

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022529Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-529

Belviq (lorcaserin hydrochloride) tablets

Arena Pharmaceuticals, Inc.

Olen M. Stephens
Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch VII
for the
Division of Metabolism and Endocrinology Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE [Name, Manufacturer].....	9
P DRUG PRODUCT [Name, Dosage form].....	13
A APPENDICES	20
R REGIONAL INFORMATION	21
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	21
A. Labeling & Package Insert	21
B. Environmental Assessment Or Claim Of Categorical Exclusion	21
III. List Of Deficiencies To Be Communicated.....	21

Chemistry Review Data Sheet

1. NDA 22-529
2. REVIEW #: 2
3. REVIEW DATE: 4-May-2012
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment (0034)* -- Resubmission

23-Dec-2011

Amendment (0047) – Stability Data

27-Jan-2012

* The amendment sequence in eCTD is not chronological. In DARRTS this amendment is listed as supporting document 0046.

7. NAME & ADDRESS OF APPLICANT:

Name:	Arena Pharmaceuticals, Inc.
Address:	6166 Nancy Ridge Drive San Diego, CA 92121
Representative:	Craig Audet, Vice President, Reg. Affairs
Telephone:	858-453-7200; ext 1612

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lorquess
b) Non-Proprietary Name (USAN): Lorcaserin hydrochloride, tablets
c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1 (new molecular entity)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Weight management

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride hemihydrate;

$C_{11}H_{15}Cl_2N \cdot 0.5H_2O$

Molecular Weight: 241.16 g/mol

Molecular Weight of the free base: 195.69 g/mol

(b) (4)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	04-Jun-10	No change as of Jan-20-12
	III		4	N/A			
	III		4	N/A			
	III		4	N/A		(b) (4)	
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	III		4	N/A			
	II		1	Adequate	04-Jun-10	No amendments since last review	
	III	4	N/A		Only contact is through seal		

Chemistry Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP2 Meeting minutes	IND 69,888	Agency agreements & advice
Pre-NDA Meeting minutes	IND 69,888	Agency agreements & advice
Original Application	NDA 22-529	Review Cycle 1

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	06-Jan-2012	(re-evaluation 23-Jul-2012)

The Chemistry Review for NDA 22-529

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-529 received a complete response on 22-Oct-2010 on the basis of nonclinical and clinical deficiencies. There were no pending CMC deficiencies from the first cycle of review and there are no pending deficiencies to resolve. The overall recommendation from the Office of Compliance for GMP inspections is 'acceptable' (6-Jan-2012). The CMC recommendation for NDA 22-529 is for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Arena Pharmaceuticals submitted NDA 22-529 in support of a new molecular entity, lorcaserin hydrochloride, indicated for weight management. The drug product is an immediate release film-coated tablet with 10-mg Lorcaserin HCl. The drug substance is lorcaserin HCl hemihydrate. All excipients are common and compendial, with the exception of the (b) (4) and the silicified microcrystalline cellulose, which is (b) (4).

The drug product is stored at room temperature conditions (25°C [77°F]; excursions 15-30°C [59-86°F]). 24 months of long-term stability data on the primary stability batches support an expiration dating period of 36 months for lorcaserin HCl 10-mg tablets packaged in the proposed commercial presentation (60cc 100-count high-density polyethylene [HDPE] bottle); an expiration period of 24 months for lorcaserin HCl 10-mg tablets packaged in the proposed physician sample (10-count blister strips) is also granted. All registration batches are at least (b) (4) intended commercial scale.

The lorcaserin HCl 10-mg tablets are round, biconvex, film-coated, blue-colored, immediate-release tablets that are debossed with an "A" on one side and a "10" on the other side. In addition to the primary stability batches, supportive stability data is provided for tablet formulations that are the same except for product identifiers, i.e., color and debossing codes.

Several Designs of Experiments (DoE's) were conducted in the drug product manufacturing development; however, Arena is *not* claiming a Design Space. These DoE's were

Executive Summary Section

conducted to enhance process understanding only. Control of the manufacturing process is maintained through the traditional control of process parameters.

