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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208524
Supporting document/s:	electronic NDA
Applicant's letter date:	Sept 18, 2015
CDER stamp date:	Sept 18-2015
Product:	Lorcaserin HCl-XR (BELVIQ XR®, 20mg QD)
Indication:	Treatment of obesity (BMI ≥30 kg/m^2)
Applicant:	Arena Pharmaceuticals Inc.
Review Division:	DMEP
Reviewer:	Fred Alavi, Ph.D.
Supervisor/Team Leader:	Todd Bourcier, Ph.D.
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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability: Recommended for approval

1.1.2 Additional Non-Clinical Recommendations: none

1.1.3 Labeling- Current label (subject to change/does not include juvenile animal data)

8.1 Pregnancy

Risk Summary

BELVIQ XR is contraindicated during pregnancy. 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.

No adverse developmental (b) (4) were observed (b) (4) pregnant rats and rabbits (b) (4) 44 and 19 times (b) (4) the clinical dose. In rats, maternal exposure to lorcaserin in late pregnancy resulted in lower body weight in offspring which persisted to adulthood.

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 is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

(b) (4) 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 the clinical dose in pregnant 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. Stillborns and lower pup viability was observed at 50mg/kg, or 44 times the clinical dose, based on AUC. All other doses lowered pup body weight similarly at birth which persisted to adulthood; however, no developmental abnormalities were observed and reproductive performance was not affected.

8.2 Lactation

Risk Summary

There are no data on the presence of lorcaserin in human milk, effects on the breastfed infant, or 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.

8.4 Pediatric Use

The safety and effectiveness of BELVIQ XR in pediatric patients below the age of 18 have not been established and the use of BELVIQ XR is not recommended in pediatric patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Mutagenesis

Lorcaserin hydrochloride was not mutagenic in an *in vitro* bacterial mutation assay (Ames test), was not clastogenic in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, and was not genotoxic in an *in vivo* micronucleus assay in rat bone marrow.

Carcinogenesis

The carcinogenic potential of lorcaserin hydrochloride was assessed in two-year carcinogenicity studies in mice and rats. CD-1 mice received doses of 5, 25 and 50 mg/kg. There were no treatment-related increases in the incidence of any tumor in mice at doses that produced plasma exposure in males and females of 8 and 4-times the daily human clinical dose, respectively.

In the rat carcinogenicity study, male and female Sprague-Dawley rats received 10, 30, and 100 mg/kg lorcaserin hydrochloride. In females, mammary adenocarcinoma increased at 100 mg/kg, which was associated with plasma exposures that were 87-times the daily human clinical dose. The incidence of mammary fibroadenoma was increased in female rats at all doses with no safety margin to the clinical dose. The increases in adenocarcinomas and fibroadenomas may be associated with lorcaserin hydrochloride-induced changes in prolactin homeostasis in rats. The relevance of the increased incidence of mammary adenocarcinomas and fibroadenomas in rats to humans is unknown.

In male rats, treatment-related neoplastic changes were observed in the subcutis (fibroma, Schwannoma), the skin (squamous cell carcinoma), mammary gland (adenocarcinoma and fibroadenoma), and the brain (astrocytoma) at greater than or equal to 30 mg/kg (plasma exposure 17-times human clinical dose). At higher exposure, liver adenoma and thyroid follicular cell adenoma were increased but were considered secondary to liver enzyme induction in rats and are not considered relevant to humans. Human brain exposure (AUC24h,ss) to lorcaserin at the clinical dose is estimated to be 70-fold lower than brain exposure in rats at the dose at which no increased incidence of astrocytoma was observed. Excluding the liver and thyroid tumors, these neoplastic findings in male rats are of unknown relevance to humans.

Impairment of Fertility

Potential effects on fertility were assessed in Sprague-Dawley rats in which males were dosed with lorcaserin hydrochloride for 4 weeks prior to and through the mating period, and females were dosed for 2 weeks prior to mating and through gestation day 7. Lorcaserin hydrochloride had no effects on fertility in rats at exposures up to 29 times the human clinical dose.

1.2 Brief Discussion of Nonclinical Findings

The sponsor is seeking the approval of once a day, extended release lorcaserin tablet (BELVIQ® XR, 20 mg QD) for the treatment of obesity in subjects with BMI ≥30 kg/m2. The active ingredient, lorcaserin hydrochloride is a serotonin $5HT_{2C}$ agonist approved by the FDA in June of 2012 for the same indication but administered twice a day (BELVIQ, 10 mg BID). The new 20 mg dose formulation is designed to extend the period of drug absorption and deliver the same degree of exposure to lorcaserin without doubling of the Cmax. In the bioequivalence studies in humans, the Cmax for 20 mg BELVIQ® XR was similar to 10 mg BELVIQ, suggesting that the risk of adverse effects related to Cmax (e.g., cognitive/psychiatric effects, priapism) will not differ from 10 mg BELVIQ. As total exposure and Cmax of the new formulation does not differ substantially from the IR formulation, no additional nonclinical studies with lorcaserin were needed, and interpretation of the toxicology profile of lorcaserin has not changed.

