CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208524Orig1s000

CHEMISTRY REVIEW(S)

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

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

BELVIQ XR® (lorcaserin hydrochloride) extended release tablets for oral use, CIV
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

BELVIQ XR is a serotonin 2C receptor agonist indicated 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) (1) 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) (1)

Limitations of Use:

- The safety and efficacy of coadministration with other products for weight loss have not been established (1)
- The effect of BELVIQ XR on cardiovascular morbidity and mortality has not been established (1)

DOSAGE AND ADMINISTRATION

- One tablet of 20 mg once daily (2)
- Discontinue if 5% weight loss is not achieved by week 12 (2)

DOSAGE FORMS AND STRENGTHS

20 mg film-coated tablet (3)

CONTRAINDICATIONS

Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions: The safety of coadministration with other serotonergic or antidopaminergic agents has not been established. Manage with immediate BELVIQ XR discontinuation and provide supportive treatment. (5.1)
- Valvular heart disease: If signs or symptoms develop consider BELVIQ XR discontinuation and evaluate the patient for possible valvulopathy. (5.2)
- Cognitive Impairment: May cause disturbances in attention or memory. Caution with use of hazardous machinery when starting BELVIQ XR treatment. (5.3)
- Psychiatric Disorders, including euphoria and dissociation: Do not exceed recommended dose of 20 mg per day. (5.4)
- Monitor for depression or suicidal thoughts. Discontinue if symptoms develop. (5.4)
- Use of Antidiabetic Medications: weight loss may cause hypoglycemia. Monitor blood glucose. Lorcaserin has not been studied in patients taking insulin. (5.5)
- Priapism: Patients should seek emergency treatment if an erection lasts >4 hours. Use BELVIQ XR with caution in patients predisposed to priapism. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (greater than 5%) in non-diabetic patients are headache, dizziness, fatigue, nausea, dry mouth, and constipation, and in diabetic patients are hypoglycemia, headache, back pain, cough, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or at *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Serotonergic drugs (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), triptans, bupropion, dextromethorphan, St. John's Wort): use with extreme caution due to the risk of serotonin syndrome. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: (b) (4) (8.2)

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

Revised: xx/201x

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Belviq extended release tablets (lorcaserin hydrochloride)	**Adequate accepted by DMEPA**
Dosage form, route of administration	tablets for oral use	**Adequate**
Controlled drug substance symbol (if applicable)	Not required	**Adequate**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended release tablets: 20 mg	**Adequate**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

(b) (4) 20 (b) (4).

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	tablet	**Adequate**
Strengths: in metric system	20 mg	**Adequate**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	BELVIQ XR is provided as orange, film-coated, tablet for oral administration in the strength of 20 mg (b) (4) lorcaserin hydrochloride. The tablets are round, biconvex, debossed with "A" on one side and "20" on the other (b) (4) side.	**Adequate**

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

Lorcaserin hydrochloride hemihydrate is a white to off-white powder with solubility in water greater than 400 mg/mL. Each BELVIQ XR tablet contains 20.8 mg of crystalline lorcaserin hydrochloride hemihydrate, equivalent to 20.0 mg anhydrous lorcaserin hydrochloride, and the following inactive ingredients: microcrystalline cellulose NF; mannitol USP; hypromellose 2208 USP; ethylcellulose dispersion Type B NF; hypromellose 2910 USP; colloidal silicon dioxide NF; polyvinyl alcohol USP; polyethylene glycol NF; titanium dioxide USP; talc USP; FD&C yellow #6/sunset yellow FCF; aluminum lake; iron oxide yellow NF; iron oxide red NF; and magnesium stearate NF.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Provided	**Adequate**
Dosage form and route of administration	Provided	**Adequate**
Active moiety expression of strength with equivalence statement for salt (if applicable)	Provided	**Adequate**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	**Adequate**
Statement of being sterile (if applicable)	Not required	**Adequate**
Pharmacological/ therapeutic class	Provided	**Adequate**
Chemical name, structural formula, molecular weight	Provided	**Adequate**
If radioactive, statement of important nuclear characteristics.	Not required	**Adequate**
Other important chemical or physical properties (such as pKa, solubility, or pH)	Provided	**Adequate**

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	20 mg	**Adequate**
Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets	**Adequate**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided	**Adequate**
Special handling (e.g., protect from light, do not freeze)	Provided	**Adequate**
Storage conditions	Provided	**Adequate**

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Arena Pharmaceuticals GmbH Untere Brühlstrasse 4 CH-4800 Zofingen Switzerland	**Adequate**

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

[redacted]

Reviewer's Assessment: **The container label is adequate.**

QUALITY ASSESSMENT

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Belviq® extended release tablets (lorcaserin hydrochloride)	**Adequate**
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	20 mg tablets. An equivalency statement is also provided: Each BELVIQ XR tablet contains 20.8 mg of crystalline lorcaserin hydrochloride hemihydrate, equivalent to 20.0 mg anhydrous lorcaserin hydrochloride	**Adequate**
Route of administration 21.CFR 201.100(b)(3))	Oral	**Adequate**
Net contents* (21 CFR 201.51(a))	30 tablets	**Adequate**
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Not required for an oral dosage form	**Adequate**
Lot number per 21 CFR 201.18	Space is provided	**Adequate**
Expiration date per 21 CFR 201.17	Space is provided	**Adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	**Adequate**
Storage (not required)	Provided	**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	**Adequate**
Bar Code per 21 CFR 201.25(c)(2)***	Provided	**Adequate**
Name of manufacturer/distributor (21 CFR 201.1)	Provided	**Adequate**
Warnings	Store at 25°C (77°F): excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].	**Adequate**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate

2) Carton Labeling

The drug product is supplied only in bottles, there is no secondary packaging.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Belviq® extended release tablets (lorcaserin hydrochloride)	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	20 mg An Equivalency statement is also provided: Each BELVIQ XR tablet contains 20.8 mg of crystalline lorcaserin hydrochloride hemihydrate, equivalent to 20.0 mg anhydrous lorcaserin hydrochloride	Adequate
Net contents (21 CFR 201.51(a))	30 tablets	Adequate
Lot number per 21 CFR 201.18	Space is provided	Adequate
Expiration date per 21 CFR 201.17	Space is provided	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(d)(2)]	Not required for an oral dosage form	Adequate
Sterility Information (if applicable)	Space is provided	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Adequate
Storage Conditions	Provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
"See package insert for dosage information" (21 CFR 201.55)	Provided	Adequate
"Keep out of reach of	Keep BELVIQ XR and all medicines out of the	Adequate

children" (optional for Rx, required for OTC)	reach of children.	
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	Not required	Adequate

Conclusion: There is no carton for the drug product, it is provided only in the bottles described above. As there is no need for secondary packaging, this is adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Recommendation:
APPROVAL
(including the Overall Manufacturing Inspection Recommendation)

NDA 208524
Review #2
Review Date (see page 2)

Drug Name/Dosage Form	lorcaserin extended release tablet
Strength	20 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Arena

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	8/18/2015
0005	12/4/2015
0006	12/21/2015
0009	3/11/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Product	Christopher Galliford	New Drug Products II/ONDP
Biopharmaceutics	Mei Ou	Biopharmaceutics/ONDP
Process	Oxana Selivanova	Process Assessment II/OPF
Microbiology	Oxana Selivanova	Process Assessment II/OPF
Facility	Donald Lech	Inspectional Assessment/OPF

Executive Summary

I. Recommendation

The FINAL recommendation from the Office of Pharmaceutical Quality (OPQ) is for APPROVAL.

- This recommendation replaces the 06/01/2016 recommendation that was finalized to meet the GRMP goal but the Overall Manufacturing Inspection Recommendation was still pending on that date.
- The Overall Manufacturing Inspection Recommendation for "Approval" was finalized in Panorama on 06/01/2016. The Facilities review was finalized on 06/01/2016 (attached).