The USAN and INN name for the drug substance is lorcaserin HCl, which is a new molecular entity with one chiral center. Lorcaserin HCl hemihydrate drug substance was granted BCS Class I status for its high solubility (>400 mg/mL in aqueous solutions with no pH effect) and high availability. The maximum daily dose is 20 mg anhydrous lorcaserin hydrochloride (i.e. two 10-mg tablets daily). Two acceptable manufacturing sites will supply the drug substance (b) (4). All individual impurities are limited to NMT (b) (4) as per ICH Q3A with the exception of (b) (4) which is controlled at NMT (b) (4). 36-months of stability data supports a (b) (4) retest date for the drug substance as per ICH Q1E.

B. Description of How the Drug Product is Intended to be Used

The drug product will be dispensed by prescription only, indicated for weight management with a reduced-calorie diet and a program of regular exercise. The recommended dose is 10 mg twice daily with or without food. The bottle configurations are heat induction-sealed (HIS) with a child resistant (CR) closure. The 60cc bottle with a 100-count fill is intended for initial commercial launch. The 10-count blisters will be used as physician samples. A 36-month expiration date is granted to the 100-ct HDPE bottle configuration when stored at room temperature conditions (25°C [77°F]; excursions 15-30°C [59-86°F]). (b) (4)

As such, an expiration period of 24 months is granted for lorcaserin HCl 10-mg tablets packaged in the proposed physician sample (10-count blister strips) when stored at room temperature conditions.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug substance and drug product were communicated 06-Jun-2010 and have been adequately addressed. There are no CMC deficiencies and the OC has rendered an acceptable recommendation (6-Jan-2012).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Olen M. Stephens
Chemistry Branch Chief: Ali Al Hakim

C. CC Block

CMC Lead: Suong Tran
Project Managers: Patricia Madara, Don Henry, and Khushboo Sharma

18 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

OLEN M STEPHENS

05/04/2012

CMC Recommendation: Approval

ALI H AL HAKIM

05/04/2012

NDA 22-529

Lorqess, (lorcaserin hydrochloride) tablets

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Arena Pharmaceuticals, Inc.
6166 Nancy Ridge Drive
San Diego, CA 92121

Indication: Weight management with a reduced-calorie diet and a program of regular exercise.

Presentation: The drug product will be marketed in bottle that are heat induction sealed (HIS) with a child resistant (CR) closure. The 60cc bottle with a 100-count fill is intended for initial commercial launch. The 10-count blisters will be used as physician samples. The product is stored at room temperature, protected from heat and moisture.

Establishments Evaluation Report (EER) Status: Acceptable

Consults:	EA –	Acceptable
	Statistics –	N/A
	Methods Validation –	Not recommended
	Biopharm–	Satisfactory
	Microbiology –	N/A
	Pharm/toxicology –	Satisfactory

Original Submission: December 18, 2009

Re-submissions: N/A

Post-Approval CMC Agreements: None beyond the typical post-approval stability protocol and agreements, there are no other CMC agreements or risk management steps.

Background:

This is a 505(b)(1) application. The associated IND is IND 69888. The drug substance lorcaserin hydrochloride hemihydrate is a New Molecular Entity (NME) and a small synthetic compound. It is a selective serotonin 2C agonist indicated for weight management. The drug product is a 10 mg (anhydrous) lorcaserin hydrochloride immediate-release tablet. Maximum daily dose is 20 mg anhydrous lorcaserin hydrochloride (i.e., two 10-mg tablets daily).

Drug Substance:

The USAN and INN name for the drug substance is lorcaserin HCl, which is a new molecular entity with one chiral center. Lorcaserin HCl hemihydrate drug substance was granted

BCS Class I status for its high solubility (>400 mg/mL in aqueous solutions with no pH effect) and high availability.

Chemical name, structural formula, molecular formula and molecular weight



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

Molecular formula: C₁₁H₁₅Cl₂N·0.5H₂O

Molecular weight: 241.16g/mole

The drug substance (Lorcaserin HCl) is chemically synthesized via a series of chemical reactions starting with compound (b) (4) (see above scheme).

Except for the (b) (4), the impurities are limited at 0.10% as per ICH Q3A identification threshold. The (b) (4) is limited to (b) (4) and it is excluded from qualification and identification thresholds as allowed by ICH Q6A. The ClinPharm filing review states that there is no in vitro or in vivo chiral conversion. Specifications for the drug substance include Identity (FTIR and HPLC), Impurities, (b) (4) (b) (4) and Absorbance of solution.

