

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-500

CHEMISTRY REVIEW(S)

Tradename
(clonidine) extended-release tablets
NDA 22-500

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

Applicant: Tris Pharma, Inc.
2033 Route 130, Manmouth Junction, NJ 08502

Indication: Indicated for the treatment of hypertension.

Presentation: Clonidine extended-release tablets are white to off-white (0.17 mg) or yellow (0.26 mg), capsule shaped coated tablets, debossed with "NP2" (for 0.17 mg) and "NP3" (for 0.26 mg) on one side and scored on the other side. The tablets will be available in 0.17 mg and 0.26 mg strengths in the following packaging configurations;

_____, HDPE, _____, 90 count bottles _____ for 0.17 mg.
_____, HDPE, _____, 90 count bottles _____ for 0.26 mg. **b(4)**

EER Status: Acceptable (6-Nov-09)

Consults: ONDQA Biopharmaceutics – Acceptable

Post-Approval Agreements: None

Drug Substance:

Clonidine hydrochloride is a white to almost white, crystalline powder soluble in water and ethanol, slightly soluble in chloroform. The CMC information for the manufacturing of the drug substance has been referenced to DMF [redacted]. The DMF was found to be adequate to support this NDA. The drug substance is manufactured by [redacted] b(4)

[redacted] Clonidine hydrochloride has a USP monograph. The drug substance quality is ensured by the applicant through its conformance to specification which includes tests and acceptance criteria for description, identification (IR, UV), test for chloride, pH, LOD, residue on ignition, assay (HPLC), impurities (HPLC), and residual solvents. The non-compendial analytical procedures used by the DMF holder have been transferred to the NDA applicant.

Conclusion: Acceptable.

Drug product: The drug product is manufactured in two strengths containing 0.17 mg and 0.26 mg of clonidine base equivalent to 0.2 mg and 0.3 mg of clonidine hydrochloride. [redacted] The two strengths are differentiated from each other by color and by markings on the tablets. Clonidine hydrochloride is [redacted] b(4)

[redacted] extended-release b(4)

[redacted] The other inactive ingredients in tablet formulation are povidone, polyvinyl acetate, triacetin, microcrystalline cellulose, lactose monohydrate, crospovidone, dental-type silica, magnesium stearate and [redacted], or [redacted] b(4)

The quality of the final product is ensured through a combination of in-process controls and final drug product testing. The final product specification includes tests and acceptance criteria for description, identification (HPLC), assay (HPLC), dissolution, uniformity of dosage units, [redacted] and related substances (HPLC). All analytical procedures used for the product testing are appropriately validated. b(4)

A shelf life of 24 month is granted for the product stored under controlled room temperature.

Conclusion: Acceptable. All the CMC issues were resolved based on the sponsor's responses on FDA's comments during the review process. From a CMC perspective, the applicant has submitted sufficient and adequate information to support the approval of the drug product.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion: The application is recommended for approval from CMC perspective.

Ramesh Sood, Ph.D.
Branch Chief, DPA I/ONDQA

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22500

ORIG-1

TRIS PHARMA INC

CLONIDINE _____ ER
ORAL TABLETS

b(4)

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/s/

RAMESH K SOOD

11/25/2009



NDA 22-500

(Clonidine extended release tablets)

Tris Pharma

Amit K. Mitra, Ph.D
Office of New Drug Quality Assessment

**Reviewed for the Division of Cardiovascular and Renal
Products**



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Chemistry Review Data Sheet

1. NDA 22-500
2. REVIEW #:1
3. REVIEW DATE:
4. REVIEWER: Amit K. Mitra, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

13-JAN-2009

Amendment

6-MAR-2009

Amendment

5-JUN-2009

Amendment

7-AUG-2009

Amendment

17-AUG-2009

Amendment

26-AUG-2009

Amendment

25-SEP-2009

Amendment

08-OCT-2009

Amendment

18-NOV-2009

Amendment

24-NOV-2009

7. NAME & ADDRESS OF APPLICANT:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Name: Tris Pharma, Inc.
Address: 2033 Route 130, Monmouth Junction, NJ 08502
Representative: W. Scott Groner
Telephone: (732)940-0358

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: _____ **b(4)**
b) Non-Proprietary Name (USAN): Clonidine extended release tablets
c) Code Name/# (ONDC only):
d) 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: 0.17 mg and 0.26 mg clonidine per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: x ___ Rx ___ OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