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable

2. Action letter language: not applicable

II. Summary of Quality Assessment

See the OPQ Integrated Quality Assessment/Review #1 finalized on 06/01/2016.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:
I concur with the reviewers' conclusions.

Suong T. Tran -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.06.02 10:35:07 -04'00'

Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ

ASSESSMENT OF THE FACILITIES

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

S.2.1 Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		API manufacturing, analytical and stability testing, and regulatory release; finished drug product stability sample storage - CSN	Moderate	NAI	Acceptable

Applicant's Response:

(b) (4)

This facility's previous inspections were completed on (b) (4) and were classified NAI, VAI, NAI, respectively. The last coverage of the CSN profile code was done during the (b) (4) inspection, and was classified as acceptable.

Reviewer's Assessment:

(b) (4) This site will be responsible for the manufacturing, analytical and stability testing, and regulatory release for the Lorcaserin Hydrochloride hemihydrate drug substance, and stability sample storage for the BELVIQ XR (Lorcaserin Hydrochloride hemihydrate) finished product. The facility's initial moderate risk assessment is due to the VAI classification of the previous (b) (4) inspection. However, corrections for the listed deficiencies were verified during the most recent (b) (4) inspection. The most recent NAI inspection coupled with verified corrections of deficiencies found during the previous inspection appears to indicate low risk. In addition, no FARs and Recalls were found since the last inspection, which also indicate a low risk facility. This site appears to have low risk, and is considered acceptable based on the firm's history and past performance.

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

P.3.1 Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
Arena Pharmaceuticals GmbH Switzerland	3007045622	Finished drug product manufacturing, packaging, analytical and stability testing, and quality release - TTR	High	NAI	Acceptable
(b) (4)			Moderate	VAI	Acceptable

Applicant's Response:

Arena Pharmaceuticals GmbH, FEI: 3007045622 (TTR)
Untere Bruhlstrasse 4, Zofingen, Switzerland 4800.

This facility's previous inspections were completed on [redacted] (b) (4) and [redacted] (b) (4) and both were classified NAI. The TTR profile code was a new profile for the firm. Due to the new profile code, a PAI inspection was requested to be done and was scheduled for March 2016.

[redacted] (b) (4)

This facility's previous inspections were completed on [redacted] (b) (4) and were classified VAI, NAI, VAI, respectively. The last coverage of the CTL profile code was done during the [redacted] (b) (4) inspection, and was classified as acceptable.

Reviewer's Assessment:

Arena Pharmaceuticals GmbH: This site will be responsible for the manufacturing, packaging, analytical and stability testing, and quality release for the BELVIQ XR (Lorcaserin Hydrochloride hemihydrate) finished product. The facility's initial high risk assessment is due to the new TTR profile code. A PAI inspection was completed March 18, 2016, classified NAI, and found acceptable for the TTR profile code. One Class III recall was reviewed during the most recent 2016 inspection. This recall, which involved Arena Pharmaceuticals GmbH, was reported to FDA by Eisai Inc. of Woodcliff, New Jersey for missing or illegible bottle labels. The FDA investigator's review of the firm's investigation conveyed that Arena Pharmaceuticals GmbH appeared to recognize the possible reasons for the issues and found no significant deficiencies; the recall was concluded complete by FDA on May 21, 2015. A solid inspectional history, the results from the most recent PAI inspection covering the new TTR profile code, no FARs, and an adequate investigation of the one recall found since the last inspection indicates a low risk facility. The firm is listed as acceptable.

[redacted] (b) (4): This site is listed as a control testing laboratory responsible for microbial testing of the BELVIQ XR (Lorcaserin Hydrochloride hemihydrate) finished product. The facility's initial moderate risk assessment is due to the two VAI classified inspections done in [redacted] (b) (4) and [redacted] (b) (4). Regarding the most recent VAI inspection, an examination of the one observation reported did not rise to an egregious state, and appears to indicate a low risk history. In addition, no FARs and Recalls were found since the last inspection, which also indicate a low risk facility. This site appears to have low risk and was considered acceptable based on the firm's history and past performance.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature: The overall assessment for NDA 208524,

QUALITY ASSESSMENT

BELVIQ XR (Lorcaserin Hydrochloride hemihydrate) Tablets is recommended approval. This decision is based on the current acceptable final recommendations for each of the three firms listed.

Donald Lech
June 1, 2016

Secondary Review Comments and Concurrence:

I concur with the overall recommendation.

Juandria Williams, PhD; DIA/B3
June 1, 2016

Recommendation:
Approval
(This Recommendation is finalized to meet the GRMP goal and does not include the Facility Review/Manufacturing Inspection Recommendation, which is pending)

NDA 208524
Review #1
Review Date (see page 5)

Drug Name/Dosage Form	lorcaserin extended release tablet
Strength	20 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Arena

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	8/18/2015
0005	12/4/2015
0006	12/21/2015
0009	3/11/2016

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
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Biopharmaceutics	Mei Ou	Biopharmaceutics/ONDP
Process	Oxana Selivanova	Process Assessment II/OPF
Microbiology	Oxana Selivanova	Process Assessment II/OPF
Facility	Donald Lech	Inspectional Assessment/OPF

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
[redacted] (b) (4)				For these Type III DMFs: Adequate information provided in the NDA (by C. Galliford/D. Christodoulou).		

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	69888	
NDA	22529	same applicant

2. CONSULTS: not applicable

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality is for Approval (this recommendation is finalized to meet the GRMP goal and does not include the Facility Review/Manufacturing Inspection Recommendation, which is pending).

- The recommendation in this Quality Review covers all CMC information submitted in the NDA.
- The Facility/Manufacturing Inspection review will be finalized at a later date, prior to the PDUFA goal, as an addendum in Panorama.

Labeling comments will be finalized during the multi-disciplinary OND-managed labeling review.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable

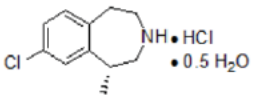
B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

II. Summary of Quality Assessment

This is a 505(b)(1) (not NME) application for a new dosage form of lorcaserin, extended release tablet. The same applicant has the approved NDA 22529 for the immediate release tablet.

A. Drug Substance

Lorcaserin is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate. The empirical formula is C11H15Cl2N·0.5H2O, and the molecular weight of the hemihydrate form is 241.16 g/mol.



NDA 22529 (same applicant) is referenced for all CMC information on the drug substance.

B. 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 [redacted] (b) (4)

(b) (4) ethylcellulose dispersion Type B (b) (4)

- orange-colored, round, biconvex, film-coated tablets debossed with "A" on one side and "20" on the other side

Excipients are microcrystalline cellulose NF; mannitol USP; hypromellose 2208 USP; ethylcellulose dispersion Type B NF; hypromellose 2910 USP; colloidal silicon dioxide NF; polyvinyl alcohol USP; polyethylene glycol NF; titanium dioxide USP; talc USP; FD&C yellow #6/sunset yellow FCF; aluminum lake; iron oxide yellow NF; iron oxide red NF; and magnesium stearate NF.

The product manufacturing process consists of: (b) (4) (b) (4)

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. (b) (4) . Microbial limits testing is included in the drug product specification.

Container Closure systems: HDPE bottles (b) (4)

Expiration Date & Storage Conditions: 24 months at room temperature
The primary stability batches have the commercial formulation (except for color, (b) (4) for the stability batches and (b) (4) Orange for the commercial product), commercial container closure systems, and were manufactured at the commercial site, greater than (b) (4)-fold commercial scale, and using the commercial process. Photostability data are provided for the orange commercial product, bridging this formulation to that of the primary stability batches with respect to stability trending.

