

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-499

CHEMISTRY REVIEW(S)

Tradename
(clonidine) extended-release oral suspension
NDA 22-499

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 oral suspension is available as 0.09 mg/ml suspension in _____, 4 oz _____ containers with a _____ closure. A _____ adapter for dispensing is provided in the package. A _____ oral syringe dispenser _____ are also provided in the carton.

b(4)

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. The DMF was found to be adequate to support this NDA. The drug substance is manufactured by [redacted]

b(4)

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 clonidine extended release oral suspension is manufactured in 0.09 mg/ml concentration which is equivalent to 0.1 mg/ml of clonidine hydrochloride. The manufacturing process involves [redacted]

b(4)

[redacted]. The other excipients present are povidone, polyvinyl acetate, triacetin, purified water, citric acid anhydrous, polysorbate 80, high fructose corn syrup, sucrose, glycerin, methylparaben, propylparaben, xanthan gum and [redacted] strawberry banana flavor. The excipients are either compendial or their quality is ensured through appropriate specification.

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), pH, deliverable volume, microbial limits, viscosity, [redacted] content, assay (HPLC), dissolution, [redacted] and impurities (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 CMC issues were resolved based on the sponsor's responses to all 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-22499

ORIG-1

TRIS PHARMA INC

CLONIDINE ER
ORAL SUSPENSION

b(4)

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/s/

RAMESH K SOOD

11/25/2009



NDA 22-499

(Clonidine extended release oral suspension)

Tris Pharma

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

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

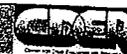


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Chemistry Review Data Sheet

- 1. NDA 22-499
- 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:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	13-JAN-2009
Amendment	06-MAR-2009
Amendment	09-MAR-2009
Amendment	27-MAR-2009
Amendment	05-JUN-2009
Amendment	23-JUL-2009
Amendment	17-AUG-2009
Amendment	24-AUG-2009
Amendment	4-SEP-2009
Amendment	3-NOV-2009
Amendment	18-NOV-2009
Amendment	24-NOV-2009
Amendment	25-NOV-2009



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

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) Non-Proprietary Name (USAN): Clonidine extended release oral suspension
- 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: Oral Suspension

12. STRENGTH/POTENCY: 0.09 mg/ml clonidine equivalent to 0.1 mg/ml clonidine hydrochloride

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC



CHEMISTRY REVIEW



Chemistry Review Data Sheet

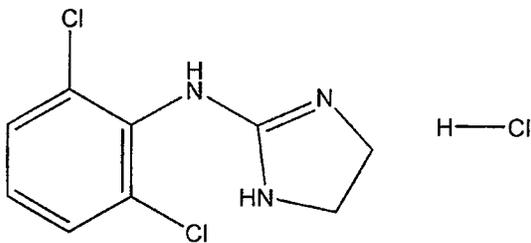
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

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: $C_9H_9Cl_2N_3 \cdot HCl$; Molecular Weight: 266.55

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
					Adequate	16-NOV-2009, Reviewed by Dr. A. K. Mitra	Adequate to support NDA 22-499 and 22-500

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	Adequate	25-JUL-2007, Reviewed by Dr. A. Amin	See Dartrts
	Not reviewed		
	Adequate	19-NOV-2009, Information Request Reviewed by Dr. A. K. Mitra	Response to the Information Adequate
	Adequate	20-NOV-2009, Reviewed by Dr. A. K. Mitra	Adequate
	Adequate	23-Nov-09, Reviewed by Dr. A. K. Mitra	Adequate to support NDA 22-499
	Adequate	4-MAY-2000	levels acceptable. is acceptable, Dr. A. Shaw.
	Adequate	22-Nov-2002	Adequate, Review #1, Dr. G. Lunn, 22-NOV-2002.

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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



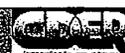
CHEMISTRY REVIEW



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	Acceptable	6-NOV-2009	Dr. T. Ghosh
LNC	Acceptable		Verbal communication
Methods Validation			
DMEPA	Trademark unacceptable	10-NOV-2009	W. Fava
EA	Satisfactory		A. K. Mitra, Ph.D
Microbiology	NA		

b(4)



The Chemistry Review for NDA 22-499

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved with respect to CMC.

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 [redacted] All issues with regard to drug substance were resolved. See the Review Notes. b(4)

The drug product is an extended release suspension dosage form for clonidine available in one strength (0.09 mg/ml). Clonidine is [redacted] b(4)

[redacted] Each milliliter of the suspension contains [redacted] of polystyrene sulfonate and 0.1 mg clonidine hydrochloride equivalent to 0.09 mg clonidine. The other excipients are: Povidone [redacted], polyvinyl acetate [redacted], triacetin [redacted], purified water [redacted], citric acid, anhydrous [redacted], polysorbate 80 [redacted], high fructose corn syrup [redacted], sucrose [redacted], glycerin [redacted], methylparaben [redacted], xanthan gum [redacted], strawberry banana flavor [redacted] b(4)

The extended release properties for a soluble drug substance such as clonidine hydrochloride were achieved [redacted] b(4)

[redacted] The applicant was [redacted]



Executive Summary Section

requested of various information with respect to CMC and the review of the responses are delineated in the Review Notes.

