CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208524Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	*See electronic stamp*
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	208524
Applicant	Arena Pharmaceuticals, Inc.
Date of Submission	18 September 2015
PDUFA Goal Date	18 July 2016
Proprietary Name / Established (USAN) names	BELVIQ XR (lorcaserin hydrochloride)
Dosage forms / Strength	Extended-release tablet / 20 mg
Proposed Indication	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)
Recommended:	Approval

Material Reviewed/Consulted & Primary Reviewer(s)		
Medical Officer Review	30 June 2016	Julie Golden, MD
Clinical Pharmacology Review	01 June 2016	Renu Singh, PhD
Pharmacology/Toxicology Review	26 May 2016	Fred K. Alavi, PhD
OPQ Review	02 June 2016	Suong T. Tran, PhD (Technical Lead)
CSS Review	08 July 2016	Alan Trachtenberg, MD, MPH and Katherine Bonson, PhD
OSE/DEPI II Memo	21 Mar 2016	Jana McAninch, MD, MPH, MS and Justin Mathew, PharmD
OSIS Memo (Clinical Site)	07 Mar 2016	Shila S. Nkah
OSIS Memo (Analytical Site)	23 Jun 2016	Melkamu Getie-Kebtie, PhD, RPh and Yiyue Zhang, PhD
DPMH Memo (PLLR labeling review)	26 May 2016	Miriam Dinatale, DO
OSE/DMEPA Label & Labeling Review	02 Mar 2016	Nicole Garrison, PharmD, BCPS
OSE/DMEPA Review - Revised Label & Labeling	14 Jul 2016	Nicole Garrison, PharmD, BCPS
Patient Labeling Review	16 Jun 2016	Sharon W. Williams, MSN, BSN, RN and Charuni Shah, PharmD
OSE/DMEPA Proprietary Name Review	03 Nov 2015	Mishale P. Mistry, PharmD, MPH

OPQ: Office of Pharmaceutical Quality; CSS: Controlled Substance Staff; OSE: Office of Surveillance and Epidemiology; DEPI: Division of Epidemiology II; OSIS: Office of Study Integrity and Surveillance; DMEPA: Division of Medication Error Prevention and Analysis

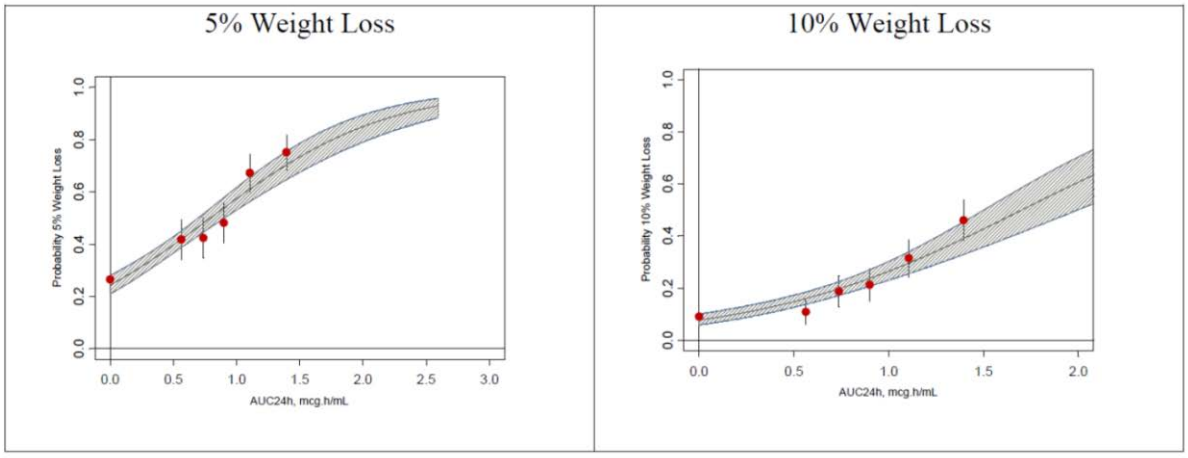
1. INTRODUCTION

The purpose of this memo is to summarize briefly the review of NDA 208524 for Belviq XR extended-release tablets for the use of chronic weight management. I am aware of no disagreements among the review team regarding the recommended regulatory action; all have recommended approval.

2. BACKGROUND

Belviq (lorcaserin hydrochloride) was approved in the United States on 27 June 2012 (NDA 22529) 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). The approved dosage for Belviq is 10 mg twice daily.