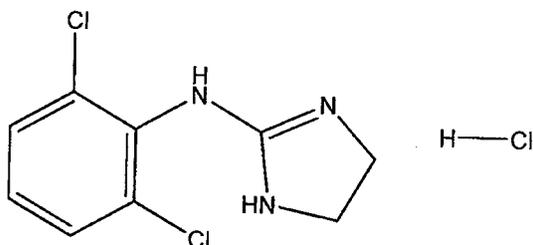
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

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 #	T Y P E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE D	COMMENTS
					Adequate	16-NOV-2009, Reviewed by Dr. A. K. Mitra	Adequate to support NDA 22-499 and 22- 500
					Adequate	25-JUL-2007, Reviewed by Dr. A. Amin	See Darrts
					Not reviewed		

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	Adequate	Dr. A. K. Mitra, 19-NOV-2009	Response to the Information Request is adequate
	Not reviewed		_____
	Not reviewed		_____
	Not reviewed		_____
	Adequate	Dr. A. K. Mitra, 16-NOV-2009	Adequate to support NDA 22-500
	Adequate	Dr. A. K. Mitra, 16-NOV-2009	Adequate to support NDA 22-500

b(4)

b(4)

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED	RECOMMENDATION	DATE	REVIEWER



CHEMISTRY REVIEW



Chemistry Review Data Sheet

REVIEWS			
Biometrics	N/A		
EES	Acceptable	6-NOV-2009	E. Johnson
Pharm/Tox	Sodium polystyrene sulfonate safe at the proposed dose	7-JUL-2009	D. N. Jensen, DVM
Biopharm	Satisfactory	4-SEP-2009	T. K. Ghosh, Ph.D
LNC	Acceptable		Verbal communication
Methods Validation			
DMEPA	Trademark " _____" unacceptable	10-NOV-2009	W. Fava
EA	Satisfactory		A. K. Mitra, Ph.D
Microbiology	N/A		

b(4)



The Chemistry Review for NDA 22-500

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved at the current form from CMC perspective.

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

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 [redacted] the sponsor of the DMF has submitted an annual report. The annual report was reviewed and it is adequate to support the NDA.

The drug product is manufactured in two strengths (0.17 mg and 0.26 mg) as clonidine extended release tablet dosage form with tablet weights of [redacted] and [redacted] respectively. Each tablet contains 170 mcg or 260 mcg of clonidine [redacted]

b(4)

The other ingredients in the tablet formulation are: Povidone [redacted], polyvinyl acetate [redacted], triacetin [redacted], microcrystalline cellulose [redacted], lactose monohydrate [redacted], crospovidone [redacted], dental-type silica [redacted], magnesium stearate [redacted] (consisting of hypromellose, polyethylene glycol, titanium dioxide) or [redacted] (consisting of talc, polydextrose, FD&C yellow #6 aluminum lake or D&C yellow # 10 aluminum lake, fractionated coconut oil and maltodextrin) [redacted]. Clonidine hydrochloride is only [redacted] of the tablet formulation.

b(4)

b(4)

b(4)

[redacted] The extended release properties for a soluble drug substance such as clonidine hydrochloride were achieved by [redacted]

b(4)

[redacted] The CMC information for the [redacted] is provided in the DMF [redacted] The DMF was found deficient by OGD for another drug product. The response to the deficiencies was received on 12-NOV-2009 and it was found adequate



CHEMISTRY REVIEW



Executive Summary Section

to support the NDA.

b(4)

b(4)

The Pharmaceutical Development report consists of selection of components, various processing steps, process controls leading to scale-up to produce the drug product with content uniformity and appropriate in vitro extended release characteristics in acidic environment during the first hour followed by extended release characteristics under alkaline environment (0.27M phosphate buffer).

