CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-331

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-331

CC:

From: Amit K. Mitra, Ph.D

Through: Ramesh Sood, Ph.D

Date: 9/29/2009

Re: NDA 22-331, Memo to the file.

The CMC reviewer via Chemistry review # 3, dated 25-SEP-2009 recommended that the established name be changed to "Clonidine hydrochloride tablets". Since then the applicant has submitted the revised container label and PI with the recommended change. Therefore, the application is now recommended to be approved with respect to CMC.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICALS INC	JENLOGA
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICALS INC	JENLOGA

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

/s/

AMIT K MITRA
09/29/2009

RAMESH K SOOD
09/29/2009

Jenloga
(clonidine hydrochloride) tablets
NDA 22-331

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Addrenex Pharmaceuticals, Inc.
Durham, NC 27703

Indication: Indicated for the treatment of hypertension.

Presentation: Jenloga (clonidine hydrochloride) tablets, 0.1 mg, are available in the following packaging configurations.

— bottles, 30 cc (60 count). b(4)
— bottles, 40 cc (180 count)

EER Status: Acceptable, 4-Jun-09

Consults: ONDQA Biopharmaceutics : The ONDQA biopharmaceutics reviewer and the company has agreed upon the following revised acceptance criterion for the drug product.

	% Released			
pH	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Accepted limits	—	—	—	—

b(4)

Methods Validation – Revalidation by Agency was not requested.
EA – categorical exclusion granted

II. Summary of Chemistry Assessments

The applicant has provided response to the CMC deficiencies identified in the previous review cycle. The deficiencies were reviewed and found to be acceptable in this review cycle. There are only two pending issues that remain unresolved at the time of writing this memorandum. One issue relates to the dosage form designation for this product. The firm had initially designated this product as extended-release tablets. The product shows extended-release characteristics in the in vitro dissolution test. However, this product is indicated to be taken twice-a-day which is the same dosing frequency that is approved for

the currently approved immediate product Catapres (NDA-17-407). The FDA Data Standard Manual (DST) defines an extended-release tablet as "a solid dosage form containing a drug which allows at least a reduction in dosing frequency as compared to that drug presented in conventional dosage form". [

b(4)

] This matter was discussed with the ONDQA Labeling and Nomenclature Committee (LNC). The committee recommended that the product should be considered as conventional immediate release product and labeled accordingly. The alternate designation of "modified release" was also found to be unacceptable because this dosage form is not an FDA and USP recognized dosage form. Based on these considerations, it is recommended that this product be considered as immediate release tablets and labeled as "Tablets" accordingly.

Based on the available data a shelf life of 24 months may tentatively be granted for the product when stored under controlled room temperature.

Overall conclusion: The "approval" recommendation from CMC perspective is contingent upon "Tablets" dosage form designation of the product. The agreed upon dissolution acceptance criteria should be included in the action letter.

Additional Items: None

Ramesh Sood, Ph.D.
Branch Chief/DPA1/Branch 1/ONDQA

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

/s/

RAMESH K SOOD
09/25/2009

NDA 22-331

JENLOGA (Clonidine hydrochloride) tablets

Addrenex Pharmaceutical Co. Ltd
Amit K. Mitra, Ph.D
Office of New Drug Quality Assessment

Reviewed for the Division of Cardiovascular and Renal Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-331

2. REVIEW #3

3. REVIEW DATE: 25-SEP-2009

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	15-FEB-2008 15-FEB-2008
Amendment	15-MAY2008 15-MAY-2008
Amendment	07-NOV-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (Complete Response)	27-MAR-2009
Amendment	27-JUL-2009
Amendment	14-AUG-2009
Amendment	25-AUG-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Addrenex Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Address:	4825 Creekstone Drive, Suite 100, Durham, NC 27703
Representative:	Mr. Moise Khayrallah
Telephone:	(919)-941-0800 x 202

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: JENLOGA
b) Non-Proprietary Name (USAN): Clonidine hydrochloride. Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.1 mg

13. ROUTE OF ADMINISTRATION: Oral

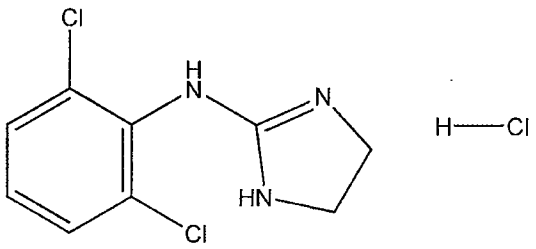
14. Rx/OTC DISPENSED: x___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride



Molecular Formula: $C_9H_9Cl_2N_3.HCl$; Molecular Weight: 266.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	2	—	Clonidine hydrochloride		1	24-SEP-2008	See Chemistry Review # 3, Adequate to support the NDA 22-331
—	3	—	—		4		
—	3	—	—		4		
—	3	—	—		4		

b(4)