C. Summary of Drug Product Intended Use

Proprietary Name	[not finalized by GRMP goal; see CDTL's memo]
Non Proprietary Name of the Drug Product	lorcaserin HCl extended release tablet
Non Proprietary Name of the Drug Substance	lorcaserin HCl
Proposed Indication(s)	[not finalized by GRMP goal; see CDTL's memo]
Duration of Treatment	chronic
Maximum Daily Dose	20 mg
Alternative Methods of Administration	not applicable

D. Biopharmaceutics Considerations

Batch 14254006 used in the pivotal BE study and the commercial product have the same formulation with the exception of the color [redacted] (b) (4) for the clinical batch and [redacted] (b) (4) Orange for the commercial product). Both formulations have adequately similar dissolution profiles; no impact on the bioavailability and bioequivalence of the drug product is expected. The commercial formulation was used in the in vitro alcohol dose-dumping study, which found no dose-dumping issue.

Adequate data have been provided in support of the final dissolution test method and acceptance criteria. The initially submitted In Vitro In Vivo Correlation (IVIVC) data did not support the dissolution acceptance criteria. However, a validated IVIVC model is not necessary because the final dissolution acceptance criteria with adequate discriminatory power are supported by actual data.

E. Novel Approaches: not applicable
F. Any Special Product Quality Labeling Recommendations: not applicable
G. Life Cycle Knowledge Information (see Attachment)

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:
I concur with the reviewers' conclusions.

Suong T. Tran -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.06.01 10:09 35 -04'00'

Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The sponsor notes that the Environmental Assessment prepared for NDA 22,529 in accordance with 21 CFR Part 25 evaluates the potential environmental impacts of lorcaserin hydrochloride. As part of the September 2010 review, FDA concluded with a finding of no significant impact on the human environment at the expected levels of exposure as per 21 CFR 25.31.

Reviewer's Assessment:

The claim for the categorical exclusion is acceptable and the provided information and data are adequate for approval of the NDA application.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
ADEQUATE

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Suong T. Tran -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2015.11.16 13:37:45 -05'00'

Suong (Su) Tran
Application Team Lead, OPQ

Application #: N208524

Submission Type: 505b1 (not NME)

Established/Proper Name: lorcaserin

Applicant: Arena

Letter Date: 9/18/15

Dosage Form: Extended release tablet, oral

Chemical Type: 3

Stamp Date: 9/18/15

Strengths: 20 mg

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	x		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?	x		Biopharmaceutics: 1) Provide the complete Dissolution Method Development Report for Methods: QBRAM115165.02, and Diss-296932 (the same as Dissolution Method: Z TM 0158) and the justification for choosing your proposed dissolution method and acceptance criteria. In order to support the discriminating ability of your proposed dissolution method, provide the comparative dissolution data profile and similarity factor calculation of your target product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical quality attributes (CQAs) of your product and critical process parameters (CPPs) that mostly would affect the manufacturing process (i.e. ±10-20% change to the specification ranges of these variables). If available, provide data to show that the selected dissolution method is able to reject batches that are not bioequivalent. 2) Provide the Dissolution Method Validation Report for Dissolution Method: QBRAM115165.02.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]		x	
2.	Botanical[1]		x	
3.	Naturally-derived Product		x	
4.	Narrow Therapeutic Index Drug		x	
5.	PET Drug		x	
6.	PEPFAR Drug		x	
7.	Sterile Drug Product		x	
8.	Transdermal[1]		x	
9.	Pediatric form/dose[1]		x	
10.	Locally acting drug[1]		x	
11.	Lyophilized product[1]		x	
12.	First generic[1]		x	
13.	Solid dispersion product[1]		x	
14.	Oral disintegrating tablet[1]		x	
15.	Modified release product[1]	x		
16.	Liposome product[1]		x	
17.	Biosimilar product[1]		x	
18.	Combination Product _____		x	
19.	Other			

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FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
	Regulatory Considerations				
20.	USAN Assigned		x		
21.	End of Phase II/Pre-NDA Agreements				
22.	SPOTS			x	
23.	Citizen Petition and/or Controlled Correspondence			x	
24.	Comparability Protocol(s)[2]			x	
25.	Other				
	Quality Considerations				
26.	Drug Substance Overage			x	
27.	Design Space	Formulation		x	
28.		Process		x	
29.		Analytical Methods		x	
30.		Other		x	
31.	Real Time Release Testing (RTRT)			x	
32.	Parametric Release in lieu of Sterility Testing				n/a - not a sterile product
33.	Alternative Microbiological Test Methods			x	
34.	Process Analytical Technology[1]			x	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	x		no compendial monograph for this new product
36.		Excipients	x		(b) (4)
37.		Microbial		x	
38.	Unique analytical methodology[1]			x	
39.	Excipients of Human or Animal Origin			x	Magnesium stearate is vegetable-derived
40.	Novel Excipients			x	
41.	Nanomaterials[1]			x	
42.	Hold Times Exceeding 30 Days				
43.	Genotoxic Impurities or Structural Alerts				
44.	Continuous Manufacturing			x	
45.	Other unique manufacturing process[1]				
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		x		
47.	New delivery system or dosage form[1]			x	
48.	Novel BE study designs				See Clinical Pharmacology review
49.	New product design[1]			x	
50.	Other				

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C.	FILING CONSIDERATIONS				
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?			x	Categorical exclusion request
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? For ANDAs: Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records	x			

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FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Method Validation Package ○ Comparability Protocols				
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	x			
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	x			
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?			x	
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ❑ reference standards or materials ❑ container closure system ❑ stability				referencing approved NDA 22529 for all CMC information on the drug substance

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FILING REVIEW

C. FILING CONSIDERATIONS					
	○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development ❑ Manufacture ❑ Control of Excipients ❑ Control of Drug Product ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System ○ Include data outlined in container closure guidance document ❑ Stability ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment ❑ APPENDICES ❑ REGIONAL INFORMATION	x			
BIOPHARMACEUTICS [Per Biopharmaceutics reviewer's filing assessment- Mei Ou and Albert Chen]					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?		x		One BA (Study APD356-031) and two BE studies (Study APD356XR-101, and APD356XR-102) were submitted, which will be reviewed by the Office of Clinical Pharmacology (OCP).
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to	x			In vitro dissolution testing and IVIVC study (No. QBR115165) were submitted and will be reviewed by Division of Biopharmaceutics

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*				(DB). Two Information Requests are going to be conveyed to the Applicant in the 74-day letter (see Biopharmaceutics Brief Review Summary attached at the end of this document).
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.		x		
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	x			In vitro alcohol dose dumping study was submitted and will be reviewed by Division of Biopharmaceutics (DB).
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	x			
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	x			The active drug substance lorcaserin hydrochloride hemihydrate was approved on 06/27/2012 (NDA 022529), the detail physical, chemical and pharmaceutical properties of the active drug substance can be found in NDA 22529, section 2.3.P.2 and 3.2.P.2.2. The drug substance (DS) and drug product (DP) of NDA 022529 have been reviewed by the FDA BCS Committee and determined as a BCS Class I drug in May, 2010.
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x		
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x			
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ❑ novel excipients			x	
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: ❑ Compliance to 21 CFR 601.2(a):			x	

OFFICE OF PHARMACEUTICAL QUALITY

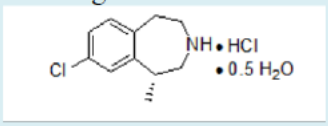
FILING REVIEW

Kick-off meeting handout

NDA 208524 by Arena Pharmaceuticals
Application Type: 505(b)(1) – Not NME
Submission Classification: 3
Trade or Proprietary Name: Pending
Established Name (USAN): lorcaserin
Dosage Form, route of administration and strength:
Extended release tablet, oral, 20 mg/
Indication: Weight management

Is the Quality Section of the application fileable? Yes

Drug Substance: The applicant references the drug substance information in their approved NDA 22529 for lorcaserin IR tablets.
Lorcaserin is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate. The empirical formula is C11H15Cl2N·0.5H2O, and the molecular weight of the hemihydrate form is 241.16 g/mol.