The revised drug product specification includes: Description, Identification, Uniformity of dosage units, Assay, Dissolution, Related substances and _____ attributes. The microbiological attributes are controlled via excipient quality control.

b(4)

The applicant did not conduct any formal clinical study. Instead, the applicant conducted single dose and multiple dose bioequivalence study comparing blood levels from once a dosing of the tablets (0.17 mg clonidine extended release tablet) to bid dosing of 0.1 mg Catapres tablet followed by various maintenance doses. The summary of the pharmacokinetic studies are as follows: 1) A pilot single dose bioavailability study in healthy human subjects with the extended release formulation under fed and fasted conditions versus Catapres under fed condition; 2) A multiple dose bioavailability study to evaluate steady state plasma concentration in mild to moderate hypertensive patients with extended release formulation versus Catapres under fasted conditions. The applicant referred to an agreement with the agency as follows: “---approval of Tris’ proposed formulations will be primarily driven by the ability of their formulations to produce plasma concentrations in the therapeutic range (concentrations achieved by 0.2 to 0.6 mg clonidine). If Tris’ formulations cannot achieve these concentrations, additional clinical assessments (e.g., pharmacokinetic/pharmacodynamic [PK/PD] study) would be necessary.

Two lots of the clinical supply (Lot TB-021A for 0.17mg and Lot TB-020A for 0.26 mg extended release tablets) were used during the PK studies.

All issues related to the drug product manufacturing and controls are resolved.

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

Clonidine extended release tablets are proposed to be used for hypertension and are available in two strengths, 0.17 mg and 0.26 mg tablets. Clonidine extended release tablet, 0.17 mg, is a white to off-white, capsule shaped coated tablet, debossed with “NP 2” on one side and scored on the other side. Clonidine extended release tablets, 0.26 mg, is a yellow, capsule shaped coated tablet, debossed with “NP 3” on one side and scored on the other side. The initial recommended dose is 0.17 mg once daily. Further increment of 0.1 mg per day (as clonidine hydrochloride) may be made at weekly intervals if necessary until the desired



CHEMISTRY REVIEW



Executive Summary Section

response is achieved. The therapeutic doses most commonly employed have ranged from 0.2 mg to 0.6 mg per day as clonidine hydrochloride.

Both tablet strengths are proposed to be supplied in 90 count bottles.

The storage statement is "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.]"

Based on the available data a shelf life of 24 months may tentatively be granted.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues are resolved. Therefore, the application may be approved with respect to CMC.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

61 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22500

ORIG-1

TRIS PHARMA INC

CLONIDINE ER
ORAL TABLETS

b(4)

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/s/

AMIT K MITRA
11/25/2009

RAMESH K SOOD
11/25/2009

Initial Quality Assessment
Branch I

OND Division: Division of Cardiovascular and Renal Products
NDA: 22-500
Applicant: Tris Pharma
Letter Date: 13 Jan 2009
Status Date: 03 Feb 2009
PDUFA Date: 03 Dec 2009
Tradename: None
Established Name: Clonidine hydrochloride
Dosage Form: Extended release tablets, 0.2 and 0.3 mg
Route of Administration: Oral
Indication: Hypertension
Assessed by: Kasturi Srinivasachar
ONDQA Fileability: Yes

Summary

This 505(b)(2) NDA, in e-CTD format, is for a new dosage form of clonidine HCl. Clonidine is a well-known centrally acting alpha-agonist which was originally approved under the tradenames Catapres and Catapres TTS as immediate release tablets (NDA 17-407) and a transdermal patch (NDA 18-891) respectively. A companion NDA, 22-499, for an extended release oral suspension of clonidine hydrochloride has also been submitted by Tris Pharma. Currently, no extended release oral dosage form is approved for clonidine. Bioavailability and pharmacokinetic studies were conducted under IND 101,635 in support of this NDA. There was only one meeting with the Applicant - a multidisciplinary pre-IND meeting on April 4, 2008 where Tris Pharma was told that separate NDAs should be submitted for the extended release oral suspension and tablet dosage forms. The only CMC issue addressed was the timing of stability updates during the review process.

Drug Substance

Clonidine hydrochloride is a white to almost white crystalline powder which is soluble in water and ethanol and slightly soluble in chloroform. It is a synthetic achiral molecule for which DMF is referenced for CMC information. The manufacturer is _____, in _____. The DMF was last reviewed on July 28, 2008 and deemed to be adequate. A specification sheet has been provided which includes _____ testing. Clonidine hydrochloride is also the subject of an USP monograph. It is stated that the manufacturer has assigned a _____ retest period.

b(4)

b(4)

Drug Product

Clonidine hydrochloride extended release tablets are formulated using _____ excipients.