The excipients in the tablet are hypromellose, Ethylcellulose dispersion Type B and (b) (4) The sponsor has provided a DMF letter of authorization and specification from (b) (4), the manufacturer of (b) (4) products. All the excipients have been used in other FDA approved drugs and considered safe and pose no known safety risk. The label for lorcaserin XR is in PLLR format and subject to change. The findings of the juvenile rat study may be incorporated in the label pending the outcome of the pediatric clinical studies.

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.

2 Drug Information

2.1 Drug: Belviq XR ®

2.1.1 CAS Registry Number: 856681-05-5

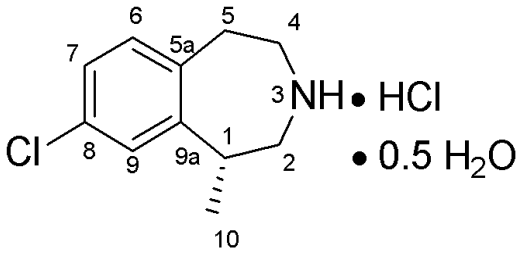
2.1.2 Generic Name: Lorcaserin

2.1.3 Code Name: APD356 hemihydrate, AR226173 hydrochloride hemihydrate

2.1.4 Chemical Name: *(R)*-8-Chloro-1-methyl-2,3,4,5 tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate

2.1.5 Molecular Formula/Molecular Weight: $C_{11}H_{15}Cl_2N.5H_2O$, FW 241.16 g/mol

2.1.6 Structure:



2.1.7 Pharmacologic class: Serotonin receptor 2 C ($5HT_{2C}$) agonist

2.2 Relevant IND/s, NDA/s:

IND 69888, immediate release lorcaserin (Arena pharmaceuticals)
NDA 22529, immediate release lorcaserin, BELVIQ® (Eisai Pharmaceuticals)
IND 119664, extended release lorcaserin (Arena Pharmaceuticals)

2.3 Clinical Formulation: 20 mg QD lorcaserin hydrochloride XR tablets (b) (4)

2.3.1 Drug Formulation

Active ingredient: (b) (4) mg of lorcaserin hydrochloride hemihydrate

Inactive ingredients: Hypromellose (b) (4) Microcrystalline cellulose (b) (4) Mannitol (b) (4), Colloidal silicon dioxide (b) (4) Magnesium stearate (b) (4), Ethylcellulose dispersion type B (b) (4) (b) (4) (b) (4) The sponsor had used (b) (4) in the bioequivalence studies. The commercial BELVIQ XR will be coated with (b) (4) orange.

Composition of Lorcaserin HCl 20-mg Extended-Release Tablets

Component	Grade	Function	mg/tablet	%w/w
Core				
Lorcaserin HCl hemihydrate	In-house[a]	Drug substance	(b) (4)	
Microcrystalline cellulose	NF, Ph. Eur.			
Mannitol	USP, Ph. Eur.			
Hypromellose	USP, Ph. Eur.			
Colloidal silicon dioxide	NF, Ph. Eur.			
Magnesium stearate	NF, Ph. Eur.			
(b) (4)				
Ethylcellulose dispersion Type B (b) (4)	NF Noncompendial			
(b) (4)				

[a] Refer to NDA 22,529, Section 3.2.S.4.1, Specification [Lorcaserin HCl Hemihydrate, (b) (4)

[b] Equivalent to 20 mg lorcaserin HCl and (b) (4) (b) (4)

(b) (4) % polyvinyl alcohol (b) (4) USP/Ph. Eur./JPE (E1203)
% talc, USP/Ph. Eur./JP (b) (4)
% (b) (4)
% titanium dioxide, USP/Ph. Eur./JP (b) (4)
% Hypromellose, USP/Ph. Eur./JP (b) (4)
(b) (4) % FD&C Yellow #6/sunset yellow FCF aluminium lake (b) (4)
% iron oxide yellow, NF/JPE (b) (4)
% iron oxide red, NF/JPE (b) (4)

2.3.2 Comments on Novel Excipients: There are no novel excipients. None of the excipients are derived from human or animal materials. All the excipients including the ingredients in the proprietary coating agents (b) (4) are listed in the inactive ingredients list, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. The sponsor has obtained a DMF letter (DMF # (b) (4)) of authorization and specification for the agents from (b) (4) manufacturer of (b) (4) (b) (4)

orange for commercialization of BELVIQ XR. All the excipients have been used in other FDA approved drugs and considered safe and pose no known safety risk.