The drug product quality is maintained via specifications. It includes drug product specification, process controls, and in-process tests. The drug product specifications include: Description, Identification, pH, Deliverable volume, Microbial limits, Viscosity, ~~_____~~ assay, Assay for clonidine, Dissolution, Related substances, and ~~_____~~. The content uniformity is controlled via in-process tests.

b(4)

The applicant conducted the following two PK studies. 1. A pilot single-dose bioavailability study conducted in healthy subjects (n = 12) with the extended release oral suspension versus Catapres under fasting conditions. 2) a single-dose bioavailability study conducted in healthy subjects (n = 26) with the extended release oral suspension (fed and fasted) vs. Catapres (fasted).

Clonidine extended release oral Suspension (0.09 mg/mL)
Lot #: TB-013A was used in the PK studies above.

Facilities inspection report is acceptable. See EES report for details.

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

The initial dose is reported to be 0.17 mg. As a maintenance dose further increments of 0.09 mg per day may be made at weekly intervals if necessary until the desired response is achieved. The therapeutic doses most commonly employed have ranged from 0.17 mg (2 ml) to 0.52 mg (6 ml) per day. Studies have indicated that 2.1 mg (24 ml) is the maximum effective daily dose, but doses as high as this have rarely been employed.

Bioavailability and bioequivalence studies were conducted with Clonidine hydrochloride oral suspension. Clonidine hydrochloride oral suspension produced plasma concentrations that were in the range (0.2 - 2.0 ng/mL) which is claimed to be within the therapeutic range.

Clonidine extended release oral suspension is supplied as light beige to tan viscous suspension containing 0.09 mg of clonidine per milliliter in 4 oz 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

Executive Summary Section

All issues with respect to CMC are resolved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

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

C. CC Block

71 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Establishment: CFN: FEI: 3004712471
TRIS PHARMA INC
2033 US HIGHWAY 130 STE D
MONMOUTH JUNCTION, NJ 088529003

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: LIQUIDS (INCLUDES SOLUTIONS, SUSPENSIONS, ELIXIRS, **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-NOV-2008

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22499

ORIG-1

TRIS PHARMA INC

CLONIDINE ER
ORAL SUSPENSION

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: 22-499
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 oral suspension, 0.1 mg /mL
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. Currently, no extended release oral dosage form is approved for clonidine. Bioavailability and pharmacokinetic studies were conducted under IND 102,108 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)

Drug Product

Clonidine hydrochloride (0.1 mg/mL) is formulated as an extended release oral suspension using _____ excipients. The flavoring agent, _____ Strawberry Banana Flavor _____ is claimed to be GRAS. Clonidine hydrochloride is _____

b(4)

_____ The final formulation also contains a citric acid

_____ xanthan gum and _____ polysorbate 80 _____ glycerin and purified water, methyl and propylparaben _____ and a flavoring agent. The drug product is packaged in 4 ounce _____ containers with _____ The carton contains a _____ adapter and an oral dispenser. _____

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, 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. Experiments were performed to determine optimum conditions for each of the unit operations –

_____ Critical process steps identified are the _____ The process has been scaled up from laboratory scale of _____ to _____ and modifications needed for the registration batch scale and proposed commercial scale production have been investigated.

b(4)

The proposed specification for the oral suspension includes testing for pH, deliverable volume, _____ assay and microbial limits in addition to the standard attributes of appearance, assay, identification, impurities and dissolution. Stability data have been provided for 3 exhibit batches of _____ size which is _____ the proposed production scale. The parameters monitored are description, pH, microbial limits, _____ assay, clonidine HCl assay, dissolution and impurities. Six months' data at long term, intermediate and accelerated conditions have been submitted and a 2 year expiration date is proposed.

b(4)

b(4)

b(4)

Critical Review Issues

Drug substance

- Any Amendments to DME _____ submitted after the last documented review should be evaluated.

Drug Product

- It is stated that sodium polystyrene sulfonate USP is treated _____ What are _____ and is testing performed? _____ that will be used for _____

b(4)

Also, _____ 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)

- The strawberry banana flavoring agent doesn't appear to have been used in approved drug products but is stated to be GRAS by the manufacturer. Is this a commonly used food flavor? What additional information is needed to qualify its use in this product?
- Are the ranges for the critical process parameters identified for the _____ process adequately justified?
- Viscosity of the suspension is neither tested in-process nor included in product specifications. Is this acceptable?

b(4)

- The identification test proposed in the specification (HPLC retention time) is not specific as defined in ICH Q6A and should be revised.
- Are the proposed ranges for methyl and propyl paraben properly justified. Have these _____ shown to be effective at the lowest permissible levels? b(4)
- Is _____ impurity or degradant? If the former, its limit in the product should be no higher than in the substance.
- How did the Applicant arrive at the limit of _____ for unspecified impurities? b(4)
- Is a total impurity limit of _____ acceptable?
- Should particle size distribution be included in the specification?
- Since this is an extended release product, the Biopharmaceutics team should be involved in the review of the dissolution method and acceptance criteria. b(4)
- Is there justification for not including a _____ test in the specification?
- Have any extractable studies been performed with this container closure system? b(4)
- _____ Only one packaging configuration is described in the application so it is not clear what this statement refers to. These batches should be subjected to testing under accelerated conditions in addition to long term conditions.
- Are the humidity conditions, for storage of stability samples, appropriate for the container closure system used?

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. b(4)
- The need for a description of the _____ between clonidine and sodium polystyrene sulfonate along with the structure of the latter in the PI is not obvious.
- Since this is a suspension, sedimentation is always a possibility. Is _____ as part of the dosing instructions sufficient to ensure uniform dispersion of the suspension? Have any studies been carried out to show that duration of shaking is immaterial? 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

Feb. 23, 2009
Date
Feb. 23, 2009
Date

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Ramesh Sood
2/24/2009 10:44:25 AM
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