Clonidine hydrochloride is _____

_____. Extended release properties were achieved _____

_____ The drug release mechanism is stated to be by _____

b(4)

[
] b(4)
The drug product is packaged in _____ HDPE containers with _____. b(4)

A formulation development report is submitted in Mod. 3 and describes how the proposed commercial formulation was selected based on in-vitro release, content uniformity, stability characteristics and scale-up. The goal was to develop an extended release product that would provide a therapeutic effect over 24 hrs, i.e. once daily dosing as opposed to Catapres tablets which are dosed b.i.d. _____ were considered the key steps in final product performance. _____ b(4)

Both tablet strengths are dose weight proportional. Critical process steps identified are the _____ clonidine _____ and tablet _____. The process has been scaled up from laboratory scale of _____ to a batch size of _____ for _____ and no inherent scale-up issues were identified. Test batches of _____ tablets have been manufactured and it is stated that this is also the intended production batch size. b(4)

The proposed specification for the extended release tablets includes the standard test attributes of appearance, assay, identification, impurities and dissolution (USP apparatus 2, 50 rpm, 500mL 0.1N HCl for 1 hr. followed by addition of 400 mL 0.27M phosphate buffer). The acceptance criteria for dissolution and impurities are the same as for the suspension formulation in NDA 22-499. Stability data have been provided for 3 exhibit batches of _____ tablets for each strength packaged in _____ (0.2 mg) and _____ (0.3 mg) containers. The parameters monitored are description, assay, dissolution and impurities. Six months' data for long term, intermediate and accelerated conditions have been submitted and a 2 year expiration date is proposed. b(4)

Critical Review Issues

Drug substance

- Any Amendments to DMF _____ submitted after the last documented review should be evaluated. b(4)

Drug Product

- It is stated that sodium polystyrene sulfonate USP is _____. What are these _____ and is testing performed to show their _____ that will be used for _____. Also, since _____ is _____ USP, is the qualitative acceptance criterion for its _____ as proposed in the in-process test for "sodium polystyrene sulfonate" acceptable? Is there a need for tests which are additional to those in the USP monograph, e.g. particle size, for this _____ grade? b(4)
- Are the ranges for the critical process parameters identified for the _____ process and _____ adequately justified? b(4)
- The identification test proposed in the specification (HPLC retention time) is not specific as defined in ICH Q6A and should be revised.

- Is _____ impurity or degradant? If the former, its limit in the product should be no higher than in the substance. **b(4)**
- How did the Applicant arrive at the limit of NMT _____% for unspecified impurities? **b(4)**
- Is a total impurity limit of _____ acceptable?
- Should a test for _____ be included in the specification?
- Should a microbial limit test be included in the specification?
- The specification does not include a test for content uniformity. Is the proposed test for content uniformity using stratified sampling on _____ tablets sufficient for this low dose product? Is there a need to demonstrate adequacy of _____ uniformity as well? **b(4)**
- _____ of the tablets are neither tested in-process nor on finished product. Is this acceptable?
- Since this is an extended release product, the Biopharmaceutics team should be involved in the review of the dissolution method and acceptance criteria. It should be noted that the cover letter states that an error was discovered in the in-vitro dissolution studies reported and an amendment would be submitted to correct this.
- Since these are scored tablets, have supporting data been provided on content uniformity and dissolution of split versus whole tablets?

Labeling

- No proprietary name has been formally proposed for this product although the cover letter mentions the name "_____". "_____" cannot be part of the established name and should be removed from the labeling wherever it is used. **b(4)**
- The strength is based on the hydrochloride salt, hence, the established name should be clonidine hydrochloride not clonidine as stated on the container labels.
- The need for a description of the _____ along with the structure of the latter in the PI is not obvious. **b(4)**
- The list of inactive ingredients in the Description section of the Package Insert should not include proprietary names like _____. The components of these coating _____ should, however, be included. **b(4)**

Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities have been entered into EES and the reviewer should verify the accuracy and completeness of the entries. Some of the issues identified above could be conveyed to the Applicant in the 74 Day Letter after further evaluation by the reviewer. A single CMC reviewer is recommended for this application.

Kasturi Srinivasachar
 Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
 Branch Chief

Mar. 4, 2009
 Date
Mar. 4, 2009
 Date

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/s/

Kasturi Srinivasachar
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CHEMIST

Ramesh Sood
3/5/2009 12:39:06 PM
CHEMIST