Submission Date:	September 18, 2015
OSE RCM #:	2015-2143
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Belviq XR extended release tablet, (NDA 208524) for areas of vulnerability that could lead to medication errors. Belviq XR is a schedule IV extended release formulation of lorcaserin HCl. The Division of Metabolism and Endocrinology Products (DMEP) requested this review as part of their evaluation to the 505(b)(1) submission for Belviq XR extended release tablet.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D- N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Arena Pharmaceuticals, Inc. submitted a 505 (b)(1) NDA to obtain marketing approval of Belviq XR for the treatment of weight management. We performed a risk assessment of the proposed Prescribing Information (PI) and container labels for Belviq XR to identify areas of vulnerability that may lead to medication errors. Our review identified the following areas of vulnerability to error:

- The lack of prominence of the dosage form statement
- The lack of prominence of the established name on the principal display panel
- Inadequate differentiation between product strengths
- The omission of important administration warnings

4 CONCLUSION & RECOMMENDATIONS

We conclude 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.

4.1 RECOMMENDATIONS FOR THE ARENA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container label
    1. Increase prominence of the dosage form statement, extended release tablets. We recommend relocating it outside of the parenthesis of the established name in title case to mitigate potential confusion.
       For example:

       BELVIQ XR
       (lorcaserin HCl) Extended-release tablets

    2. Ensure the established name (active ingredient and dosage form) is at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
    3. There are two C-IV symbols on the container. We recommend removing the C-IV next to the established name, to make room for increased prominence of the dosage form.
    4. Add the statement, "Swallow tablets whole and must not be chewed, crushed, or divided" to the principal display panel to mitigate the risk of wrong technique errors. If additional space on the principle display panel is needed to place this statement, consider moving the statement "Each tablet contains 20 mg lorcaserin hydrochloride." to the side panel to make room for this important information.
    5. The layout of the container label is very similar between Belviq XR 20 mg and Belviq 10 mg. Both container labels have a white background with the font of the proprietary name in red and established name in dark blue. The color used to differentiate the 20 mg extended release strength (lighter blue) is the similar to the color used for the 10 mg immediate release formulation (darker blue), which may lead to errors when selecting the correct strength. We recommend you provide additional differentiation for the 20 mg strength to prevent selection errors between Belviq XR 20 mg and Belviq 10 mg.

B. Professional Sample Container label
    1. As currently presented, the product code of the NDC number is denoted by a placeholder. Please include the full NDC on the principal display panel.

2. The professional sample's strength color is different from the strength on the full label. Consider using the same colors for strength on the professional sample and the full label to avoid confusion when patients receive the full prescription.
3. See A.1 through A.4 and revise the professional sample container label accordingly.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Belviq XR that Arena Pharmaceuticals, Inc. submitted on September 18, 2015.

Table 2. Relevant Product Information for Belviq XR	
Initial Approval Date	N/A
Active Ingredient	lorcaserin HCl
Indication	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of; • 30 kg/m^2 or greater (obese), or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes) Limitations of Use: • The safety and efficacy of coadministration with other products for weight loss have not been established. • The effect of Belviq XR on cardiovascular morbidity and mortality has not been established.
Route of Administration	Oral
Dosage Form	Extended release tablet
Strength	20 mg
Dose and Frequency	• The recommended dose is 20 mg administered orally once daily. The tablet must be swallowed whole and must not be chewed, crushed, or divided. • Do not exceed recommended dose. • Belviq XR can be taken with or without food. • Response to therapy should be evaluated by week 12. If a patient has not lost at least 5% of baseline body weight, discontinue Belviq XR, as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.
How Supplied	Supplied as orange-colored, round, biconvex, film-coated tablets debossed with “A” on one side and “20” on the other side and are available as follows: • NDC 62856-535-30 Bottle of 30

Storage	Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 18, 2016, we searched the L: drive and AIMS using the terms, Belviq XR to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two proprietary name reviews[1,2]. There were no previous labeling reviews found.

[1] Mistry M. Proprietary Name Review for Belviq XR (IND 119664). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Mar 4. 11 p. OSE RCM No.: 2014-45073.