Chemistry Review Data Sheet

—	3	—			4		
—	3	—			4		
—	3	—	Packaging components (nothing specific)		4		
—	4				4		
—	4		Magnesium stearate, dated 6-SEP-2002		3	23-JUL-2004	See Chemistry Review #3, Adequate to support NDA 21-592
—	3	—	—		4		

b(4)

[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

Chemistry Review Data Sheet

IND	75614	Original IND for treatment of hypertension

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None		
EES	Satisfactory	4-JUN-2009	Ms. S. L. Adams
Pharm/Tox	None		
Biopharm	Satisfactory, based on a T.con agreement	23-SEP-2009	Dr. T. Ghosh
LNC	Established name is recommended to be "Clonidine hydrochloride tablets" unless the clinical division objects	01-DEC-2008 and 02-DEC-2008 E-mail	Dr. Rik Lostritto and Ms. Yana Mille
Methods Validation	None		
DMEPA	Trademark Jenloga is acceptable	13-AUG-2009	Ms. Latoya S Toombs
EA	Categorical exclusion request provided	12-NOV-2008	Dr. Amit Mitra
Microbiology	None		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-331

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can not be approved at the current form from CMC perspective unless the applicant agrees to revise the established name from "Clonidine hydrochloride modified release tablets" to "Clonidine hydrochloride tablets", as proposed in item C.

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)

The drug substance chemistry, manufacturing control information is cross referenced to DMF —— The DMF is adequate to support this NDA. All issues with drug substance were resolved in this review cycle. b(4)

The drug product is manufactured at one strength (100 mcg) as an extended release (in vitro) tablet dosage form with a tablet weight of 120 mg. Each tablet contains 100 mcg of clonidine hydrochloride, —— sodium lauryl sulfate, —— mg lactose monohydrate, —— hypromellose type 2208, —— partially gelatinized starch, —— ; colloidal silicon dioxide, and —— magnesium stearate. The drug product is manufactured by a [ ] Some of the steps in the manufacturing process are [ ] For the drug product to deliver consistent dose of clonidine hydrochloride the uniformity of clonidine hydrochloride, [ ] needs to be maintained in the whole batch. The sponsor has manufactured 3 commercial scale batches to produce tablets with acceptable content uniformity of clonidine hydrochloride. However, the applicant's quality control is based on end product testing using only small number of tablets. Therefore, the sponsor was requested to introduce several controls for drug substance and the excipients and the sponsor adopted those controls. The sponsor was requested to adopt a blend uniformity test to provide statistical assurance that the tablets in a batch are uniform with respect to clonidine hydrochloride. Even though, ——— is not an ideal process [ ] for such a low dose b(4)

tablet (0.1 mg/tablet) according to the reviewer, the applicant was able to maintain blend uniformity in the three batches. Blend uniformity would also be the part of in-process test during routine production.

The applicant was requested to develop a stability indicating assay method for determination of impurities in the drug product. The applicant successfully developed a stability indicating assay method in this review cycle.

The sponsor conducted two clinical studies with the proposed formulation. The first study was a single dose PK trial. The second study was a double blind dose ranging PK study with 0.2 mg, 0.4 mg, or 0.6 mg in twice daily dosing regimen for 26 day. A single lot of the clinical supply was used during the clinical trial.

The Information Request (see Chemistry Assessment) sent to the sponsor of the NDA in the last review cycle is reviewed here.

Based on the review of the response one issue remains unresolved. See below in item C.

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

Jenloga tablets are indicated in the treatment of hypertension. Jenloga is available in one strength:0.1 mg tablet. The tablet is white, standard convex, non-scored with product code de-bossed on one side. The doses should be taken in the morning and at bed time (twice a day) and further titrated for desired effect but not exceeding 0.6 mg per day. The dosing frequency for Jenloga tablets is the same as that of Catapres^{R} tablets which is marketed as an immediate release product.

The tablets are proposed to be supplied as 60 counts in 30 ml —— bottles and 180 tablets in 40 ml —— bottles. 8 counts in 30 ml bottle is probably the physician's sample. b(4)

The storage statement is: "Store at 20-25°C (68-77°F) [see USP controlled room temperature].

Based on the available data a shelf life of 24 months may tentatively be granted provided the issue below is resolved.

C. Basis for Approvability or Not-Approval Recommendation

The dosing frequency for Jenloga tablets is the same as that of the Catpres immediate release tablets. The currently proposed established name is "Clonidine hydrochloride modified release tablets". The term "modified release" is not a recognized pharmaceutical dosage form in the USP and it is not in the CDER Data Standards Manual.

