

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-500

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Tris Pharma Inc.
Clonidine — ER Tablets

b(4)

1.3.5.2 Patent Certifications

In this section are a Patent Certification and Exclusivity Statement for the Tris Pharma Inc. New Drug Application for Clonidine — ER Tablets. These statements are in accord with the Federal Food, Drug and Cosmetic Act, as amended September 24, 1984, and with the final regulations effective November 2, 1994.

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1. Patent Certification (Paragraph II):

A Paragraph II patent certification is hereby provided for our New Drug Application for Clonidine — ER Tablets, eq. to — mg and 0.2 mg clonidine hydrochloride. As of the date of this filing, there are no United States Patents listed in the Orange Book for the Reference Listed Drugs ("RLDs") Catapres® Tablets, 0.3 mg and Catapres-TTS®-3, 0.3mg/24hr, held by Boehringer Ingelheim.

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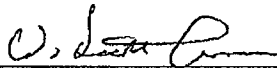
b(4)

"There are no unexpired patents for this product in the Orange Book Database."

2. Exclusivity Statement (§ 314.94(a)(3))

In accordance with 21 CFR § 314.94(a)(3)(ii), Tris Pharma, Inc. states that the "Approved Drug Products with Therapeutic Equivalence Evaluations," Electronic Version, updated as of December 2008, published by the Food and Drug Administration, lists the following information regarding exclusivity for Reference Listed Drugs ("RLDs") Catapres® Tablets, 0.3 mg and Catapres-TTS®-3, 0.3mg/24hr, held by Boehringer Ingelheim:

"There is no unexpired exclusivity for this product."



W. Scott Groner
Director, Regulatory Affairs and Compliance

3/26/08

Date

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 7/31/10 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>			
NDA NUMBER 022500		NAME OF APPLICANT/NDA HOLDER Tris Pharma, Inc.	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) _____ or _____ (Pending)			
ACTIVE INGREDIENT(S) Clonidine Hydrochloride USP		STRENGTH(S) 0.2 mg and 0.3 mg	
DOSAGE FORM Oral Tablet			
This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number		b. Issue Date of Patent	
c. Expiration Date of Patent		d. Name of Patent Owner	
Address (of Patent Owner)		City/State	
ZIP Code		FAX Number (if available)	
Telephone Number		E-Mail Address (if available)	
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)		Address (of agent or representative named in 1.e.)	
City/State		ZIP Code	
FAX Number (if available)		E-Mail Address (if available)	
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		☐ Yes ☐ No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		☐ Yes ☐ No	

b(4)

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). ☐ Yes ☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) ☐ Yes ☐ No

2.6 Does the patent claim only an intermediate? ☐ Yes ☐ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

3.2 Does the patent claim only an intermediate? ☐ Yes ☐ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) ☐ Yes ☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

☒ Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

W. Scott Groner

Date Signed

3/26/08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder

☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

☐ Patent Owner

☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

W. Scott Groner (Director Regulatory Affairs and Compliance)

Address

Tris Pharma, Inc.
2033 Route 130

City/State

Monmouth Junction, NJ

ZIP Code

08852

Telephone Number

(732) 940-0358

FAX Number (If available)

(732) 940-0374

E-Mail Address (If available)

reg.affairs@trispharma.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 022500

SUPPL #

HFD # 110

Trade Name N/A

Generic Name Clonidine (ER) Tablets

Applicant Name Tris Pharma, Inc.

Approval Date, If Known 12/03/09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

To support the claim, the sponsor submitted three bioavailability trials with pharmacodynamic (PD) and adverse event data. The pharmacokinetic (PK) results from the trials meet the bioavailability criteria for ER products.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☐

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	017407	Catapres Tablets
NDA#	018891	Catapres TTS
NDA#	020615	Duraclon
NDA#	022331	Jenloga

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES ☐ NO ☐

Investigation #2

YES ☐

NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

!

IND #

YES ☐

!

! NO ☐

! Explain:

Investigation #2

!

IND #

YES ☐

!

! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2
!
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Devi Kozeli
Title: Regulatory Health Project Manager
Date: 12/03/09

Name of Office/Division Director signing form: Norman Stockbridge
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22500

ORIG-1

TRIS PHARMA INC

CLONIDINE : ER
ORAL TABLETS

b(4)

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

/s/

DEVI KOZELI
12/03/2009

NORMAN L STOCKBRIDGE
12/03/2009

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22500 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: Cardio-Renal PDUFA Goal Date: 12/03/09 Stamp Date: 02/03/09 (Userfee Received)
Proprietary Name: _____ **b(4)**
Established/Generic Name: Clonidine HCL
Dosage Form: Tablet
Applicant/Sponsor: Tris Pharma, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only): **b(4)**
(1) Tablet is indicated in the treatment of hypertension.
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____ Tablet is indicated in the treatment of hypertension. **b(4)**

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- ☐ Yes. Please proceed to Section D.
☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☒ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
☐ No: Please check all that apply:
☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
☐ Completed for some or all pediatric subpopulations (Complete Sections D)
☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- ☐ Necessary studies would be impossible or highly impracticable because:
- ☐ Disease/condition does not exist in children
 - ☐ Too few children with disease/condition to study
 - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)

☒ Justification below:

We are waiving pediatric requirement for NDA 22500, tablet formulation because the efficacy and safety information will be provided by the pediatric studies to be conducted under NDA 22499 _____ oral suspension) by the same sponsor.

b(4)

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22500

ORIG-1

TRIS PHARMA INC

CLONIDINE _____ .ER
ORAL TABLETS

b(4)

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

/s/

DEVI KOZELI
11/30/2009

Tris Pharma Inc.

Clonidine ER Tablets

b(4)

1.3.3 Debarment - GDEA Certification

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Tris Pharma, Inc. hereby certifies that Tris Pharma, Inc. did not and will not use, in any capacity, the services of any person **debarred** under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA.

Tris Pharma, Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsections (a) or (b) of the **Generic Drug Enforcement Act** of 1992. In addition, to the best of Tris Pharma, Inc.'s knowledge, no person affiliated with Tris Pharma, Inc. that was responsible for the development or the submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.



W. Scott Groner
Director, Regulatory Affairs and Compliance

12/30/05
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22500 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: N/A Established/Proper Name: Clonidine (ER) Oral Tablet Dosage Form: Tablet (mg): 0.17, 0.26 clonidine base		Applicant: Tris Pharma, Inc. Agent for Applicant (if applicable):
RPM: Devi Kozeli, RAC.		Division: Division of Cardiovascular and Renal Products
NDA: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) 505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): NDA 017407 Catapres® NDA 018891 Catapres-TTS® Provide a brief explanation of how this product is different from the listed drug. Clonidine ER Tablet is an extended release formulation. ☐ If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. ☒ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug. On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.		
❖ User Fee Goal Date Action Goal Date (if different)		12/03/09
❖ Actions		
• Proposed action		☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions (specify type and date for each action taken)		☒ None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
--	--

❖ Application Characteristics ²	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☐ Accelerated approval (21 CFR 314.510) ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	11/18/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire _____
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☒ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

☐ Yes ☐ No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

☐ Yes ☐ No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 12/03/09
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	12/03/09
Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
Original applicant-proposed labeling	02/03/09
Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Catapres Tablets Catapres TTS Jenloga
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☒ None

³ Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent division proposal for (only if generated after latest applicant submission)	12/03/09
• Most recent applicant-proposed labeling	11/30/09
❖ Proprietary Name	
• Review(s) (indicate date(s))	11/10/09
• Acceptability/non-acceptability letter(s) (indicate date(s))	11/16/09
❖ Labeling reviews (indicate dates of reviews and meetings)	☐ RPM ☒ DMEPA 11/10/09 ☐ DRISK ☒ DDMAC 11/10/09 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (e.g., RPM Filing Review ⁴ /Memo of Filing Meeting) (indicate date of each review)	Filing Review: 04/04/09
❖ NDAs only: Exclusivity Summary (signed by Division Director)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo (indicate date)	
○ If yes, OC clearance for approval (indicate date of clearance communication)	☐ Not an AP action
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	☒ Verified, statement is acceptable
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC (indicate date of mtg; approvals only)	☐ Not applicable 11/18/09
• Pre-Approval Safety Conference (indicate date of mtg; approvals only)	☒ Not applicable
• Regulatory Briefing (indicate date of mtg)	☒ No mtg