Drug Product: Each tablet contains 20.8 mg of lorcaserin hydrochloride hemihydrate, equivalent to 20.0 mg anhydrous lorcaserin hydrochloride. There is no novel excipient and no animal-derived excipient.

- One pivotal BE study was conducted to compare the extended release product to the approved immediate release product. With the exception of color, the formulation is the same for the clinical batches, stability batches, and commercial product. The NDA includes photostability data for one commercial batch with the orange color (clinical and primary stability batches have the (b) (4) color). The manufacture of all clinical and stability batches was at the commercial site, by the commercial process, and at a scale > (b) (4) x commercial scale.
- The NDA includes information on IVIVC and alcohol dumping- to be evaluated by the Biopharmaceutics reviewer.

The drug substance is BCS I and crystalline: (b) (4) No polymorph change in the drug product was observed in the stability studies. Drug substance particle size was found to have no impact on content uniformity, processability, and dissolution of the drug product- to be confirmed by the primary reviewers *as applicable*.

Product manufacture. (b) (4)

Drug product specification. The drug product specification includes attributes standard for this type of dosage form. (b) (4) A justification is provided for the omission of chirality testing, to be reviewed by the Drug Product reviewer.

- Dissolution information (test and limits) will be evaluated by the Biopharmaceutics reviewer.

- [redacted] (b) (4) . Microbial limits testing is included in the drug product specification of both approved IR and new XR products.
- Degradants [redacted] (b) (4)

Container closure systems. The commercial drug product will be packaged in HDPE bottles [redacted] (b) (4) USP testing per <661> and <671> was conducted.
Safety of the product-contact components = regulations for indirect food additives.
Compatibility = stability data.

Stability.

- Registration stability batches = Six batches of the commercial formulation (except for color) packaged in all the commercial container closure systems, manufactured at the commercial site, > [redacted] (b) (4) x commercial scale, and using the commercial process.
- The NDA includes data from 12 months at 25 °C/60% RH, and 30 °C/75% RH and for 6 months at 40 °C/75% RH.
- Additional stability data include bulk packaging and photostability of the commercial orange tablets.

Table 1. Composition of Lorcaserin HCl 20-mg Extended-Release Tablets

Component	Grade	Function	mg/tablet	%w/w
				(b) (4)
Lorcaserin HCl hemihydrate	In-house[a]	Drug substance	20.776[b]	(b) (4)
Microcrystalline cellulose	NF, Ph. Eur.			(b) (4)
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	NF			(b) (4)

(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 (b) (4)
% 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)

Table 15. Specification for Lorcaserin HCl 20-mg Extended-Release Tablet

Attribute	Test Method	Acceptance Criterion
Appearance	Z TM 0050	Orange, film-coated tablets, round, biconvex, debossed "A" on one side and "20" on the other side
Identity by HPLC[a]	Z TM 0253	Retention time conforms to retention time of reference standard
		UV spectrum conforms to the spectrum of the reference standard
Uniformity of dosage units[a] (by content uniformity)	Z TM 0161 (USP <905>/Ph. Eur. 2.9.40)	USP <905>
Assay by HPLC	Z TM 0252	90.0% to 110.0% label claim
Degradation products by HPLC (b) (4) Any unspecified degradation product Total degradation products	Z TM 0252	NMT (b) (4)% (w/w) NMT % (w/w) NMT % (w/w)
Dissolution	Z TM 0158 (USP <711>/Ph. Eur. 2.9.3)	NMT (b) (4)% at 2 hours (b) (4)% to (b) (4)% at 5 hours NLT (b) (4)% at 14 hours
Water content	Z TM 0159 (USP <921> Method Ia/ Ph. Eur. 2.5.12 Method A)	NMT (b) (4)% (w/w)
Microbial limits Total aerobic microbial count (TAMC) Total combined yeast and mold count (TYMC) *E. coli*	Z TM 0230 (USP <61>/Ph. Eur. 2.6.12; USP <62>/Ph. Eur. 2.6.13)	NMT (b) (4) CFU/g[b] NMT CFU/g[c] Absence/1 g

[a] Only applies at release.

[b] NMT (b) (4) CFU/g per USP <61>/Ph. Eur. 5.1.4, which is interpreted as maximum acceptable count = (b) (4) CFU/g.

[c] NMT CFU/g per USP <61>/Ph. Eur. 5.1.4, which is interpreted as maximum acceptable count = CFU/g.

HPLC = high-performance liquid chromatography

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FILING REVIEW

Biopharmaceutics Brief Review Summary (by Mei Ou and Albert Chen)

From the Biopharmaceutics perspectives, this NDA 208524 is fileable. No filing issues are identified.

1. Composition of the Proposed Drug Product

Lorcaserin HCl (APD356) is a selective serotonin 2C (5-HT_{2C}) receptor agonist that reduces body weight by selectively mimicking the effects of serotonin at the 5-HT_{2C} receptor. Lorcaserin HCl hemihydrate (HH) is a highly soluble and highly permeable active substance. The drug substance (DS) and drug product (DP) of the Immediate Release (IR) tablet (BELVIQ®), 10 mg had been reviewed and accepted by the FDA Biopharmaceutics Classification System (BCS) Committee and was classified as a BCS Class 1 drug in May 2010.

The proposed drug product is Lorcaserin HCl Extended-release (ER) tablet, 20 mg. The components and composition of commercial and clinical study formulation of proposed drug are listed in Table 1 below (from M.2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Method).

Table 1: Components of Lorcaserin HCl ER Tablet, 20 mg, Clinical Studies and Commercial Formulation

Component	Grade	Function	Formulation Number				
			APD356-2013-01	APD356-2013-02	APD356-2013-03	APD356-2014-02	APD356-2014-04 (Commercial Presentation)
			(b) (4)			Arena GmbH	Arena GmbH
							(b) (4)
			mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet
(b) (4)							
Lorcaserin HCl hemihydrate	Arena	Drug substance	20.78[a]	20.78[a]	20.78[a]	20.776[a]	20.776[a]
Microcrystalline cellulose	NF						(b) (4)
Mannitol	USP						
Hypromellose	USP						
Colloidal silicon dioxide	NF						
Magnesium stearate	NF						
Total							
							(b) (4)
Ethylcellulose dispersion Type B	NF						(b) (4)
							(b) (4)

[a] Amounts of API per tablet reflect rounding differences at different scale, equivalent to 20 mg lorcaserin HCl.

The clinically tested formulation APD356-2014-02 employed in the pivotal PK studies (APD356XR-101 and APD356XR-102) is the same as the commercial formulation APD356-2014-04 except for the color coating.

2. In Vitro Dissolution Testing

The in vitro dissolution method for proposed lorcaserin HCl ER tablet, 20 mg, is listed in Table 2 below (from M.2.7.1.1.2.1 Overview of Dissolution Test Methods). The dissolution method for clinical

formulation APD356-2014-02 (Method Diss-296932) is the same as that for commercial formulation APD356-2014-04 (Method Z TM 0158).

Table 2: Summary of Dissolution Test Methods

Formulation	APD356-2013-01, -02, -03	APD356-2014-02
Clinical study	APD356-031	APD356XR-101 APD356XR-102
Dissolution test method number	QBRAM115165.02	Diss-296932
Medium	0.1 N HCl	
Apparatus	1 (baskets)	
Agitation speed (rpm)	100	
Sampling time points (h)	(b) (4)	1, 2, 4, 5, 6, 8, 10, 12, 14, and 20

Three prototype formulations of ER drug product (b) (4) composition and varied functional coating were developed based on in vitro dissolution testing, which were shown in Figure 1 below (from M.2.3 Quality Overall Summary).