24-months of stability data supports a (b) (4) retest date as per ICH Q1E.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is formulated as a tablet with the following excipients: silicified microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, (b) (4) Lorcasein HCl 10-mg tablets intended for commercial distribution are round, biconvex, filmcoated, blue-colored, immediate-release tablets. Identifiers include a debossed “A” on one side of the tablet and a “10” on the other. The manufacturing of the tablet i (b) (4)

Drug product specifications include appearance (visual), identity by HPLC (achiral and chiral), content uniformity (USP 905), assay (HPLC), degradation products, dissolution, (b) (4) and microbial limits.

A 36-month expiration date is granted to the 100-ct HDPE bottle configuration when stored at room temperature conditions (25°C [77°F]; excursions 15-30°C [59-86°F]).

Conclusion: Drug product is satisfactory.

Additional Items: All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: The CMC recommendation for NDA 22-529 is approval. There are no pending deficiencies to resolve.

Eric Duffy, Ph.D.
Director, Division III
ONDQA/CDER

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

/s/

ERIC P DUFFY
10/22/2010

**CMC Memo to File**

To:	NDA
Date	30 Sep 2010
Sponsor:	Arena Pharmaceuticals, Inc.
Drug:	Lorqess (lorcaserin hydrochloride) tablets
Subject	Approval recommendation
Reviewer	Dr. Olen Stephens

Pursuant the overall “acceptable” recommendation given on 29-Sep-2010 for the manufacturing facilities by the Office of Compliance and FONSI issued 15-Sep-2010 by the OPS Environmental Assessment Team, CMC recommends that NDA application 22-529 be approved. All labeling changes have been communicated to the applicant through the clinical project manager. There are no pending CMC deficiencies.

HFD-/Division File
HFD-510
HFD-510/P. Madara

Olen Stephens, Ph.D.
Chemistry Reviewer

Ali Al-Hakim, Ph.D.
Branch VII Chief, ONDQA

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

/s/

OLEN M STEPHENS

09/30/2010

CMC recommendation: Approval

No pending deficiencies

ALI H AL HAKIM

09/30/2010

NDA 22-529

Lorqess, (lorcaserin hydrochloride) tablets

Arena Pharmaceuticals, Inc.

**Olen M. Stephens
Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch VII
for the
Division of Metabolism and Endocrinology Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	8
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [Name, Manufacturer].....	10
P DRUG PRODUCT [Name, Dosage form].....	70
A APPENDICES	106
R REGIONAL INFORMATION	106
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	106
A. Labeling & Package Insert	106
B. Environmental Assessment Or Claim Of Categorical Exclusion	106
III. List Of Deficiencies To Be Communicated.....	107

Chemistry Review Data Sheet

1. NDA 22-529
2. REVIEW #: 1
3. REVIEW DATE: 23-AUG-2010
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original submission

18-Dec-2009

Amendment (0001) – Response to Inspection
readiness

31-Dec-2009

Amendment (0018) – Response to CMC
Information Request

16-Jul-2010

Amendment (0020) – Response to CMC
Information Request

20-Jul-2010

Amendment (0023) – Change in Dissolution
Specifications

3-Aug-2010

Amendment (0026) – Response to CMC
Information Request

12-Aug-2010

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Arena Pharmaceuticals, Inc.
Address: 6166 Nancy Ridge Drive
San Diego, CA 92121
Representative: Mark Brunswick, Ph.D., Sr. Director, Reg. Affairs
Telephone: 858-453-7200

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lorquess
- b) Non-Proprietary Name (USAN): Lorcaserin hydrochloride, tablets
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Weight management

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate;

C₁₁H₁₅Cl₂N•0.5H₂O

Molecular Weight: 241.16 g/mol

Molecular Weight of the free base: 195.69 g/mol



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b)(4)	II	[Redacted]	[Redacted]	(b)(4)	1	Adequate	04-Jun-10
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		(b)(4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		Only contact is through seal
	III			4	N/A		

Chemistry Review Data Sheet

(b) (4)	III		(b) (4)	4	N/A		
	III		4	N/A			
	II		1	Adequate	04-Jun-10		
	III		4	N/A		Only contact is through seal	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
EOP2 Meeting minutes	IND 69,888	Agency agreements & advice
Pre-NDA Meeting minutes	IND 69,888	Agency agreements & advice

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Pending		John Duan, Ph.D.
LNC	N/A		
EA	Pending		

The Chemistry Review for NDA 22-529

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC recommendation for NDA 22-529 is for approval. There are no pending deficiencies to resolve.