Searching Enterprise and Mercado data base for [redacted] identified two FDA approved tablets that contain more [redacted] than BELVIQ XR (see below).

Drug A is a sustained release tablet approved by the FDA for chronic treatment, and contains [redacted]

Drug B is an extended release capsule approved by the FDA chronic treatment, and contains [redacted]

2.3.3 Comments on Impurities/Degradants of Concern: Discussed in the original NDA 22529. The excipient compatibility and drug product studies with the new formulation show only one degradant, [redacted] This degradant was also identified in the original lorcaserin tablets (BELVIQ 10 mg BID). According to the sponsor, the levels of this degradant rise slowly from interaction between lorcaserin and excipients at levels similar to or less than that observed in immediate release lorcaserin tablets (BELVIQ 10 mg BID). The projected levels will not be exceeding the [redacted]% specification limit over the proposed shelf life of the BELVIQ XR.

Justification of Specification

Attribute	Acceptance Criterion	Justification
Appearance	Orange, film-coated tablets, round, biconvex, debossed "A" on one side and "20" on the other side	The appearance specification is based on the physical characteristics of the lorcaserin HCl 20-mg extended-release tablet (commercial presentation).
Identity by HPLC	Retention time conforms to retention time of reference standard UV spectrum conforms to the spectrum of the reference standard	The identification of the active ingredient in the solution is accomplished by comparing the retention times and UV spectra obtained in chromatograms from the analysis of the lorcaserin HCl reference standard and the lorcaserin HCl drug product sample.
Uniformity of dosage units	USP <905>	Uniformity of dosage units is tested by content uniformity in accordance with USP <905>.
Assay by HPLC	90.0% to 110.0% label claim	The assay test is performed to quantify lorcaserin HCl in the drug product. The acceptance criterion is based on available batch analysis data, and allows for normal manufacturing, analytical, and stability related variations.
Degradation products [redacted] Any unspecified degradation product Total degradation products	NMT [redacted]% (w/w) NMT [redacted]% (w/w) NMT [redacted]% (w/w)	The maximum daily dose of 20 mg for lorcaserin HCl allows a proposed specification limit of NMT [redacted]% for any identified degradation product per the qualification threshold defined in the ICH guideline Q3B(R2). The maximum daily dose of 20 mg for lorcaserin HCl allows a proposed specification limit of NMT [redacted]% for any unspecified degradation product per the identification threshold defined in the ICH guideline Q3B(R2). The proposed specification limit of NMT [redacted]% for total degradation products accounts for potential degradation products in lorcaserin HCl 20-mg extended-release tablets. This limit was established based on available batch analysis data, and allows for normal manufacturing, analytical, and stability related variations.
Dissolution	NMT [redacted]% at 2 hours [redacted]% at 5 hours NLT [redacted]% at 14 hours	The proposed three point specification covering the early, middle, and late stages of the dissolution profile is based on the clinical/bioavailability batch and the FDA guidance *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations*. A specification of not more than [redacted]% released at 2 hours is proposed for the early stage. A specification of [redacted] released at 5 hours is proposed for the middle stage, which is bracketed range around the desired release of [redacted]% and whose upper limit of [redacted]% is based on the established level [redacted]IVIVC. A specification of not less than [redacted]% at 14 hours is proposed for the late stage.
Water content	NMT [redacted]% (w/w)	The acceptance criterion is proposed based on release and stability data available to date.
Microbial limits	USP <61> and USP <62>	The acceptance criteria of [redacted] and [redacted] for TAMC and TYMC, respectively, are based on compendial requirements for solid oral dosage formulations (USP <1111>). In addition, the specification requires the absence of *E. coli*.

2.4 Proposed Clinical Population and Dosing Regimen: Obese adult population of 18 years of age with BMI of 30 kg/m2 or over weight population with BMI ≥ 27 with existing risk factor (diabetes, hypertension) to be treated with 20 mg once a day BELVIQ XR.

2.5 Regulatory Background: The IND for extended release lorcaserin was submitted to the FDA on Aug 30, 2014. The application was submitted in accordance with 505(b)(1) and cross referenced all the nonclinical data submitted for the immediate release lorcaserin IND and NDA. Immediate release lorcaserin (BELVIQ, 10 mg BID) was approved by the FDA on June 27, 2012. The NDA application for extended release lorcaserin was submitted to the agency on Sept 18, 2015. The sponsor has completed the PMR (b) (4)

3 Studies Submitted:

No new nonclinical studies were submitted for approval of once a day 20 mg BELVIQ XR.