[2] Mistry M. Proprietary Name Review Memorandum for Belviq XR (NDA 208524). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Nov 3. 7 p. OSE RCM No.: 2015-1524259.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Belviq XR labels and labeling submitted by Arena Pharmaceuticals on September 18, 2015.

- Container label
- Professional Sample Container label
- Prescribing Information (not listed)

G.2 Label and Labeling Images

Container label

(b) (4)

Prescribing Information: (not listed)

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

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

/s/

NICOLE B GARRISON
02/29/2016

YELENA L MASLOV
03/02/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

<table>
<tr><th colspan="3">Application Information</th></tr>
<tr><td>NDA # 208524
BLA#</td><td>NDA Supplement #: S-
BLA Supplement #: S-</td><td>Efficacy Supplement Category:
☐ New Indication (SE1)
☐ New Dosing Regimen (SE2)
☐ New Route Of Administration (SE3)
☐ Comparative Efficacy Claim (SE4)
☐ New Patient Population (SE5)
☐ Rx To OTC Switch (SE6)
☐ Accelerated Approval Confirmatory Study (SE7)
☐ Labeling Change With Clinical Data (SE8)
☐ Manufacturing Change With Clinical Data (SE9)
☐ Animal Rule Confirmatory Study (SE10)</td></tr>
<tr><td colspan="3">Proprietary Name: Belviq XR
Established/Proper Name: lorcaserin HCl extended release
Dosage Form: tablet
Strengths: 20 mg</td></tr>
<tr><td colspan="3">Applicant: Arena Pharmaceuticals
Agent for Applicant (if applicable):</td></tr>
<tr><td colspan="3">Date of Application: 9/18/15
Date of Receipt: 9/18/15
Date clock started after UN: N/A</td></tr>
<tr><td colspan="2">PDUFA/BsUFA Goal Date: 7/18/16</td><td>Action Goal Date (if different):</td></tr>
<tr><td colspan="2">Filing Date: 11/17/15</td><td>Date of Filing Meeting: 11/5/15</td></tr>
<tr><td colspan="3">Chemical Classification (original NDAs only) :
☐ Type 1- New Molecular Entity (NME); NME and New Combination
☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination
☐ Type 3- New Dosage Form; New Dosage Form and New Combination
☐ Type 4- New Combination
☒ Type 5- New Formulation or New Manufacturer
☐ Type 7- Drug Already Marketed without Approved NDA
☐ Type 8- Partial Rx to OTC Switch</td></tr>
<tr><td colspan="3">Proposed indication(s)/Proposed change(s): same indication as NDA 22529 – new formulation – extended release tablet – 1x per day dosing</td></tr>
<tr><td colspan="2">Type of Original NDA:
AND (if applicable)
Type of NDA Supplement:

If 505(b)(2): Draft the “505(b)(2) Assessment” review found at:
http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</td><td>☒ 505(b)(1)
☐ 505(b)(2)
☐ 505(b)(1)
☐ 505(b)(2)</td></tr>
</table>

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
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***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ 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/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, 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.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
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***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		N/A
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

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 Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ 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: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☐	☒		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• 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 is 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)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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 the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
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:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
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 (3397/3792), 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 per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
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, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) 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…"*	☒	☐	☐	
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.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* : 10/20/15	☐	☐	☒	Not an NME
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage*	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829 htm

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.				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837 htm

[4]

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 applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☒	☐	☐	
Has a review of the available pregnancy and lactation data been included?	☐	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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 applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
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.***	☒	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)?	☐	☐	☐	

http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

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 sent to OSE/DMEPA?	☒	☐	☐	
Other 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:***	☐	☐	☒	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		No EoP2 mtg
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 7/13/15 ***If yes, distribute minutes before filing meeting***	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/5/15

BACKGROUND: Belviq (NDA 22529), lorcaserin HCl, immediate release formulation, is a serotonin 2C (5-HT2C) receptor agonist for oral administration, approved for treatment of obesity June 2012. Belviq is a Schedule IV drug under the Controlled Substances Act.