Note: The overall recommendation from the Office of Compliance for GMP inspections is still pending; the CMC recommendation does not incorporate any potential facility inspection issue.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Other than the typical post-approval stability protocol and agreements, there are no other CMC agreements or risk managements steps. Dissolution specifications and microbial limits testing specifications were adjusted during the review process, but are adequately controlled at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Arena Pharmaceuticals has submitted NDA 22-529 in support of a weight management drug, a New Molecular Entity named "lorcaserin hydrochloride". The drug product is an immediate release film-coated tablet with 10-mg Lorcaserin HCl. The drug substance is lorcaserin HCl hemihydrate. All excipients are common and compendial, with the exception of the (b) (4) and the silicified microcrystalline cellulose, (b) (4).

The drug product is stored at room temperature conditions (25°C [77°F]; excursions 15-30°C [59-86°F]). 24 months of long-term stability data on the primary stability batches support an expiration dating period of 36 months for lorcaserin HCl 10-mg tablets packaged in the proposed commercial presentation (60cc 100-count high-density polyethylene [HDPE] bottle), and an expiration period of 24 months for lorcaserin HCl 10-mg tablets packaged in the proposed physician sample (10-count blister strips). All registration batches are at least (b) (4) intended commercial scale.

The lorcaserin HCl 10-mg tablets are round, biconvex, film-coated, blue-colored, immediate-release tablets that are debossed with an "A" on one side and a "10" on the other side (market-image tablet). In addition to the primary stability batches, supportive stability data

Executive Summary Section

is provided for tablet formulations that are the same except for product identifiers, i.e., color and debossing codes.

Several Designs of Experiments (DoE's) were conducted in the drug product manufacturing development; however, Arena is *not* claiming a Design Space. These DoE's were conducted to enhance process understanding only. Control of the manufacturing process is maintained through the traditional control of process parameters.

The USAN and INN name for the drug substance is lorcaserin HCl, which is a new molecular entity with one chiral center. Lorcaserin HCl hemihydrate drug substance was granted BCS Class I status for its high solubility (>400 mg/mL in aqueous solutions with not pH effect) and high availability. The maximum daily dose is 20 mg anhydrous lorcaserin hydrochloride (i.e. two 10-mg tablets daily). Two acceptable manufacturing sites will supply the drug substance (b)(4). All individual impurities are limited to NMT 0.10% as per ICH Q3A with the exception of (b)(4), which is controlled at NMT (b)(4). 24-months of stability data supports a (b)(4) retest date as per ICH Q1E.

B. Description of How the Drug Product is Intended to be Used

The drug product will be dispensed by prescription only, indicated for weight management with a reduced-calorie diet and a program of regular exercise. The recommended dose is 10 mg twice daily with or without food. The bottle configurations are heat induction-sealed (HIS) with a child resistant (CR) closure. The 60cc bottle with a 100-count fill is intended for initial commercial launch. The 10-count blisters will be used as physician samples. A 36-month expiration date is granted to the 100-ct HDPE bottle configuration when stored at room temperature conditions (25°C [77°F]; excursions 15-30°C [59-86°F]). (b)(4)

As such, an expiration period of 24 months is granted for lorcaserin HCl 10-mg tablets packaged in the proposed physician sample (10-count blister strips) when stored at room temperature conditions.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug substance and drug product were communicated 06-Jun-2010 and have been adequately addressed.

The facilities used in the manufacturer and control of the drug substance and drug product have been submitted for evaluation to the Office of Compliance and are pending an overall recommendation.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Olen M. Stephens
Chemistry Branch Chief: Ali Al Hakim

Executive Summary Section

C. CC Block

CMC Lead: Suong Tran

Project Managers: Patricia Madara, Don Henry, and Khushboo Sharma

102 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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

/s/

OLEN M STEPHENS
08/23/2010
CMC Recommendation:
approval pending recommendation of OC

ALI H AL HAKIM
08/23/2010

Initial Quality/CMC Assessment
ONDQA

Division of Metabolism and Endocrinology Products

NDA: 22529

Applicant: Arena Pharmaceuticals

Stamp Date: 18-DEC-2009

PDUFA Date: 18-OCT-2010

Proposed Proprietary Name: Lorqess

Established Name: Lorcaserin hydrochloride hemihydrate

Dosage form and strength: Immediate release tablet –
10 mg (lorcaserin HCl, anhydrous)