The application remains approvable until the applicant revises the established name from "Clonidine hydrochloride modified release tablets" to "Clonidine hydrochloride tablets". The container labeling, and package insert are recommended to be revised accordingly.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Amit K. Mitra, Ph.D/
Ramesh Sood, Ph.D/Date

C. CC Block

13 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICALS INC	SYMPRES
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICALS INC	SYMPRES
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICALS INC	SYMPRES
NDA-22331	ORIG-1	ADDRENEX PHARMACEUTICALS INC	SYMPRES

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

/s/

AMIT K MITRA
09/25/2009

RAMESH K SOOD
09/25/2009

Memorandum

To: NDA 22-331

CC: Mr. R.Fortney

From: Amit K. Mitra, Ph.D

Date: 12/19/2008

Re: Facilities recommendation

The Chemistry Review #2, dated 16-DEC-2008 states that facilities recommendation was not available at the time of the Review. The facilities recommendation became available on 18-DEC-2008. The OC has given a "Withhold" recommendation for the facilities.

Project manager should convey this recommendation to the applicant of the NDA 22-331.

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

/s/

Amit K. Mitra
12/19/2008 10:43:49 AM
CHEMIST
Withhold recommendation for facilities

CHEMISTRY REVIEW

NDA 22-331

CloniBID (Clonidine hydrochloride) tablets

Addrenex Pharmaceutical Co. Ltd
Amit K. Mitra, Ph.D
Office of New Drug Quality Assessment

Reviewed for the Division of Cardiovascular and Renal Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-331

2. REVIEW #:2

3. REVIEW DATE:

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	15-FEB-2008
Amendment	15-MAY-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	7-NOV-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Addrenex Pharmaceuticals, Inc.
Address:	4825 Creekstone Drive, Suite 100, Durham, NC 27703
Representative:	Mr. Moise Khayrallah

Chemistry Review Data Sheet

Telephone: (919)-941-0800 x 202

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CloniBid
b) Non-Proprietary Name (USAN): Clonidine hydrochloride. Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.1 mg

13. ROUTE OF ADMINISTRATION: Oral

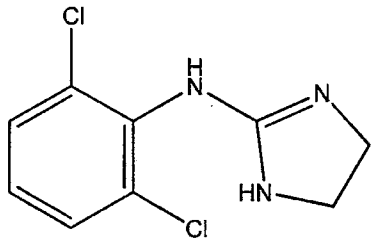
14. Rx/OTC DISPENSED: x___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride



H—Cl

Molecular Formula: $C_9H_9Cl_2N_3.HCl$; Molecular Weight: 266.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	2	—	Clonidine hydrochloride		1	24-SEP-2008	See Chemistry Review # 3, Adequate to support the NDA 22-331
—	3	—	—		4		
—	3	—			4		
—	3	—			4		

b(4)

—	3	—	—		4		
—	3	—	—		4		
—	3	—	Packaging components (nothing specific)		4		
—	4	—	—		4		
—	4	—	Magnesium stearate, dated 6-SEP-2002		3	23-JUL-2004	See Chemistry Review #3, Adequate to support NDA 21-592
—	3	—	—		4		

b(4)

[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
IND	75614	Original IND for treatment of hypertension

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None		
EES	Pending		
Pharm/Tox	None		
Biopharm	No formal consult requested. However, Dr. P. Marroum has sent an Information Request Letter separately. His and Dr. T.Ghosh's recommendation is attached in the **"Basis for Approvability or Not-Approval Recommendation"** section	15-DEC-2008	See Review by Dr. T. Ghosh
LNC	Established name is recommended to be "Clonidine hydrochloride tablets" unless the clinical division objects	01-DEC-2008 and 02-DEC-2008 E-mail	Dr. Rik Lostritto and Ms. Yana Mille
Methods Validation	None		
DMETS	Trademark CloniBID is not acceptable SYMPRES is acceptable	24-OCT-2008	Ms. Diane Smith
EA	Categorical exclusion request provided	12-NOV-2008	Dr. Amit Mitra
Microbiology	None		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			

Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-331

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can not be approved at the current form from CMC perspective.

So far, the Office of Compliance has not made any recommendation on the adequacy of the facilities.

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)

The drug substance chemistry, manufacturing control information is cross referenced to DMF —— The DMF is adequate to support this NDA. The applicant of the NDA obtains the drug substance from a vendor. The applicant was requested to adopt a specific identification test for accepting the drug substance from the vendor. All issues with drug substance were resolved. b(4)

The drug product is manufactured at one strength (100 mcg) as an extended release (in vitro) tablet dosage form with a tablet weight of 120 mg. Each tablet contains 100 mcg of clonidine hydrochloride, —— sodium lauryl sulfate, —— lactose monohydrate, —— hypromellose type 2208, —— partially gelatinized starch, —— colloidal silicon dioxide, and —— magnesium stearate. The drug product is manufactured by ⌜ ⌟. Some of the steps in the manufacturing process are ⌜ ⌟ b(4)