The same applicant who holds approved NDA 22529 sought advice from the Agency to develop an extended-release formulation that would be suitable for once-daily dosing. On 18 April 2014, FDA addressed several aspects of their proposed development of this product; importantly, FDA agreed that given the exposure-response relationship between lorcaserin concentrations and probability of weight loss previously established in their phase 3 program (NDA 22529), a pharmacokinetic bridging strategy was a reasonable approach. This relationship is depicted in the figure below. A pre-NDA meeting (written responses) on 13 July 2015 provided further guidance regarding the application, and the current 505(b)(1) application was received 18 September 2015.



Source: NDA 22529, Clin Pharm review dated 05/31/2012

3. CMC

CMC

The Office of Pharmaceutical Quality (OPQ) recommends approval. I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months under the conditions specified. There are no outstanding issues.

Drug Substance

The drug substance for the current application is the same as approved NDA 22529.

Drug Product

The drug product is an extended-release tablet for oral administration with one dosage strength, 20 mg anhydrous lorcaserin HCl, equivalent to 20.8 mg lorcaserin HCl hemihydrate. The extended drug release is by (b) (4).
The regulatory drug product specification was found adequate based on supporting release and stability data and ICH guidelines for this type of dosage form.

Biopharmaceutics

The batch used in the pivotal bioequivalence (BE) study and the commercial product have the same formulation with the exception of color. Both formulations have adequately similar dissolution profiles such that no impact on the bioavailability and bioequivalence of the drug product is expected. The commercial formulation was used in an in vitro alcohol dose-dumping study, which identified no concern for dose-dumping.

Facilities Review/Inspection

The Overall Manufacturing Inspection Recommendation is for approval (finalized 01 June 2016).

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Dr. Fred Alavi reviewed this application from the pharm/tox perspective; he recommends approval. Dr. Alavi concludes in his review, "In summary, given the pharmacokinetic profile for the new formulation, the previous finding of nonclinical safety for immediate release lorcaserin is applicable to the extended release 20 mg QD lorcaserin product. Also, no nonclinical issues were identified for the excipient profile of the new formulation." I concur that there are no pharm/tox issues outstanding that preclude approval.

5. CLINICAL PHARMACOLOGY

Dr. Renu Singh reviewed this application for clinical pharmacology; she recommends approval. As noted previously in this memo, the applicant's development of Belviq XR is based on the previously established exposure-response relationship from their phase 3 program for immediate-release (IR) lorcaserin. The applicant submitted two pivotal studies, APD356XR-101 (hereafter, Study 101) and APD356XR-102 (Study 102), to support the approval of Belviq XR. The applicant used a batch manufactured at commercial scale for these studies.

Pivotal Bioequivalence Study

Study 101 was a two-treatment, two-period, two-sequence, randomized, crossover study of single and multiple doses of lorcaserin HCl extended-release 20 mg daily and immediate-release 10 mg twice daily administered in the fasted state to 36 healthy men and women. After a single dose, only AUC-based parameters demonstrated equivalence between the two products; lorcaserin mean C_{max} was ~25% lower after a single dose of the XR formulation compared with the IR formulation. After multiple doses, however, the 90% CIs for the geometric mean ratio (GMR) for $AUC_{24,ss}$ and $C_{max,ss}$ for the XR formulation compared with the IR formulation were within the BE limits of 0.80-1.25 (see table below). Thus, BE was achieved between the two formulations at steady state. The reviewer found the lack of BE for C_{max} after single dose acceptable since (1) during the review of NDA 22529, the exposure-response analysis established that for the IR formulation, $AUC_{24,ss}$ was predictive of the probability of 5% and 10% weight loss; and (2) this drug is intended for chronic use, so the difference in C_{max} observed after a single dose is expected to have minimal impact on the long-term efficacy in patients.

Table 2. 90% CI on the GMR of lorcaserin PK parameters following multiple dose oral administration of lorcaserin HCl 20 mg XR q.d. and 10 mg IR b.i.d.

		Geometric Mean			
Parameter	N[a]	Test[b]	Reference[c]	G.M. Ratio[d]	90% CI[e]
$AUC_{0\text{-}24,ss}$ (hr·ng/mL)	34	1234	1324	0.932	(0.891, 0.975)
$C_{max,ss}$ (ng/mL)	34	73.8	79.9	0.924	(0.876, 0.975)

[a]N=34; excludes subjects #7and #34
[b]Test = 20 mg XR q.d.
[c]Reference = 10 mg IR b.i.d.
[d]GMR = Geometric mean of the test/reference ratio
[e]90% CI = Lower and upper limits of 90% confidence interval on the G.M. ratio
Source: Study APD356XR-101 study report Page 55

I do note that these results are sensitive to the exclusion of one subject (#7) who was designated an outlier; including this subject results in a failure to show BE for both C_{max} and $AUC_{0\text{-}24}$ at steady state. Dr. Singh explores data related to this subject in detail in her review, and concluded that this subject was an outlier with respect to the immediate-release (IR) product and not the extended-release product. She agreed that it is acceptable to exclude this subject from the BE analysis, which the clinical reviewer (Dr. Golden) also found reasonable. I concur with this assessment.