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
• Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 11/28/09
• Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 11/24/09
• PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	11/18/09
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See 11/18/09 medical review
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See 11/18/09 medical review
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not needed
❖ Risk Management • REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo (<i>indicate date</i>) • Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
• Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☐ None
• Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☐ None
• Statistical Review(s) (<i>indicate date for each review</i>)	☐ None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/26/09

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☐ None 09/17/09 & 11/24/09
Clinical Pharmacology review(s) (indicate date for each review)	☐ None 09/09/09
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☐ None 06/26/09
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 06/26/09 & 07/07/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☐ None 11/25/09
• Product quality review(s) (indicate date for each review)	☐ None 03/05/09, 11/25/09
• ONDQA Biopharmaceutics review (indicate date for each review)	09/04/09
• BLAs only: Facility information review(s) (indicate dates)	☐ None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	☒ Not needed
• BLAs: Sterility assurance, product quality microbiology (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	See 11/25/09 CMC review
☒ Review & FONSI (indicate date of review)	See 11/25/09 CMC review
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date)	Date completed: 11/06/09 ☒ Acceptable ☐ Withhold recommendation

• BLAs: ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22500

ORIG-1

TRIS PHARMA INC

CLONIDINE ER
ORAL TABLETS

b(4)

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

/s/

DEVI KOZELI
12/03/2009

**NDA 022500 Clonidine (ER) Oral Tablet
RHPM Overview
December 2, 2009**

Sponsor: Tris Pharma, Inc.
Type: 505(b)(2)/3S
Receipt Date: February 3, 2009 (User Fee Received Date)
Goal Date: December 3, 2009

Action: Approval
Action Date: December 3, 2009

Background

This application requests approval of a new formulation of clonidine oral suspension. The application was originally submitted on January 14, 2009. The appropriate user fee was not received at that time so an unacceptable for filing letter was sent to the sponsor. The sponsor paid the user fee on February 3, 2009, thus the PDUFA Goal Date of December 3, 2009.

This is a 505(b)(2) application with Catapres tablets (NDA 017407) and Catapres-TTS (NDA 018891) as the RLD. To support the claim, the sponsor submitted three bioavailability trials with pharmacodynamic (PD) and adverse event data. The primary objectives in these trials are bioavailability comparisons, and there are no clinical efficacy primary endpoints. The trials are summarized in Table 1 below.