Route of Administration: oral

Indications: Weight management

CMC Lead: Su (Suong) Tran, Branch II/DPA I/ONDQA

ONDQA Fileability: Yes

Initial Quality/CMC Assessment
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	<i>May Not Be Applicable: No biowaiver request. BCS determination will be completed by the ClinPharm team.</i>
CDRH or CBER	<i>Not Applicable</i>
EA	The claimed categorical exclusion will be assessed by Primary Reviewer.
EES	EER was created and sent to Compliance on 22-JAN-2010 by Don Henry (ONDQA PM)
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>May Not Be Applicable: solid oral dosage form.</i>
Pharm/Tox	No impurity/degradant (non-genotoxic) exceeds applicable ICH qualification thresholds. A consult may be requested for the evaluation of the potential genotoxic impurities.

This is a 505(b)(1) application. The associated IND is IND 69888.

The drug substance lorcaserin hydrochloride hemihydrate is a New Molecular Entity (NME) and a small synthetic compound. It is a selective serotonin 2C agonist indicated for weight management. The drug product is a 10 mg (anhydrous) lorcaserin hydrochloride immediate-release tablet. The inactive ingredients are: silicified microcrystalline cellulose; hydroxypropyl cellulose NF; croscarmellose sodium NF; colloidal silicon dioxide NF, polyvinyl alcohol USP, polyethylene glycol NF, titanium dioxide USP, talc USP, FD&C Blue #2 aluminum lake, and magnesium stearate NF. The commercial packaging is a 100-count bottle and a 10-count blister pack. The product is stored at room temperature, protected from heat and moisture.

Maximum daily dose is 20 mg anhydrous lorcaserin hydrochloride (i.e., two 10-mg tablets daily).

Initial Quality/CMC Assessment ONDQA

Has all information requested during the IND phases, and at the pre-NDA meetings been included?

The NDA includes some information as requested by FDA during the IND development. There is no item-by-item response to FDA's comments, which makes it difficult to assess in the limited time allotted for this filing memo/IQA whether the applicant has provided a satisfactory response to each question. The primary reviewer will assess the information in the NDA and decide whether issues previously raised have been satisfactorily addressed. The reviewer will also confirm that information previously agreed upon by FDA and the sponsor has not been changed in its final version in the NDA (for example, specifications, packaging systems, etc.) Major issues discussed in FDA letters dated 24-JUN-2008 and 16-JUN-2006 include:

- Data package (stability, characterization, dissolution, etc.) to support two different commercial manufacturers of the drug substance [REDACTED] (b) (4) and the change in the drug product manufacturer (from [REDACTED] (b) (4) phase 3 clinical product to Arena: commercial product)
- Starting material [REDACTED] (b) (4) (acceptability of its specification)
- Drug substance specification (acceptability of acceptance criteria and justification for the lack of testing for polymorph and particle size)
- Drug product specification (acceptability of acceptance criteria and justification for the lack of testing for dissolution, [REDACTED] (b) (4) impurity, and polymorph)
- Stability data to support the physician sample packaging

Initial Quality/CMC Assessment
ONDQA

Drug substance:

Lorcaserin hydrochloride (lorcaserin HCl) is a new chemical entity. The drug substance is the hemihydrate, lorcaserin hydrochloride hemihydrate (lorcaserin HCl HH), which is solid (b) (4). Lorcaserin HCl HH is very soluble in water (< 1 mL of water needed to dissolve 1 g of compound). It is a monobasic compound having pK_a 9.53 and logP 2.56. Although no polymorphism has been observed for the hemihydrate, the anhydrous HCl salt was observed to have (b) (4). Anhydrous lorcaserin HCl was used for Phase 1, Phase 2, and first Phase 3 clinical trials, but all anhydrous forms convert to the hemihydrate (b) (4) upon exposure to typical humidities. The hemihydrate, whose (b) (4) form are stable across a wide range of humidities, was therefore selected as the drug substance for two Phase 3 clinical trials, formulation development, and commercialization. Further details on general properties of lorcaserin HCl HH are provided in 3.2.S.1.3, General Properties [Lorcaserin HCl Hemihydrate, (b) (4)].