For the drug product to deliver consistent dose of clonidine hydrochloride the uniformity of clonidine hydrochloride, ⌜ ⌟ needs to be maintained in the whole batch. The sponsor has manufactured 3 commercial scale batches to produce tablets with acceptable content uniformity of clonidine hydrochloride. However, the applicant's quality control is based on end product testing using only small number of tablets. Therefore, the sponsor was requested to introduce several controls for drug substance and the excipients. The sponsor was also requested to submit a quality risk management plan to assure that the uniformity of clonidine hydrochloride, ⌜ ⌟ could be maintained throughout the batch. Additionally,

the sponsor was requested to adopt a blend uniformity test to assure all tablets in a batch are uniform with respect to clonidine hydrochloride. The sponsor conducted two clinical studies with the proposed formulation. The first study is a single dose PK trial. The second study was a double blind dose ranging PK study with 0.2 mg, 0.4 mg, or 0.6 mg in twice daily dosing regimen for 26 day. A single lot of the clinical supply was used during the clinical trial. The Information Request (see Chemistry Assessment) was sent to the sponsor of the NDA.

Several issues related to the drug product manufacturing and controls are still unresolved to date. See below in item C.

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

CloniBID tablets are indicated in the treatment of hypertension. CloniBID is available in one strength:0.1 mg tablet. The tablet is white, standard convex, non-scored with product code de-bossed on one side. The doses should be taken in the morning and at bed time (twice a day) and further titrated for desired effect but not exceeding 0.6 mg per day. The dosing frequency for CloniBID tablets is the same as that of Catapres^{R} tablets which is marketed as an immediate release product.

The tablets are proposed to be supplied as 60 counts in 30 ml — bottles and 180 tablets in 40 ml — bottles. b(4)

The storage statement is: "Store at 20-25°C (68-77°F) [see USP controlled room temperature].

Based on the available data a shelf life of —— may tentatively be granted provided all outstanding issues are clarified. The sponsor has not proposed a shelf life for the product. The sponsor submitted the updated stability information on 4-DEC-2008. Since the goal date for this NDA is 19-DEC-2008, the updated stability data could not be reviewed. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The Information Request listed at the end of the review was communicated to the sponsor on 23- SEP-2008 (see Chemistry Assessment). A desk copy of the amended NDA, dated 7-NOV-2008, with partial responses to the Information Request was received on 10-NOV-2008. The applicant proposed to amend the NDA with complete response as the data become available. The updated stability information provided on 4-DEC-2008 was not reviewed in this review cycle because of time constraints.

The application is approvable until the sponsor submits a complete response and takes the following corrective actions. Moreover, the Office of Compliance is yet to make a facilities recommendation.

1) **Since CloniBID tablets contain only —— of clonidine hydrochloride, adopt a blend uniformity specification for the final blend to assure that the whole blend is uniform with respect to clonidine hydrochloride. However, you may choose to follow** b(4)

the recommendation of the draft guidance "Guidance for Industry, Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment".

2) Complement the identity test by HPLC retention time method with a second identification test with a justified acceptance criteria as recommended in ICH-Q6A. Include the analytical method with methods validation and a revised specification sheet for the drug product.

3) Provide the stability data with hardness and friability values in support of in-process hardness and friability acceptance criteria. Revise the specification sheet with justified hardness and friability specification if the hardness and friability values are out of range of the in-process specifications.

4) In your validation report, identify each degradation product via relative retention time of each degradation product found during the forced degradation study. Provide the amount of each degradation product found in the forced degradation study. Provide the mass balance information in the forced degradation experiment. If known degradation products are found, provide the chemical names of those degradants and the quality of the reference standards used to identify them.

5)Report all degradation products above 0.1%, as recommended by ICH-Q3B. The degradation products should include each specified and unspecified degradation product, and total degradation products. Submit the specification sheet with revised related substances acceptance criteria. Include the analytical method and its validation.

6) Submit the revised specification sheet with microbial limits specification.

7) Provide intermediate precision results of % dissolved from tablets at all time points with different operators, different equipment and different days.

8) Since CloniBID has the same dosing frequency as that of Catapres^{R} tablets, the established name should be changed to CloniBID (clonidine hydrochloride) tablets. Make similar change in the "Description" section of PI. The Trademark "CloniBID" is not acceptable to the division, "Sympres" is acceptable.

9) Revise your post approval stability commitment to include in the stability program at least one annual batch each year in each marketed container/closure system manufactured at the commercial manufacturing site under long term storage conditions following the currently approved stability protocol

10) Revise your dissolution specification as follows: 2 hour —— 4 hr: —— ; 8 hr: —— and 16 hr: : —— b(4)

11) Submit the revised drug product specification, revised raw material specification or batch records, as committed in your cover letter, dated 7-NOV-2008.

Based on the adequacy of the responses received, recommendation will be made in the Chemistry Review #3.

The application can not be approved at the current form from CMC perspective.