Now the company has submitted NDA 208524 for a 20 mg extended-release formulation tablet (Belviq XR) for once daily oral administration. (The approved formulation is a 10 mg tablet administered twice daily.)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Pat Madara	Y
	CPMS/TL:	Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	Jim Smith		Y
Division Director/Deputy	As above		
Office Director/Deputy	N/A		
Clinical	Reviewer:	Julie Golden	Y
	TL:	Jim Smith	
Social Scientist Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review (*for OTC products*)	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	NA	
	TL:	NA	
Clinical Pharmacology	Reviewer:	Renu Singh	Y
	TL:	Jaya Vaidyanathan	Y
• Genomics	Reviewer:	TBD	N

• Pharmacometrics	Reviewer:	TBD	N
Biostatistics	Reviewer:		
	TL:		

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Fred Alavi	Y
	TL:	Todd Bourcier	Y
Statistics (carcinogenicity)	Reviewer:	NN	
	TL:	NN	
Product Quality (CMC) Review Team:	ATL:	Su Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	NN	
• Drug Product	Reviewer:	Christopher Galliford	N
• Process	Reviewer:	Oxana Selivanova	N
• Microbiology	Reviewer:	Oxana Selivanova	N
• Facility	Reviewer:	Krishna Ghosh	N
• Biopharmaceutics	Reviewer:	Mei Ou	N
• Immunogenicity	Reviewer:	NN	N
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Sharon Williams	Y
	TL:	Marcia Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Charuni Shah	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Mishale Mistry	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	NN	
	TL:	NN	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NN	
	TL:	NN	

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Kit Bonson	N
	TL:	Alan Trachtenberg	Y
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505 b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**: no comments	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: clinical pharmacology site	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, 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***	☐ YES Date if known: ☒ 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**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**: will provide requests for information	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: will provide requests for information	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>New Molecular Entity</u> (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Jim Smith **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): 2/24/16 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
NN	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
NN	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.
NN	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
NN	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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
11/25/2015

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208524

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Belviq XR (lorcaserin HCl, extended release) tablet, 20 mg

Applicant: Arena Pharmaceuticals, Inc

Receipt Date: 9/18/15

Goal Date: 7/18/16

1. Regulatory History and Applicant's Main Proposals

New formulation for once a day dosing.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

A single SRPI format deficiency was identified in the review of this PI. It is explained in Section 4 of this review. (see item #40)

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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 practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"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."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

NO 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment: *Label says "See FDA-approved patient labeling (Patient Information). Will request revision during labeling discussions.*

This minor format error was discussed with Monika Houstoun, Associate Director for Labeling in DMEP and it was agreed that no request for revised labeling was required at this time. Revision will be requested during labeling discussions.

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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
11/25/2015

CSS Filing Checklist for NDA/BLA or Supplement

NDA Number: 208524 **Applicant:** Arena Pharmaceuticals, inc. **Date:** 11/20/2015

Drug Name: Lorcaserin XR (Belviq XR) **IND Number:** 119664

	Checklist	Yes	No	N/A	Comment
	What is the regulatory history of this application?	X			Lorcaserin previously approved as IR oral formulation under NDA 022529.
	Abuse potential assessment is required if any of the following are true for a drug[1,2]:				
	It affects the CNS	X			
	It is chemically or pharmacologically similar to other drugs with known abuse potential	X			
	It produces psychoactive effects such as sedation, euphoria, and mood changes	X			
	Is the drug a new molecular entity?		X		
	Is this a new or novel drug formulation?	X			ER formulation
	Content of NDA abuse potential section:				
	Module 1: Administrative Information and Prescribing Information 1.11.4 Multiple Module Information Amendment contains:			X	Drug had information in NDA 022529 adequate for placement in C IV
	• A summary, interpretation, and discussion of abuse potential data provided in the NDA.		X		Application is missing epidemiologic data from post-marketing, but summary has been submitted in response to FDA request
	• A link to a table of contents that provides additional links to all studies (non-clinical and clinical) and references related to the assessment of abuse potential.			X	Already scheduled C IV
	• A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA			X	Already scheduled C IV
	Module 2: Summaries 2.4 Nonclinical Overview - includes a brief statement outlining the nonclinical studies performed to assess abuse potential.			X	
	Module 3: Quality				
	3.2.P.1 Description and Composition of the Drug Product - describes any additional studies performed to examine the			X	No abuse deterrent claims