Figure 1: Dissolution Profiles of Lorcaserin HCl Prototype ER Tablet, 20 mg with Reference Product of Lorcaserin HCl IR Tablet, 10 mg (BELVIQ®)

(b) (4)

The prototype formulation (b) (4)) is the same as the commercial formulation of drug product except for the color coating and the % of (b) (4) used as listed in Table 3 below (from M.2.3 Quality Overall Summary). Prototype (b) (4) formulation was selected for further clinical development to be used in BA/BE studies.

Table 3: Four Formulations of Proposed Lorcaserin HCl ER Tablet, 20 mg

Type	(b) (4)
Development/ Clinical	

Commercial	(b) (4)

** This clinical study formulation for BA food and BE studies is the same as the commercial formulation except for the color coating.*

Table 4 below summarized the representative mean dissolution profiles for proposed lorcaserin HCl ER tablets, 20 mg, used in the formulation screen, BA/BE studies and IVIVC (from 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods).

Table 4: Mean Dissolution Profiles at pH 1 (0.1 N HCl) of Proposed Lorcaserin HCl ER Tablets, 20 mg, used in Clinical Studies

Formulation	**APD356-2013-01 (Prototype (b) (4)**	**APD356-2013-02 (Prototype: (b) (4)) (Prototype (b) (4)**		**APD356-2013-03**	**APD356-2014-02**
Clinical phase	Phase 1/PK IVIVC	Phase 1/PK IVIVC	Phase 1/PK IVIVC	Phase 1/PK Preliminary food effect	Phase 1/PK Bioavailability Definitive food effect
Protocol number	APD356-031	APD356-031	APD356-031	APD356-031	APD356XR-101 APD356XR-102
Lot number	115165/C/06	115165/C/02	115165/C/04	115165/C/08	14254006
Strength (mg)	20	20	20	20	20
Drug product manufacturer	(b) (4)				Arena GmbH
Drug substance manufacturer	(b) (4)				
(b) (4)					

[a] These results are based on 12 dosage units.
NR = not required

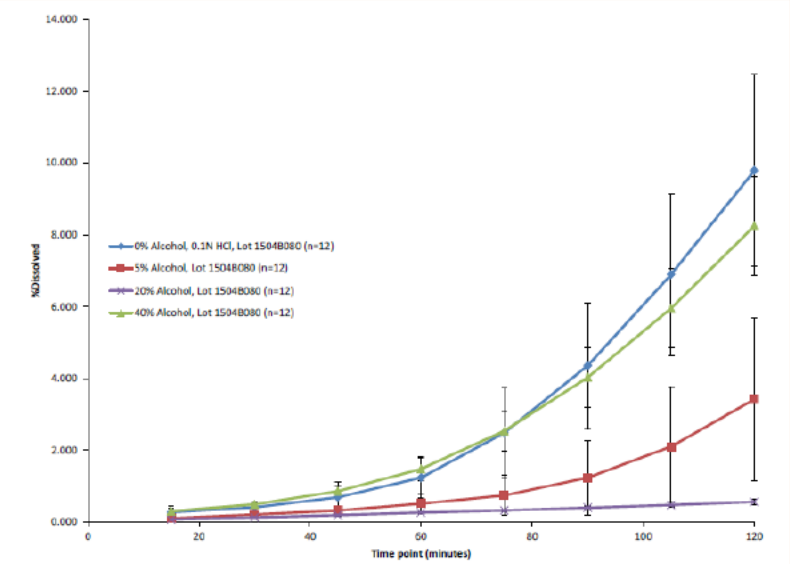
(b) (4)

[redacted]

5. In Vitro Alcohol Dose Dumping Studies

Dissolution profiles were generated on proposed lorcaserin HCl ER tablets, 20 mg (commercial formulation APD356-2014-04) using media containing 0%, 5%, 20%, and 40% alcohol USP to determine the effects on the release rate of lorcaserin from the dosage unit as shown in Figure 3. The Applicant concluded that when compared to baseline (0% alcohol), no dose dumping is observed within first 2 hours for all the alcohol concentrations tested. The Applicant also reported that the degrees of alcohol effect on dissolution profiles observed seemingly are not consistent with increasing alcohol concentration, which is unlikely due to a reduced solubility of lorcaserin HCL in the dissolution media (from 2.7.1 Summary of Biopharmaceutics Studies and Associated Analytical Methods).

Figure 3: Dissolution Testing of ER Tablets (Orange Formulation APD356-2014-04), Batch 1504B080, in 0% (0.1 N HCl), 5%, 20%, and 40% Alcohol USP



Note: Error bars correspond to the standard deviations (n = 12).

6. (**NOT filing issues**) The following ***Information Requests*** are going to be conveyed to the Applicant in the 74-Day letter:

1) Provide the complete Dissolution Method Development Report for Methods: QBRAM115165.02, and Diss-296932 (the same as Dissolution Method: Z TM 0158) and the justification for choosing your proposed dissolution method and acceptance criteria. In order to support the discriminating ability of your proposed dissolution method, you need to provide the comparative dissolution data profile and similarity factor calculation of your target product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical quality attributes (CQAs) of your product and critical process parameters (CPPs) that mostly would affect the manufacturing process (i.e. ±10-20% change to the specification ranges of these variables). If available, make sure that the selected dissolution method is able to reject bad batches that are not bioequivalent.

2) Provide the Dissolution Method Validation Report for Dissolution Method: QBRAM115165.02.

Primary Quality Review

ASSESSMENT OF THE BIOPHARMACUETICS

On 09/18/2015, the Applicant, Arena Pharmaceuticals Inc., submitted this original **NDA 208524** for their proposed drug product, BELVIQ XR® (Lorcaserin HCl) Extended-Release (ER) Tablets, 20 mg. It is indicated 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).

This NDA is a 505(b)(1) application. The Division of Biopharmaceutics (DB) focuses on the reviewing the drug product in terms of:

- In vitro dissolution method and acceptance criteria.
- In vitro alcohol dose dumping studies.
- In Vitro/In Vivo Correlation (IVIVC) analysis.

1. The composition of proposed drug product

The composition and function of the commercial formulation for the proposed drug product, Lorcaserin HCl ER Tablets, 20 mg, are listed in Table 1.

Table 1: Composition of Lorcaserin HCl ER Tablets, 20 mg (from M.2.3.P.1)

Component	Grade	Function	mg/tablet	%w/w
[redacted]				(b) (4)
Lorcaserin HCl hemihydrate	In-house[a]	Drug substance	20.776[b]	(b) (4)
Microcrystalline cellulose	NF, Ph. Eur.			(b) (4)
Mannitol	USP. Ph. Eur.			
Hypromellose	USP. Ph. Eur.			
Colloidal silicon dioxide	NF. Ph. Eur.			
Magnesium stearate	NF. Ph. Eur.			
[redacted]				(b) (4)
Ethylcellulose dispersion Type B	NF			(b) (4)
[redacted]				(b) (4)

2. BCS classification

The active ingredient of this proposed drug product is lorcaserin hydrochloride hemihydrate (Lorcaserin HCl HH). This drug substance was classified as a Biopharmaceutics Classification System (BCS) I compound referring to the approved

Reference ID: 3963811

drug product, BELVIQ® (Lorcaserin HCl) Immediate-Release (IR) Tablet, 10 mg, which has the same approved drug substance granted as a BCS I compound (NDA 022529 DARRTS Information Request document dated on 07/23/2010).