III. Administrative

Executive Summary Section

A. Reviewer's Signature

B. Endorsement Block

Amit K. Mitra, Ph.D/12-NOV-2008
Ramesh Sood, Ph.D/Date

C. CC Block

10 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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

/s/

Amit K. Mitra
12/16/2008 03:41:09 PM
CHEMIST

Ramesh Sood
12/17/2008 09:25:40 AM
CHEMIST

NDA 22-331

CloniBID (Clonidine hydrochloride) tablets

Addrenex Pharmaceutical Co. Ltd
Amit K. Mitra, Ph.D
Office of New Drug Quality Assessment

Reviewed for the Division of Cardiovascular and Renal Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-331

2. REVIEW #:1

3. REVIEW DATE:

4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	15-FEB-2008
Amendment	15-MAY2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Addrenex Pharmaceuticals, Inc.
Address:	4825 Creekstone Drive, Suite 100, Durham, NC 27703
Representative:	Mr. Moise Khayrallah

Chemistry Review Data Sheet

Telephone: (919)-941-0800 x 202

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CloniBid
b) Non-Proprietary Name (USAN): Clonidine hydrochloride. Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Antihypertensive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.1 mg

13. ROUTE OF ADMINISTRATION: Oral

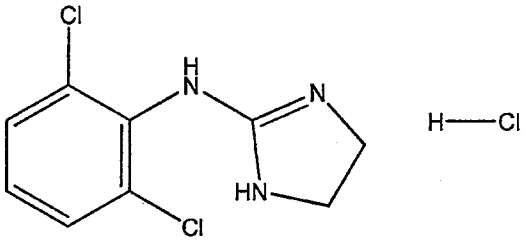
14. Rx/OTC DISPENSED: x___Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

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

N-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine hydrochloride



Molecular Formula: $C_9H_9Cl_2N_3.HCl$; Molecular Weight: 266.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	2	—			1	24-SEP-2008	See Chemistry Review # 3, Adequate to support the NDA 22-331
—	3				7		The sponsor of the NDA was requested to provide USP <661> and USP<671> information or appropriate DMF reference with submission date
—	3				4		

b(4)

Chemistry Review Data Sheet

—	3	—			4		
—	3	—			4		
—	3	—			4		
—	3		Packaging components (nothing specific)		7		The sponsor of the NDA was requested to provide USP <661> and USP<671> information or appropriate DMF reference with submission date
—	4				1	10-NOV-2008	See Chemistry Review #1, Adequate to support NDA 22-331
—	4		Magnesium stearate, dated 6-SEP-2002		3	23-JUL-2004	See Chemistry Review #3, Adequate to support NDA

b(4)

[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
IND	75614	Original IND for treatment of

		hypertension

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	None		
EES	Pending		
Pharm/Tox	None		
Biopharm	No formal consult requested. However, Dr. Marroum has sent an Information Request Letter separately. Recommendation pending		
LNC	None		
Methods Validation	None		
DMETS	Trademark CloniBID is not acceptable SYMPRES is acceptable	24-OCT-2008	Ms. Diane Smith
EA	Categorical exclusion request provided		
Microbiology	None		

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

Chemistry Review Data Sheet

The application submission(s) covered by this review was taken in the date order of receipt. _____ Yes _____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-331

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can not be approved at the current form from CMC perspective.

So far, the Office of Compliance has not made any recommendation on the adequacy of the facilities.

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)

The drug substance chemistry, manufacturing control information is cross referenced to DMF ---. The DMF is adequate to support this NDA; however, the holder of the DMF was requested to update the DMF with additional information. The applicant of the NDA obtains the drug substance from a vendor. The applicant was requested to adopt a specific identification test for accepting the drug substance from the vendor. b(4)

The drug product is manufactured at one strength (100 mcg) as an extended release tablet dosage form with a tablet weight of 120 mg. Each tablet contains 100 mcg of clonidine hydrochloride, ---- sodium lauryl sulfate, ---- lactose monohydrate, ---- hypromellose type 2208, ---- ; partially gelatinized starch, ---- colloidal silicon dioxide, and ---- magnesium stearate. The drug product is manufactured by ⌜ ⌟ Some of the steps in the manufacturing process are ⌜ ⌟ For the drug product to deliver consistent dose of clonidine hydrochloride the uniformity of clonidine hydrochloride, ⌜ ⌟ needs to be maintained in the whole batch. The sponsor has manufactured 3 commercial scale batches to produce tablets with acceptable content uniformity of clonidine hydrochloride. However, the applicant's quality control is based on end product testing using only small number of tablets. Therefore, the sponsor was requested to introduce several controls for drug of substance and the excipients. The sponsor was also requested to submit a quality risk management plan to assure that the uniformity of clonidine hydrochloride, ⌜ ⌟ could be maintained throughout the batch. Additionally, b(4)

the sponsor was requested to adopt a blend uniformity test to assure all tablets in a batch are uniform with respect to clonidine hydrochloride. The sponsor conducted two clinical studies with the proposed formulation. The first study is a single dose PK trial. The second study was a double blind dose ranging PK study with 0.2 mg, 0.4 mg, or 0.6 mg in twice daily dosing regimen for 26 day. A single lot of the clinical supply was used during the clinical trial. The Information Request (attached below) was sent to the sponsor of the NDA.