Table 1: Tabular Listing of Clinical Pharmacology Studies

Study No.	Study Objective	Study Design	Treatments [Product ID]	Subjects (No. M/F) Type Age: Mean (Range)
M1FT07010	A Pilot Relative Bioavailability Study of Clonidine 0.1 mg/mL ER Oral Suspension v. Catapres® 0.1 mg Tablets under Fasting Conditions	Randomized, Single-Dose, 2-Way Crossover, 2-Treatment, Open-Label, Under Fasted Conditions	Clonidine ER Oral Suspension 1 x 0.2 mg Dose under fasting conditions RD0072-065 [Treatment A] Catapres® IR Tablets 2 x 0.1 mg Dose under fasting conditions 755411 [Treatment B]	12 (10M/2F) Healthy subjects 38 years old (22-52)
1003390	A 3-Period, 3-Treatment, 3-Way Crossover Bioavailability Study of Clonidine Extended Release Oral Suspension 0.1 mg/mL (2 mL) Under Fed and Fasted Conditions	Randomized, Single-Dose, 3-Way Crossover, 3-Treatment, Open-Label, Under Fed and Fasted Conditions	Clonidine ER Oral Suspension 1 x 0.2 mg Dose under fasting conditions TB-013A [Treatment A] Catapres® IR Tablets 2 x 0.1 mg Dose under fasting conditions 851623 [Treatment B] Clonidine ER Oral Suspension 1 x 0.2 mg Dose under fed conditions TB-013A [Treatment C]	26 (12M/14F) Healthy subjects 29 years old (20-53)
1003391	A 3-Period, 3-Treatment, 3-Way Crossover Bioavailability Study of Clonidine Extended Release Tablet (1 x 0.2 mg) Under Fed and Fasted Conditions	Randomized, Single-Dose, 3-Way Crossover, 3-Treatment, Open-Label, Under Fed and Fasted Conditions	Clonidine ER Tablets 1 x 0.2 mg Dose under fasting conditions TB-021A [Treatment A] Catapres® IR Tablets 2 x 0.1 mg Dose under fasting conditions 851623 [Treatment B] Clonidine ER Tablets 1 x 0.2 mg Dose under fed conditions TB-021A [Treatment C]	26 (8M/18F) Healthy subjects 39 years old (21-64)
1003317	A Study to Evaluate the Steady-State Plasma Concentrations of 0.2 mg Tris Clonidine Extended Release Tablets and Steady-State Plasma Concentrations of Tris Clonidine Extended Release Tablets Versus Catapres® at a 0.6 mg Daily Dose in Mild to Moderate Hypertensive Patients	Multi-Dose, Steady State, 4-Treatment, Open-Label, Partially-Randomized	Clonidine ER Tablets 1 x 0.2 mg Dose under fasting conditions TB-021A [Treatment A] Clonidine ER Tablets 2 x 0.2 mg Dose under fasting conditions TB-021A [Treatment B] Clonidine ER Tablets 2 x 0.3 mg Dose under fasting conditions TB-020A [Treatment C] Catapres® IR Tablets 2 x 0.3 mg Dose under fed conditions 755233 [Treatment D]	32 (27M/5F) Mild to Moderate Hypertensive Patients 43 years old (21-72)

Division Director's Memo (11/28/09)

Reviewer: Norman Stockbridge, M.D., Ph.D.

Recommendation: Approval

Summary: Dr. Stockbridge's memo conveyed the Division's recommendation to approve extended-release clonidine oral tablet for treatment of hypertension.

CDTL Review (11/24/09)

Reviewer: Shari Targum, M.D.

Recommendation: Approval

Summary: The cross-discipline team leader concurs with the primary medical and clinical pharmacology reviewers in recommending approval of the clonidine extended-release oral tablet, pending resolution of outstanding chemistry issues. Chemistry review was not completed at the time when the CDTL submitted her review.

Medical Review (11/18/09)

Reviewer: Nancy Xu, M.D.

Recommendation: Approval

Summary: From the clinical perspective, Dr. Xu recommends the approval of clonidine extended-release oral tablet formulation for the treatment of hypertension in adults.

Clinical Pharmacology and Biopharmaceutics Review

Reviewer: Robert Kumi, Ph.D.: (09/09/09)

Team Leader: Rajanikanth Madabushi, Ph.D.: (09/17/09, 11/24/09)

Recommendation: Approval

Summary: The Office of Clinical Pharmacology (OCP) has reviewed the information submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 22-499 and 22-500 and finds the information acceptable. OCP supports approval of both clonidine extended-release products (ER): 0.1 mg/mL suspension and 0.2 and 0.3 mg tablets.

Chemistry Review (11/25/09)

Reviewer: Amit Mitra, Ph.D.

Recommendation: Approval

Summary: In his review, Dr. Mitra recommended approval for clonidine extended-release oral tablet. Facilities inspection were completed on 11/06/09 and found acceptable.

Dissolution Specifications Review (09/03/09)

Reviewer: Tapash Ghosh, Ph.D.