3.3 Previous Reviews Referenced: Nonclinical studies in support of the original NDA were reviewed in 2010.

4 Pharmacology

Lorcaserin selectively binds to serotonin 2C receptors (5HT2C). Rats pretreated with $5HT_{2C}$ antagonist (SB242084) had reduced response to lorcaserin suggesting that the appetite suppressant effect of lorcaserin is mediated via activation of the $5HT_{2C}$ receptor (Ki 23 nM). Based on receptor binding studies, lorcaserin has approximately 14 fold and 61 fold selectivity over $5HT_{2A}$ and $5HT_{2B}$ receptors, respectively. Changes in the XR formulation should not alter the selectivity of lorcaserin in vivo, as the maximal drug concentration will be similar to the IR product.

5 Pharmacokinetics

Lorcaserin pharmacokinetic studies had been reviewed in the original NDA 22529. The new formulation of BELVIQ XR is designed to match the total daily exposure (AUC) and drug concentration achieved with the twice-daily IR product, but with once-daily dosing. Not exceeding the Cmax of the IR product is important, as the risk of certain adverse effects (such as cognitive and psychiatric effects) would rise with an increase in plasma drug concentration. The bioequivalence studies in humans with the new (20 mg BELVIQ XR) and old (10 mg BID

BELVIQ IR) show Cmax to be similar in the two formulations, suggesting that once daily 20 mg dose of BELVIQ XR will not raise the potential adverse CNS safety profile of lorcaserin. As the exposure profile of the IR and XR products are similar (per daily exposure), the nonclinical studies conducted in support of the IR product are directly applicable to supporting the safety of the XR product.

Pharmacokinetics of BELVIQ under different conditions in humans (APD356031)

Regimen	A (10 mg)	B (20 mg)	C (20 mg)	D (20 mg)	E (20 mg)
Formulation	IR	MR prototype 1	MR prototype 2	MR prototype 3	MR prototype 2
(b) (4)	NA	(b) (4) Release)	(b) (4) Release)	Not applied (b) (4) Release)	(b) (4) Release)
Fasted/Fed	Fasted	Fasted	Fasted	Fasted	High Fat Breakfast
Population	PK Analysis Dataset 1 (n = 10)[a]				
T_{lag} (h)[b]	0.00 (0.00–0.00)	0.50 (0.00–0.50)	1.00 (0.50–1.50)	0.00 (0.00–0.50)	1.50 (1.00–2.00)
T_{max} (h)[b]	1.50 (1.00–6.00)	7.00 (6.00–12.00)	12.00 (8.00–23.53)	6.00 (6.00–8.00)	12.00 (6.00–20.00)
C_{max} (ng/mL)	35.6 (31.9)	38.2 (29.2)	33.8 (29.0)	44.8 (25.0)	51.1 (22.6)
C_{12} (ng/mL)	16.4 (32.0)	34.0 (30.9)	31.4 (26.5)	32.5 (24.1)	46.7 (23.3)
C_{24} (ng/mL)	5.86 (43.6)	18.7 (32.1)	23.6 (26.6)	16.6 (32.6)	20.8 (39.9)
AUC_{0-t} (ng.h/mL)	479 (30.7)	907 (27.1)	927 (24.7)	886 (23.0)	1020 (23.5)
AUC_{0-inf} (ng.h/mL)	568 (20.1) [n = 8]	909 (24.4) [n = 7]	978 (33.5) [n = 5]	887 (31.5) [n = 5]	1060 (25.3) [n = 8]
$t_{1/2el}$ (h)	11.45 (19.6) [n = 8][d]	12.90 (23.1) [n = 7]	12.21 (14.4) [n = 5]	11.37 (17.8) [n = 5]	10.52 (15.3) [n = 8]
Frel (%)[c]	NA	99.4 (5.5) [n = 7]	104.3 (7.3) [n = 5]	94.5 (10.0) [n = 5]	103.8 (14.9) [n = 8]

NA: not applicable

[a] Subject 003 excluded; did not receive Regimen D; Subject 010 excluded withdrew from the study

[b] Median (range)

[c] Relative bioavailability based on $AUC_{(0-inf)}$ for the test formulation (Regimen B, C, D or E) compared to the reference formulation (Regimen A) adjusted for dose differences

[d] Number of subjects with a definable terminal phase

6 General Toxicology: See lorcaserin NDA 22529 / IND69888

The toxicity of lorcaserin was evaluated in mice, rats, rabbits and monkeys which was reviewed under lorcaserin NDA 22529. Carcinogenicity and reproductive toxicity of lorcaserin has been addressed in the label. The XR formulation does not warrant a change in the interpretation of the toxicity profile for lorcaserin and thus supports approval of the XR product. (b) (4)

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/s/

FRED K ALAVI
05/25/2016
Pharmtox reviewer recommends approval of Lorcaserin XR (BELVIQ XR), NDA208524

TODD M BOURCIER
05/26/2016
I concur