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

CloniBID extended release tablets are indicated in the treatment of hypertension. CloniBID is available in one strength:0.1 mg tablet. The tablet is white, standard convex, non-scored with product code de-bossed on one side. The doses should be taken morning and at bed time (twice a day) and further titrated for desired effect but not exceeding 0.6 mg per day.

The tablets are proposed to be supplied as 60 counts in 30 ml —— bottles and 180 tablets in 40 ml —— bottles. b(4)

The storage statement is: "Store at 20-25°C (68-77°F) [see USP controlled room temperature].

Based on the available data a shelf life of ——— may tentatively be granted provided all outstanding issues are clarified. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The Information Request listed at the end of the review has already been communicated to the sponsor on 23- SEP-2008. A desk copy of the amended NDA, dated 7-NOV-2008, with partial responses to the Information Request was received on 10-NOV-2008. The applicant proposed to amend the NDA with complete response by 30-NOV-2008.

One additional comment "Revise your post approval stability commitment to include in the stability program at least one annual batch each year in each marketed container/closure system manufactured at the commercial manufacturing site under long term storage conditions following the currently approved stability protocol" was sent to the sponsor on 10-NOV-2008 via the clinical project manager.

Based on the adequacy of the responses received, recommendation will be made in the Chemistry Review #2.

The application can not be approved at the current form from CMC perspective.

III. Administrative

Executive Summary Section

A. Reviewer's Signature

B. Endorsement Block

Amit K. Mitra, Ph.D/12-NOV-2008
Ramesh Sood, Ph.D/Date

C. CC Block

Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE

S.1 General Information **SATISFACTORY**

S.1.1 Nomenclature

Generic Name: Clonidine hydrochloride (USAN)

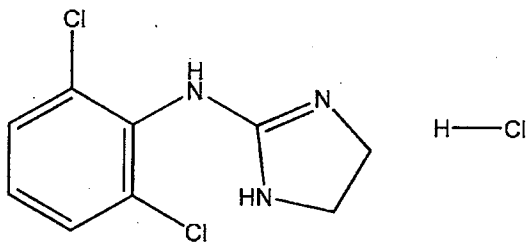
Chemical Name: USAN

(1) Benzenamine, 2,6-dichloro-*N*-2-imidazolidinylidene-, monohydrochloride; (2) 2-[(2,6-Dichlorophenyl)imino]imidazolidine monohydrochloride

CAS Registry Number: *CAS-4205-91-8*

Reviewer's comment: The drug substance established name is designated by USAN

S.1.2 Structure



33 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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

/s/

Amit K. Mitra
11/12/2008 10:55:28 AM
CHEMIST

Ramesh Sood
11/12/2008 11:03:57 AM
CHEMIST

Office of New Drug Quality Assessment
Pre-Marketing Assessment Division I (Branch I)

Initial Quality Assessment
NDA: 22-331

OND Division:	Division of Cardiovascular and Renal Products
Applicant:	Addrenex Pharmaceuticals, Inc.
NDA Filing Category:	505(b)(2)
Letter Date:	15-FEB-08
Stamp Date:	19-FEB-08
Assigned Date:	28-FEB-08
PDUFA Date:	18-DEC-08
Proposed Trade Name:	CloniBID™
Trademark:	Catapress®, Catapres-TTS®, Duralon®
Established Name:	Clonidine Hydrochloride
USAN Name:	Clonidine Hydrochloride
Dosage Form:	Tablet (extended-release)
Strengths:	0.1 mg
Route of Administration:	Oral
Indication:	Hypertension
Assessor:	**Chhagan G. Tele, Ph.D.**
ONDQA Fileability:	Yes
Comments for 74-Day Letter:	No

SUMMARY AND CRITICAL ISSUES:

Summary

Clonidine HCl is centrally acting alpha-2 adrenergic agonist that has been used effectively since the early 70s to treat mild to moderate hypertension. Clonidine stimulates alpha-adrenoceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system and deceases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Clonidine is currently approved for the treatment of hypertension in the US in three formulations, immediate release oral tablet (Clonidine HCl, Catapres® NDA 17-407) and transdermal patch (Clonidine, Catapres-TTS NDA 18-891), and injection (Clonidine HCl, Duraclon® NDA 20-615) for general anesthesia. The applicant is seeking approval using the 505(b)(2) NDA pathway and relying on the Agency's finding of safety and efficacy for Catapres® (clonidine HCl tablets, USP, Boehringer Ingelheim), approved in September 1974 (NDA 17-407) for the treatment of hypertension, as Reference Listed Drug (RLD) available for oral administration in three dosage strengths, 0.1 mg, 0.2 mg, and 0.3 mg (as HCl salt). The applicant has developed clonidine hydrochloride for extended release tablet under IND —— The applicant did not have either an EOP2 or a pre-NDA meeting with the Division of Cardiovascular and Renal Products. The applicant provided Quality overall Summary in the submission. At this time a paper submission is provided for the CMC information for the review.