Food-Effect Study

Study 102 was an open-label, randomized, two-treatment, two-period, two-sequence, crossover study to assess single and multiple doses of lorcaserin HCl extended-release 20 mg daily for food effect, under fasting and fed conditions. The approved labeling for Belviq states that the drug can be taken with or without food. In Study 102, intake of a high-fat, high-calorie breakfast before a single 20 mg oral dose of lorcaserin extended-release results in ~46% increase in C_{max} and 17% increase in $AUC_{0\text{-}inf}$ but no change in t_{max}. Under steady-state dosing conditions, the food effect was attenuated; BE was demonstrated for both the $C_{max,ss}$ and $AUC_{24,ss}$ parameters. The higher concentrations observed after a single dose in the fed state were similar to those observed with the immediate-release formulation in a fasted state, so this did not present a safety concern to either the clinical pharmacology or the clinical reviewer (Dr. Golden). Dr. Singh agrees with the applicant that because the steady-state parameters are more relevant to chronic use, this extended-release formulation may be taken without regard to food.

See Dr. Singh's review for additional details. I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. SAFETY

Dr. Julie Golden reviewed this application from the clinical perspective, and her review contains a succinct summary of all disciplines. From a clinical safety perspective, she identified no new safety concerns in the studies that were conducted to support this NDA. I agree that there are no clinical safety concerns that would preclude approval.

7. ADVISORY COMMITTEE MEETING

An advisory committee was not convened to discuss this application, as no issues were identified by reviewers that required external advice and discussion.

8. PEDIATRICS

This application was reviewed by the PeRC PREA subcommittee on 08 June 2016. In the current NDA, the applicant has requested a partial waiver for 0-6 years, which should be granted because the product fails to represent a meaningful therapeutic benefit over existing therapies in this age group and is not likely to be used in a substantial number of pediatric patients in this age group. Weight maintenance, not weight loss, is the clinical goal for obese children 2 to 6 years of age. Weight loss is not recommended in children less than 2 years of age. The applicant has requested a deferral for pediatric patients 7-17 years of age, which should be granted since the current application is ready for approval in adults before the pediatric studies have been completed.

The requirements under PREA stated in the approval letter for NDA 22529 for Belviq tablets will also apply to the current NDA.

9. OTHER RELEVANT REGULATORY ISSUES

Financial Disclosures

Dr. Golden notes that the applicant provided a signed form FDA 3454, certifying that no financial arrangements or interests were held by the listed clinical investigators for the clinical pharmacology studies conducted to support approval of this application.

Clinical/Analytical Inspections

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data from the clinical site without an on-site inspection, since the site was recently inspected and the outcome was classified No Action Indicated (NAI). OSIS inspection for the bioanalytical site was conducted during the week of (b) (4). No Form FDA 483 was issued, and it was recommended that the data for the analytical portion of the study (Study 101) be accepted for Agency review.

Controlled Substance Staff Review

Dr. Alan Trachtenberg and Dr. Katherine Bonson reviewed this application from the controlled substance perspective. They comment that 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 (a conclusion supported by a consult by DEPI reviewers). Nevertheless, they found no evidence to indicate that this product will pose an abuse liability substantially greater than that of the original IR product. Thus, they recommend that both the immediate-release and this proposed extended-release product should remain in Schedule IV of the Controlled Substances Act and no changes are needed in Section 9 of the proposed product's label.

10. LABELING

Proprietary Name Review

DMEPA reviewed the proprietary name "Belviq XR"and found it acceptable from both a promotional and safety perspective.

Labeling

Labeling will largely reflect the approved labeling for Belviq, aside from changes related to the dosage change to 20 mg daily. The Division of Pediatric and Maternal Health provided input regarding Pregnancy and Lactation labeling; see the related consult memo for details.

11. DECISION/ACTION/RISK BENEFIT ASSESSMENT

Risk/Benefit Assessment

The applicant has demonstrated that administration of Belviq XR 20 mg daily is bioequivalent to the approved Belviq 10 mg twice daily, at steady state. Given that the exposure-response relationship was previously established for lorcaserin and weight loss, approval based on bioequivalence was deemed reasonable by the Agency, and the current review team agrees. No deficiencies that would preclude approval have been identified. Thus, I concur with the recommendations of the reviewers to approve this application.

Recommended Regulatory Action

Approval

Recommendations for Risk Evaluation and Mitigation Strategies

None.

Recommendations for Post-marketing Requirements and Commitments

See Pediatrics section of this memo for comment regarding PREA PMRs.

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

/s/

JAMES P SMITH
07/15/2016