1 21 CFR 314.50(d)(5)(vii1): If the drug has a potential for abuse, a description and analysis of studies or information related to abuse of the drug, including a proposal for scheduling under the Controlled Substances Act. A description of any studies related to overdosage is also required, including information on dialysis, antidotes, or other treatments, if known.

2 21USC811(f) Abuse potential: If, at the time a new-drug application is submitted to the Secretary for any drug having a stimulant, depressant, or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall be forwarded by the Secretary to the Attorney General.

CSS Filing Checklist for NDA/BLA or Supplement

	extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).				
	Is there an assessment of extractability/formulation release characteristics of intact and manipulated product?			X	
	3.2.P.2 Description and Composition of the Drug Product - describes the development of any components of the drug product that were included to address accidental or intentional misuse.			X	
	Is this an extended release or abuse-resistant formulation?	X			Extended release
	Module 4: Nonclinical Study Reports			X	
	4.2.1 Pharmacology				
	4.2.1.1 Primary Pharmacodynamics - contains study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.				
	Are in vitro receptor binding studies included?				
	Are functional assays included?				
	4.2.3.7.4 Dependence – section includes:				
	• A complete discussion of the nonclinical data related to abuse potential. • Complete study reports of all nonclinical abuse potential studies.				
	Animal Behavioral and Dependence Pharmacology: note all primary data need to be included in the NDA			X	
	Was a self administration study conducted?				
	Was a conditioned place preference study conducted?				
	Was a drug discrimination study conducted?				
	Was a physical dependence study conducted?				
	Module 5: Clinical Study Reports 5.3.5.4 Other Study Reports - section contains complete study reports of all clinical abuse potential studies.			X	
	Human abuse potential study:			X	
	Was a human abuse potential study conducted?				
	Are all the primary data included in the NDA?				
	Is a Statistics consult necessary?				
	Other Clinical trials:			X	
	Is there evidence of drug accountability issues or overt evidence of misuse, abuse, or diversions?				
	Are all abuse/misuse Case Report Forms submitted [addiction, abuse, misuse, overdose, drug diversion/drug accountability, discrepancies in amount of the clinical supplies of the study drug, noncompliance, protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons why subjects dropped out of the study]?				
	Does Compliance need to be consulted re: site inspection for data integrity or other issues?			X	

CSS Filing Checklist for NDA/BLA or Supplement

	5.3.6.1 Reports of Postmarketing Experience - includes information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product		X		Brief summary information provided in response to FDA request, needs expansion
	Did you review the scientific literature?	X			No significant abuse reported under PubMed search, but several interesting papers about potential utility as an anti-addiction agent.
	Did you conducted a search of databases and other information related to misuse, abuse, and addiction?	X			
	Is there evidence for any of the following:				
	Accidental overdose in the patient population and vulnerable populations		X		
	Overdose associated with misuse and abuse		X		
	Unintended pediatric exposures to product		X		
	Labeling issues		X		
	Drug disposal issues?		X		
	Postmarketing activities [PMRs, PMCs, REMS]		X		
	Scheduling activities			X	Already scheduled C IV

Is NDA FILEABLE from a CSS perspective? Yes, but more information will be required during review

If the Application is not fileable, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. Will require more in depth post-marketing epidemiologic data for previously marketed API product (non-extended release lorcaserin).

CSS Reviewers: Alan Trachtenberg, MPH, MD	Date: 11/19/15
CSS Reviewer: Katherine Bonson, PhD	Date: 11/19/15
Director: Michael Klein, PhD	Date: 11/19/15

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

/s/

ALAN I TRACHTENBERG
11/20/2015

KATHERINE R BONSON
11/20/2015

MICHAEL KLEIN
11/20/2015