b(4)

Drug Substance

Clonidine hydrochloride is a white to off-white, odorless, bitter tasting, and crystalline powder soluble in water and in ethanol. Clonidine HCl does not contain asymmetric carbon atoms; therefore any possibility of optical isomerism is excluded. No polymorphism forms have been reported. Clonidine HCl USP, is cross-referenced to ⌜ ⌟ for information regarding manufacturer, control, reference standards, stability, and packaging. — has had an active DMF since April 1982 and has been referenced in approximately 6 abbreviated applications in the US. The applicant provided a LoA dated March 1, 2007. The drug substance will be manufactured commercially by —— The last updated (June 19, 2007) DMF was found adequate (see review by Shastri Bhamidipati dated September 25, 2007) for IND — . Dr. DMF —— will need to be found adequate to support NDA.

b(4)

Drug Product

CloniBid™ (clonidine hydrochloride) extended-release tablets will be available in 0.1 mg tablet strength. The applicant used sustained as well as extended-release formulation names for cloniBid tablets throughout submission. Extended–release cloniBid tablet formulation is appropriate for release profile of approximately 16 hours. The extended release parameters are achieved by mixing the drug substance with ingredients that form ⌜ ⌟ The reviewer needs to ask applicant to use only one (e.g., extended-release tablets) form and changes needs to be seen in labeling and package insert. The proposed oral extended-release tablets contain 0.1 mg of clonidine as the hydrochloride salt (matches with the labeling) with dissolution profile approximately 16 hours. The tablets will be white round, standard convex with 651 debossed on one side.

b(4)

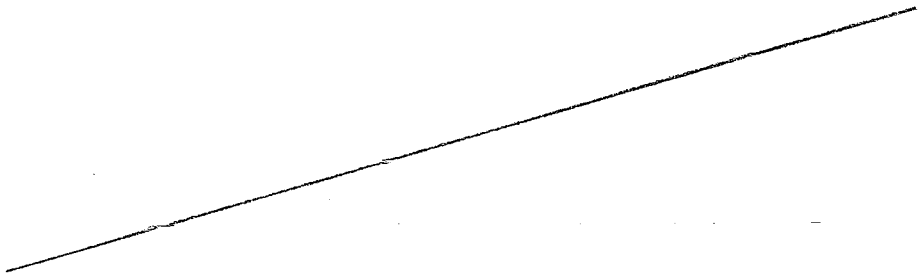
The commercial formulation is comprised of clonidine HCl USP, sodium lauryl sulfate, NF, lactose monohydrate NF, hypromellose type 2208 USP, partially pregelatinized starch NF, colloidal silicon dioxide NF, and magnesium stearate NF. All excipients are either USP or NF grade and commonly used in the solid dosage forms (no novel excipients). None of the excipients are of human or animal origin. The applicant provided pharmaceutical and manufacturing process development studies ⌜ ⌟ to achieve required scale up, dissolution profile, and content uniformity. The assigned reviewer will need to review in detail about these studies for the compatibility and robust manufacturability of the drug product.

b(4)

Clonibid extended-release tablets are manufactured using ⌜ ⌟ No overages of clonidne HCl is used in the commercial formulation. The commercial drug product will be manufactured at UPM Pharmaceuticals, Inc. (Baltimore, MD, USA). The proposed regulatory specifications for CloniBid exended-release tablets involve straight forward analytical procedures. Validated analytical methods are provided for the determination of ID, assay, content uniformity, impurity, and dissolution. The reviewer needs to look for the adequacy of the validation parameters.

b(4)

Several critical processing steps and factors were identified by the applicant (feasibility, Scale up and CTM) from the knowledge of the batches that have been manufactured so far. Many controls are critical to overcome the challenge of a [redacted] low dose product. The reviewer needs to evaluate following parameters in development of robust process: b(4)



b(4)

Following critical factors were provided without any data, the reviewer needs to confirm that on what experimental data these factors are critical to ensure the robustness of the manufacturing process:

- Particle size of the API to ensure the content uniformity
- Mixing and screening steps to ensure the content uniformity
- Material transfer [redacted] to minimize the loss in API, thus to achieve good label claim b(4)
- Moisture and processing time control to preserve blend compressibility
- Tablet weight control during compression to ensure the content uniformity and compression good label claim

Container closure systems for the bulk storage prior to final packaging for [redacted] batches are provided [redacted] CloniBid extended tablets will be packaged in [redacted] bottles in the following configurations: 30 mL [redacted] container (8 counts), 30 mL [redacted] container (60 counts), and 40 mL [redacted] container (180 counts). b(4)

Batch analysis data of three commercial batches (batch size [redacted] and one clinical trial material batch (batch size [redacted] is provided. b(4)

Limited stability package (i.e., 6 months accelerated and 6 months long-term data) is provided in the initial NDA submission for the clinical trial material batch and one month data for three commercial batches. The firm has committed to submit an update (with no time frame) for long-term and accelerated data for the commercial batches to support expiry date.