Lorcaserin HCl HH drug substance is very soluble in water [redacted] (b) (4) [redacted] (b) (4) and in physiological buffers with pH 1.0, 4.5 and 7.5. The solubility of Lorcaserin HCl HH in buffers is summarized in Table 2 below (from M.3.2.P.2). BELVIQ® has been concluded as a BCS Class I drug substance and drug product by FDA.

Table 2: Solubility of Lorcaserin HCl HH in aqueous media at pH 1-7.5 at 37°C ± 1°C for ~24 hours (from M.3.2.P.2.1.1)

Intended pH (Observed Range)	Average Solution Concentration ± SD (mg/mL)[a]	Solubility (mg/mL)
1 (1.09-1.06)	483 ± 6	> 400
4.5 (4.48-4.51)	476 ± 5	> 400
7.5 (7.49 to 7.46)	418 ± 8	> 400

[a] Solutions not saturated, concentrations determined from three injections of each sample, for nine observations per pH.

3. In vitro dissolution method

The proposed in vitro dissolution method (**Method No. Z TM 0158**) and acceptance criteria for drug product, Lorcaserin HCl ER Tablets, 20 mg, are summarized in Table 3. The detailed dissolution analytical procedure was provided in M.3.2.P.5.2.4, and M.3.2.R Attachment 13.

Table 3: Proposed in vitro dissolution parameters and specification for Lorcaserin HCl ER Tablets, 20 mg (from M.2.3.P, M.3.2.P.5.1 and M.3.2.P.5.2)

Apparatus	I (Basket)
Medium	0.1N Hydrochloride Acid (HCl), deaerated
Volume	900 mL
Rotation Speed	100 rpm
Temperature	37°C ± 0.5°C
Sampling Time	1, 2, 4, 5, 6, 8, 10, 12, 14 and 20 hours
Proposed Specifications	2 hours: NMT (b) (4) % 5 hours: (b) (4) % 14 hours: NLT (b) (4) %

(1) In vitro dissolution method development and discriminating ability

The in vitro dissolution method development and data was originally provided in M.3.2.P.2.2.3. The following dissolution conditions were evaluated for the drug product:

- Dissolution profiles of drug product in multi-media, e.g. pH 1.0 (0.1N HCl), 4.5 [redacted] (b) (4) and 6.8 [redacted] (b) (4)

Reference ID: 3963811

(b) (4)

[redacted]

Reviewer's Assessment:

The Biopharmaceutics review team considered the dissolution method development was not complete in the original M.3.2.P.2.2.3 submission. Because the Applicant mentioned that there was historical dissolution method development report for their prototypes of the drug product formulations in M.3.2.P.5.4.2; therefore, we had one request related to the dissolution method development. This information request was conveyed to the Applicant in the Filing Review Issues Identified Letter (74-Day Letter) on 11/22/2015:

1st Biopharmaceutics IR #1 (in 74-Day Letter #1)

Provide the complete Dissolution Method Development Report for Methods: QBRAM115165.02, and Diss-296932 (the same as Dissolution Method: Z TM 0158) and the justification for choosing your proposed dissolution method and acceptance criteria. In order to support the discriminating ability of your proposed dissolution method, provide the comparative dissolution data profile and similarity factor calculation of your target product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical quality attributes (CQAs) of your product and critical process parameters (CPPs) that mostly would affect the manufacturing process (i.e. ±10-20% change to the specification ranges of these variables). If available, provide data to show that the selected dissolution method is able to reject batches that are not bioequivalent.

On 12/21/2015, the Applicant responded this IR#1 as (see details in M.1.11.1):

*Dissolution method development is summarized in section 3.2.P.2.2.3.3, and the complete dissolution development report, **PDR-14-061**, with the justification for the proposed methodology, is provided with this submission.*

In support of the discriminating ability of the proposed dissolution method, an evaluation of potential critical quality attributes (CQAs), critical process parameters (CPPs), and the dissolution method's ability to reject non-bioequivalent batches is provided with this response.

The supplemented dissolution method development report (**PDR-14-061**) was submitted in M.3.2.P.2.2.3. The following dissolution parameters were evaluated using both of clinical and commercial formulations of drug product:

- Apparatus 1 (Baskets) [redacted] (b) (4)

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(b) (4)

[redacted]

Reviewer's Assessment:

The overall provided in vitro dissolution method development report for the drug product, BELVIQ XR® (Lorcaserin HCl) ER Tablets, 20 mg, is acceptable, with reasonable discriminating ability.

(2) In vitro dissolution method validation

(b) (4)

[redacted]

Reference ID: 3963811

Reviewer's Assessment:

Based on the above mentioned dissolution method development for the prototype formulations of drug product in M.3.2.P.5.4.2, a second request related to the dissolution method validation was conveyed to the Applicant in the same Filing Review Issues Identified Letter (74-Day Letter) on 11/22/2015, as:

1st Biopharmaceutics IR #2 (in 74-Day Letter #2)

Provide the Dissolution Method Validation Report for Dissolution Method: QBRAM115165.02.

On 12/21/2015, the Applicant responded this IR#2 as (see details in M.1.11.1):

The method qualification protocol and report for dissolution method QBRAM115165.02 are provided with this submission. Dissolution method QBRAM115165.02 was used at (b) (4) *Clinical for testing the extended release, prototype formulations used in the Phase 1 extended release PK study APD356-031 (QBR115165).*

The dissolution method QBRAM115165.02 analytical protocol and validation report were provided in M.1.11.1 for details, which is acceptable for testing the prototype formulations of drug product in formulation development.

Reviewer's Assessment:

The overall provided in vitro dissolution method validation reports for the drug product, BELVIQ XR® (Lorcaserin HCl) ER Tablets, 20 mg, is acceptable.

4. The in vitro dissolution testing for drug product formulation development

(b) (4)

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Reference ID: 3963811

(b) (4)

[redacted]

Reviewer's Assessment:

Based on the data, the Biopharmaceutics review team considered the proposed dissolution specification of *2 hours: NMT* (b)(4)*%, 5 hours:* (b) (4)*%, and 14 hours: NLT* (b)(4)*%* is liberal for the drug product at the 5 hour time point. The submitted In Vitro/In Vivo Correlation (IVIVC) report will be further reviewed in order to evaluate if this proposed specification will be supported by the IVIVC model.

6. In Vitro/In Vivo Correlation (IVIVC)

A Level (b)(4) IVIVC was submitted for three extended-release prototype formulations of the proposed drug product (b) (4) release). The detailed IVIVC report (Report No. QBR115165) and WinNonlin data set were submitted in M.3.2.P.2 and M.5.3.1. A (b)(4) stage model independent (b) (4) approach was employed to perform the IVIVC analysis. A (b) (4) crossover pharmacokinetic clinical study (APD356-031/QBR115165) involving 12 healthy subjects was performed to evaluate the PK performance of all extended-release formulations. The currently approved immediate-release formulation was the reference drug product. The PK study datasets were used for the IVIVC analysis. Meanwhile, the in vitro dissolution data of all extended-release prototype formulations of drug product were used for IVIVC analysis.

Reviewer's Assessment:

The (b) (4) release formulation (b) (4) -release) was used as the target formulation during the IVIVC model development. With no extrapolation rule in IVIVC modeling, per Guidance for Industry*: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro / In Vivo Correlation*, the submitted IVIVC report was thoroughly reviewed and found not acceptable (also refer to PIND 119664 meeting minutes, DARRTS document dated on 04/20/2015 and 05/27/2015, for the same comments from Biopharmaceutics communicated to the Applicant related to the IVIVC development). Therefore, the submitted IVIVC does not support the proposed dissolution specification, especially for 5 hours: (b) (4) %.

Because the overall dissolution data already supported the specification as mean target

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dissolution (b)(4)% variation without a validated IVIVC, the following dissolution acceptance criteria of *2hr: NMT (b)(4)%, 5hr: (b)(4)%, 14hr: NLT (b)(4)%* were recommended by the Agency and conveyed to the Applicant on 02/19/2016.