Name: lorcaserin hydrochloride hemihydrate

CAS registry number: 856681-05-5

Structural formula:



Molecular formula: C₁₁H₁₅Cl₂N·0.5H₂O

Molecular weight: 241.16 g/mol

Melting point: On heating at 10°C/min, lorcaserin HCl HH (b) (4) dehydrates between 80°C and 120°C to anhydrous (b) (4) which melts at onset 199°C

Review comments:

- **Polymorphism and particle size.** Based on the information provided by the applicant (previously requested by FDA), the primary reviewer will determine whether testing for the polymorph and particle size of the drug substance should be included in the drug substance specification. The applicant states that the hemihydrate (b) (4) was the drug substance used for the clinical product of two Phase 3 clinical studies and is the same as that of the commercial product.
- **Two alternate manufacturers of the drug substance.** Based on the data package provided by the applicant (previously requested by FDA), the reviewer will determine whether the

Initial Quality/CMC Assessment ONDQA

information (stability, characterization, dissolution, etc.) is adequate to support two different commercial manufacturers of the drug substance (b) (4). The same regulatory specification is used by both manufacturers (see copied on pages 19-20 of this review). Based on the characterization report, the reviewer will evaluate the adequacy of the proposed specification in defining the identity, purity, strength, and consistency of the drug substance.

- **Impurities.** Except for the (b) (4), the impurities are limited at 0.10% as per ICH Q3A identification threshold. The (b) (4) (b) (4) is limited to (b) (4) and it is excluded from qualification and identification thresholds as allowed by ICH Q6A. The ClinPharm filing review states that there is no in vitro or in vivo chiral conversion. The applicant states that there is no impurity in the (b) (4)

(b) (4)
The reviewer will determine whether the lack of specified impurities and the limit on the (b) (4) impurity are adequately justified based on all available data. The reviewer will also evaluate the applicant's statement that potential genotoxic impurities (see structures on page 21 of this review) in the drug substance are present at levels less than (b) (4) and confirm with the PharmTox team that these levels are below the threshold of toxicological concern for the maximum daily dose of 20 mg.

Initial Quality/CMC Assessment
ONDQA

Drug product

The composition of the drug product is copied below.

Table 1. Composition of Lorcaserin HCl Tablets

Component	Grade	Function	mg/tablet	%w/w
Core				
Lorcaserin HCl Hemihydrate	Arena	Drug substance	(b) (4)	(b) (4)
Silicified microcrystalline cellulose ^b	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hydroxypropyl cellulose	NF	(b) (4)	(b) (4)	(b) (4)
Croscarmellose sodium	NF	(b) (4)	(b) (4)	(b) (4)
Magnesium stearate	NF	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)	(b) (4)

^a Equivalent to 10 mg lorcaserin HCl.

^b Detailed information and qualitative compositions can be found in 3.2.P.4, Control of Excipients [Lorcaserin HCl, Tablet, 10 mg].

(b) (4)

Review comments:

- Established name and dosage strength.** The proposed established name of the product is “lorcaserin hydrochloride”, which is acceptable because it correlates with the dosage strength of 10 mg of the anhydrous salt, as per current CDER policy on nomenclature. The reviewer will ensure that the full amount of the hemihydrate salt is included in the prescribing information and packaging labels, but it should not have the prominence as the dosage strength.
- Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that, except for the color, the commercial formulation is the same as for the Phase 3 studies APD356-010 and ADP356-011 (white tablets) lots 3057171R, 3057172R, 3057173R and the PK studies APD356-015, APD356-016, and APD356-018 (blue

Initial Quality/CMC Assessment
ONDQA

commercial tablets) lots 3064542R, 0818B002, 0820B008. The clinical lots 0818B002 and 0820B008 (commercial formulation, blue tablets) are also the primary stability batches and were manufactured at the commercial manufacturer Arena GmbH.

- **Noncompendial excipients.** Silicified microcrystalline cellulose and (b) (4) are noncompendial excipients that are composed of compendial ingredients. None of the ingredients is novel. Silicified microcrystalline cellulose (b) (4) (b) (4) is polyvinyl alcohol (b) (4) (b) (4) USP, (b) (4) NF, titanium dioxide USP, talc USP, FD&C Blue # (b) (4) aluminum lake (b) (4) The reviewer will evaluate the referenced DMFs (b) (4) (Silicified microcrystalline cellulose) and (b) (4) (b) (4) as necessary and confirm whether the amount of each ingredient is within the levels previously approved for other products of the same dosage form and route of administration.

17 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22529	ORIG-1	ARENA PHARMACEUTICA LS INC	LORQESS (lorcaserin hydrochloride) Tablets

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

/s/

SUONG T TRAN
02/17/2010

PRASAD PERI
02/17/2010
I concur