Critical Issues for Review

- The control for the drug substance is cross referenced to DMF [redacted] The drug substance is manufactured under DMF [redacted] DMF should be reviewed to support this NDA. b(4)

- Drug substance is ——— and screened through ——— during the manufacture of the registration batches of the drug product. This does not ensure a consistent particle size distribution (e.g., D10, D50, D90) to achieve consistent content uniformity and intended extended-release mechanism. b(4)
- Excipients are screened through ——— For low dose drug product, particle size of the excipients could be critical to ensure the content uniformity. Evaluation of particle size distribution of excipients is critical to ensure consistent manufacturing of the commercial drug product with acceptable content uniformity. The acceptability of the particle size of excipients (grade, change in vendors) will need to be evaluated based upon what has been used clinically. It will need to be determined whether agglomerization is a problem due to excipients or API as of function of time. b(4)
- Due to the high solubility of the active ingredient, a high concentration of the high viscosity polymer Hypromellose 2208 ——— used in the tablet formulation may have an adverse impact on tablet compression. Mixing time and screening steps are critical to ensure the content uniformity. Evaluation of the impact of excipients (——— different grade, vendor change) on blend homogeneity, release, and content uniformity is essential. b(4)
- The method of material transfer ———) to minimize the loss of drug substance needs be in place to achieve good label claim. b(4)
- Moisture and processing time control are critical factors to preserve blend compressibility. The moisture content in excipients is needed to be evaluated. How is blend homogeneity controlled during the manufacturing process? There are no in-process controls listed in the manufacturing process of the drug product.
- The effect of compression force and speed on tablet strength need to be examined closely. The pharmaceutical development section provided a summary of manufacturing process development but additional details about these factors need to be requested.
- Tablet hardness and friability needed to be evaluated (compression force, debossing process).
- The applicant has proposed the following drug product dissolution testing: after 1 h ——— after 4 h ——— after 8 h ——— and after 16 h ——— It will need to be determined the adequacy of the method (e.g.., discriminating ability). Change in quality (———, particle size, change in suppliers) of Hypromellose 2208 ——— Lactose monohydrate ——— Sodium Lauryl Sulfate (——— need to be evaluated. The reviewer needs to decide whether dissolution method is discriminatory. The reviewer need to decide the adequacy of dissolution methodology and specification. b(4)
- Justification of the exclusion of tests and acceptance criteria for tablet hardness, friability, and microbial limits needs to be requested to evaluate whether the level of process understanding and process controls is adequate.
- Evaluation is needed to determine whether the applicant has sufficiently identified possible sources of variability in the drug product manufacturing process and has explained how the associated risks are mitigated.
- Limited stability package (i.e., 6 months accelerated and 6 months long-term data) is provided in the initial NDA submission for the clinical trial material batch and

one month data for three commercial batches. The firm has committed to submit an update for long-term and accelerated data for the commercial batches to support expiry date. In accordance with our policy, the assigned expiration dating period will be based on the extent and quality of the primary stability data provided.

- HPLC method is used in for the identification for the drug product. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific to identify drug substance in the drug product and should be able to discriminate between compounds of closely related structure that are likely to be present. The reviewer needs to ask specific identity tests (e.g., ———) for the drug substance to be included in the specification of drug product. b(4)

Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is manufactured under DMF ——— DMF should be reviewed to support this NDA. Assignment of the NDA to a single reviewer is recommended. b(4)

A claim for categorical exclusion under 21 CFR §25.31 (b) is provided in Module 1. The applicant has claimed a categorical exclusion to the environmental assessment [below 1 ppb at the point of entry into the aquatic environment; 21 CFR 25.31(b)] and stated that they are unaware of any extraordinary circumstances that may exist which would significantly affect the environment from this proposed action.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to Scott Goldie (03-MAR-08) to enter into EES. Once it is done the reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered.

Tablet strengths are expressed in terms of Clonidine HCl. The current policy of established name for the product is consistent for the expression of potency is adapted.

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

/s/

Chhagan Tele
3/10/2008 02:13:09 PM
CHEMIST

Ramesh Sood
3/10/2008 03:11:30 PM
CHEMIST