2nd Biopharmaceutics IR:

Given no extrapolation rule in IVIVC modeling, your developed and submitted IVIVC model is not acceptable to support your target formulation (b)(4) release) (see Pre-IND 119664 meeting comments dated on 04/20/2015). Per Guidance for Industry: extended release oral dosage forms: development, evaluation, and application of in vitro / in vivo correlation, the dissolution acceptance criteria should be set as a mean target dissolution (b)(4)% variation without a validated/established IVIVC. Your submitted dissolution data met the dissolution criteria without the IVIVC modeling. Therefore, we recommend the dissolution acceptance criteria to be set as: 2hr: NMT (b)(4)%, 5hr: (b)(4)%, 14hr: NLT (b)(4)% for your drug product. Revise sections M.3.2.P.5.1 "Specifications", M.3.5.P.5.6 "Justification of Specification" and other related sections to reflect the new Dissolution Acceptance Criteria as quality control for Release and Stability for your drug product.

On 03/11/2016, the Applicant responded for the above 2nd IR as (see details in M.1.11.1):

We accept the Agency's recommendations regarding the following dissolution acceptance criteria:

- *Not more than (b)(4)% at 2 hours*
- *(b)(4)% at 5 hours*
- *Not less than (b)(4)% at 14 hours*

The following documents in the NDA have been updated:

- *3.2.P.5.1 Specification*
- *3.2.P.5.4 Batch Analyses*
- *3.2.P.5.6 Justification of Specification*
- *3.2.P.8.1 Stability Summary and Conclusion (Bottles)*
- *3.2.P.8.1 Stability Summary and Conclusion (Bulk)*
- *3.2.P.8.1 Stability Summary and Conclusion (Stress Studies: Photostability)*

All batches meet the revised specification.

Reviewer's Assessment:

The final in vitro dissolution method and specification for drug product, Lorcaserin HCl ER Tablets, 20 mg, are agreed by the Applicant and listed in table below:

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Apparatus	I (Basket)
Medium	0.1N Hydrochloride Acid, deaerated
Volume	900 mL
Rotation Speed	100 rpm
Temperature	37°C ± 0.5°C
Sampling Time	1, 2, 4, 5, 6, 8, 10, 12, 14 and 20 hours
Specifications	2 hours: NMT (b)(4)% 5 hours: (b)(4)% 14 hours: NLT (b)(4)%

7. In vitro alcohol dose dumping study

(1) In vitro alcohol dose dumping study

In vitro alcohol dose dumping study of the proposed drug product, Lorcaserin HCl ER Tablets, 20 mg (APD356-2014-04, orange commercial formulation) was performed using the proposed dissolution method and medium (0.1N HCl, N=12 units/batch) containing 0%, 5%, 20% and 40% alcohol USP. The detailed study report (PDR-15-035) was submitted in M.5.3.1.3. The dissolution test was conducted for 2 hours with sampling time points every 15 minutes. The alcohol dose dumping test conditions were listed in Table 20.

Table 20: Dissolution medium compositions and preparations for in vitro alcohol dose dumping study (from M.5.3.1.3)

Parameter	Medium	Description of Medium Preparation
0% alcohol (reference)[4,5]	0.1 N HCl	(b)(4) mL of concentrated HCl to (b)(4) L of water.
5% alcohol[5,7]	(b)(4) 0.1 N HCl:alcohol USP	mL of concentrated HCl into (b)(4) L of water. Added (b)(4) mL of alcohol USP.
20% alcohol[4,8-11]	0.1 N HCl:alcohol USP	(b)(4) mL of concentrated HCl into (b)(4) L of water. Added (b)(4) L of alcohol USP.
40% alcohol[5,12]	0.1 N HCl:alcohol USP	(b)(4) mL of concentrated HCl into (b)(4) L of water. Added (b)(4) L of alcohol USP.

The mean dissolution profile and individual data of in vitro alcohol dose dumping study were summarized in Figure 13 and Table 21-24 below:

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Figure 13: Dissolution testing of extended-release tablets (orange formulation APD356-2014-04), Lot 1504B080, in 0% (0.1 N HCl), 5%, 20%, and 40% alcohol USP (from M.5.3.1.3)

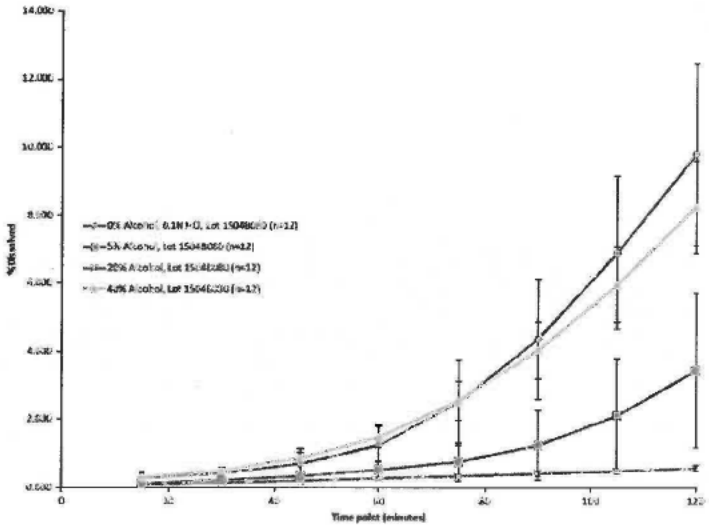

Table 21: Individual results (%dissolved) for dissolution profile of extended-release tablets (orange formulation APD356-2014-04), Lot 1504B080, in 0% alcohol USP (0.1 N HCl) (from M.5.3.1.3)

Unit	%Dissolved							
	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	0.46	0.57	0.59	1.8	3.1	5.0	7.6	10.7
2	0.30	0.37	0.57	0.92	2.1	4.2	6.8	9.7
3	0.41	0.86	2.0	1.9	4.3	6.2	9.3	12.5
4	0.64	0.51	0.61	0.75	1.2	2.1	3.8	5.8
5	0.33	0.29	0.49	0.77	1.5	2.8	4.9	7.5
6	0.25	0.50	0.71	1.0	1.9	3.5	5.9	8.7
7	0.14	0.31	0.54	1.3	2.8	5.0	7.7	10.8
8	0.14	0.30	0.56	1.7	3.9	6.5	9.7	13.1
9	0.11	0.26	0.46	0.95	1.5	3.4	5.7	8.3
10	0.20	0.37	0.88	2.3	4.7	7.7	11.0	14.7
11	0.12	0.24	0.41	0.61	1.1	2.3	4.4	6.9
12	0.16	0.29	0.40	0.65	1.7	3.5	5.9	8.6
Average	0.27	0.41	0.69	1.2	2.5	4.4	6.9	9.8
%RSD	60.8	44.0	64.5	46.6	50.6	40.4	32.6	27.3

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Table 22: Individual results (%dissolved) for dissolution profile of extended-release tablets (orange formulation APD356-2014-04), Lot 1504B080, in 5% alcohol USP (from M.5.3.1.3)

Unit	%Dissolved							
	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	0.10	0.19	0.34	0.72	0.58	0.85	1.0	1.8
2	0.10	0.17	0.24	0.28	0.35	0.48	0.79	1.4
3	0.13	0.20	0.29	0.67	0.82	1.3	2.1	3.6
4	0.12	0.22	0.33	0.45	0.54	0.78	1.4	2.6
5	0.15	0.26	0.28	0.36	0.52	0.76	1.3	2.3
6	0.12	0.29	0.39	0.61	0.84	1.3	2.3	3.6
7	0.03	0.12	0.19	0.25	0.35	0.57	1.0	1.9
8	0.14	0.30	0.58	1.2	2.4	4.2	6.6	9.3
9	0.06	0.13	0.23	0.30	0.38	0.50	0.72	1.2
10	0.09	0.19	0.30	0.41	0.55	0.85	1.8	3.2
11	0.08	0.20	0.31	0.54	0.98	2.0	3.7	5.8
12	0.09	0.19	0.30	0.39	0.60	1.3	2.6	4.4
Average	0.10	0.20	0.32	0.51	0.74	1.2	2.1	3.4
%RSD	34.0	27.6	31.7	50.0	75.4	84.1	79.0	66.5

Table 23: Individual Results (%Dissolved) for Dissolution Profile of Extended-Release Tablets (Orange Formulation APD356-2014-04), Lot 1504B080, in 20% Alcohol USP (from M.5.3.1.3)

Unit	%Dissolved							
	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	0.11	0.16	0.23	0.30	0.37	0.48	0.56	0.66
2	0.07	0.10	0.17	0.21	0.27	0.30	0.35	0.45
3	0.08	0.12	0.19	0.27	0.32	0.42	0.49	0.58
4	0.06	0.11	0.18	0.26	0.30	0.37	0.46	0.54
5	0.09	0.16	0.22	0.28	0.37	0.43	0.53	0.63
6	0.11	0.16	0.23	0.31	0.38	0.49	0.55	0.67
7	0.06	0.10	0.18	0.24	0.25	0.38	0.44	0.50
8	0.04	0.11	0.14	0.23	0.31	0.33	0.37	0.46
9	0.06	0.09	0.17	0.19	0.28	0.35	0.42	0.51
10	0.06	0.15	0.19	0.30	0.37	0.43	0.55	0.65
11	0.05	0.13	0.18	0.28	0.29	0.39	0.44	0.52
12	0.05	0.10	0.18	0.25	0.33	0.37	0.46	0.53
Average	0.07	0.12	0.19	0.26	0.32	0.39	0.47	0.56
%RSD	33.2	21.0	14.6	14.2	13.6	14.8	14.8	14.1

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Table 24: Individual results (%dissolved) for dissolution profile of extended-release tablets (orange formulation APD356-2014-04), Lot 1504B080, in 40% alcohol USP (from M.5.3.1.3)

Unit	%Dissolved							
	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	0.36	0.55	1.1	2.0	3.3	5.1	7.2	9.8
2	0.42	0.62	1.0	1.8	3.1	4.7	6.9	9.6
3	0.36	0.53	0.83	1.4	2.4	3.7	5.6	7.8
4	0.37	0.62	1.0	1.8	3.0	4.7	6.9	9.4
5	0.41	0.56	0.86	1.4	2.5	3.9	5.8	8.1
6	0.34	0.49	0.83	1.5	2.6	4.1	6.0	8.3
7	0.20	0.34	0.62	1.0	1.7	2.6	4.0	5.7
8	0.22	0.37	0.68	1.2	2.1	3.3	5.0	7.1
9	0.19	0.38	0.71	1.1	1.9	3.1	4.8	7.0
10	0.26	0.46	0.83	1.3	2.3	3.8	5.8	8.0
11	0.22	0.52	1.0	2.0	3.5	5.5	7.8	10.5
12	0.21	0.41	0.77	1.3	2.3	3.8	5.6	7.8
Average	0.30	0.49	0.85	1.5	2.5	4.0	6.0	8.2
%RSD	30.1	19.5	17.3	22.1	22.5	20.6	18.5	16.5

(2) Solubility of drug substance in alcohol

Solubility of drug substance, Lorcaserin HCl Hemihydrate, in the presence of alcohol was submitted in M.3.2.P.2.1. The drug substance showed high solubility in 0.1N HCl with different levels of alcohol with independence of alcohol level (Table 25).

Table 25: Solubility of Lorcaserin HCl Hemihydrate 0.1 N HCl with varying amounts of alcohol after 4 days at 37°C (from M.3.2.P.2.1)

Medium	Average Solubility[a] (mg/mL)	%RSD	%Relative Difference vs. 0.1-N HCl
0.1 N HCl	848.5	1.3	Not applicable
5% ethanol in 0.1 N HCl	868.1	1.0	2.3
20% ethanol in 0.1 N HCl	864.7	1.2	1.9
40% ethanol in 0.1 N HCl	878.6	2.1	3.5

Reviewer's Assessment:

Based on the results, the proposed drug product is considered to have no in vitro alcohol dose dumping potential within the first 2 hours. The above results had been communicated to the OCP review team. OCP agreed that there is no dose dumping potential after reviewing the submitted multiple in vivo BA/BE studies. Therefore, both of DB and OCP agreed that no in vivo alcohol dose dumping study is needed.

Reference ID: 3963811

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

From Biopharmaceutics perspective:

- The proposed in vitro dissolution method for the drug product, BELVIQ XR® Lorcaserin HCl ER Tablets, 20 mg, is acceptable with adequate discriminating ability.
- The in vitro dissolution method validation for the proposed drug product is well established and acceptable.
- The submitted IVIVC modeling is not acceptable to support the proposed dissolution specification for the target (b) (4) release formulation drug product, especially for 5 hour time point specification. Because the submitted data already met the specification as a mean target dissolution (b) (4) % variation without a validated IVIVC, therefore, the Applicant accepted the Agency's recommended specification as quality control for their proposed drug product. The Applicant also revised the related sections in this NDA submission to reflect the updated dissolution specification.
- The proposed drug product showed no in vitro alcohol dose dumping potential within the first 2 hours.
- The agreed in vitro dissolution method and specification for the proposed drug product are summarized as below:

Apparatus	I (Basket)
Medium	0.1N Hydrochloride Acid, deaerated
Volume	900 mL
Rotation Speed	100 rpm
Temperature	37°C ± 0.5°C
Sampling Time	1, 2, 4, 5, 6, 8, 10, 12, 14 and 20 hours
Specifications	2 hours: NMT (b) (4) % 5 hours: (b) (4) % 14 hours: NLT (b) (4) %

OVERALL COMMENTS:

This NDA 208524 for drug product, BELVIQ XR® (Lorcaserin HCl) Extended-Release (ER) Tablets, 20 mg, is reviewed and found acceptable from the Biopharmaceutics perspective; therefore, this NDA 208524 is recommended for APPROVAL.

Reference ID: 3963811

Mei Ou -S

Digitally signed by Mei Ou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mei Ou -S, 0.9.2342.19200300.100.1.1=2001622313
Date: 2016.05.23 12:11:15 -04'00'

Mei Ou, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Products

Secondary Review Comments and Concurrence:

I concur. 05/21/16

Tienmien Chen -S

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Date: 2016.05.23 12:50:46 -04'00'

Tien-Mien Chen, Ph.D.
Acting Biopharmaceutics Lead
Office of New Drug Products

Reference ID: 3963811

ASSESSMENT OF MICROBIOLOGY

10. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: Microbial limits testing has been performed according to USP <61>/Ph. Eur. 2.6.12 and USP <62>/Ph. Eur. 2.6.13

Reviewer's Assessment: See question 34.

2.3.P.7 Container/Closure System

11. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response: N/A

Reviewer's Assessment: N/A

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

12. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response: The excipients in lorcaserin HCl 20-mg extended-release tablets are not of human or animal origin nor do they come in contact with products of human or animal origin during their manufacture. The potential specified risk material (SRM) used

in the formulation is magnesium stearate. The magnesium stearate used is of vegetable origin.

Reviewer's Assessment: Adequate

The TSE/BSE free certificates for excipients that are made from vegetable origins are not required. This is adequate.

13. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: N/A

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Adequate. Oxana Selivanova, 4/25/16

Secondary Review Comments and Concurrence: Concur, Pei-I Chu, 05/11/2016