Recommendation: Approval

Summary: Per Dr Ghosh's review, the Agency's IVIVC guidance on setting dissolution specifications without an IVIVC recommends that the range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Based on the evaluation of dissolution data, the reviewer proposes the following specifications for the ER dosage forms:

Dosage Form	Strength	1 hr	3 hr	6 hr	24 hr
Suspension	0.1 mg/ml	NMT			NLT
Tablet	0.2 mg	NMT			NLT
Tablet	0.3 mg	NMT			NLT

b(4)

Also, the Agency does not recommend MR dosage forms to be scored in the first place. In general, for scored tablets, we do like to see that dissolution profiles from two halves of the scored tablet is similar (shape and f2) to that of the intact tablet. We recommend that the sponsor submit dissolution data comparing profiles from two halves of the scored tablet to that of the intact tablet as an amendment within a regulatory applicable time frame.

Pharmacology-Toxicology Review (11/25/09)

Reviewer: Charles Resnick, Ph.D.

Recommendation: Approval

Summary: The application is approvable

DSI: There were no inspections of the clinical study sites.

Pediatric Rule: This application was discussed during the November 18, 2009, meeting of the Pediatric Review Committee (PeRC). The Committee agreed to a waiver for children aged 0-1 years; a deferral for children aged 1-17 years, and completely waives the pediatric study requirement for the clonidine (ER) oral tablet.

Labeling: The labeling is similar to the most recently approved label for JENLOGA (clonidine hydrochloride) Tablets, with modifications to describe the clinical program for the current application, formulation-related differences, and the change to the PLR format.

Tradename: The sponsor originally called their product _____ but withdrew it in April 9, 2009. With their submission dated August 17, 2009, the sponsor requested that Agency accept _____ as a primary name. According to the DMEPA, this name was unacceptable because _____ is comprised of more than half the letters of the established name Clonidine (i.e., Cloni). Thus, when _____ is spoken and scripted it bears resemblance to the established name Clonidine. Additionally, these products share multiple product characteristics such as the same active ingredient, dosage form, route of administration, and overlapping product strengths of 0.2 mg and 0.3 mg. b(4)

The sponsor will submit an alternate tradename for review. The application will be approved without a tradename. b(4)

Advisory Committee: N/A

Overall recommendation: Based on the recommendations made by all discipline reviewers, this application will be approved and I have drafted approval letter for this application based in the agreed upon labeling text.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE  ER b(4) ORAL TABLETS

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/s/

DEVI KOZELI
12/03/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-500/22-499

INFORMATION REQUEST

Tris Pharma, Inc.
Attention: W. Scott Groner
Director, Regulatory Affairs and Compliance
2033 Route 130
Monmouth Junction, NJ 08852

Dear Mr. Groner:

Please refer to your January 13, 2009 new drug applications submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Clonidine. b(4)

We have reviewed your submissions and we have the following comments and information requests and request a prompt written response in order to continue our evaluation of your NDA.

Drug Product Stability

+

7

b(4)

✓

3

Label

Include the Product Characteristics for in the SPL for NDA 22-500.

b(4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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
11/17/2009

3 Page(s) Withheld

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

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-500

INFORMATION REQUEST

Tris Pharma, Inc.
Attention: W. Scott Groner
Director, Regulatory Affairs and Compliance
2033 Route 130
Monmouth Junction, NJ 08852

Dear Mr. Groner:

Please refer to your January 13, 2009 new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Clonidine ——— extended release tablets. **b(4)**

We have reviewed your submission dated October 8, 2009 in response to our information request letter dated September 17, 2009. We have the following comments and information requests and request a prompt written response in order to continue our evaluation of your NDA.

1. The individual unspecified impurity acceptance criterion should be based on identification threshold for a given daily intake as per ICH-Q3B (R2). Therefore, revise the acceptance criteria to NMT ——— (based on a 6 mg/day daily dosing of the drug). **b(4)**
2. We reiterate that your proposed established name "Clonidine ——— extended release tablets" is not acceptable. Revise the established name to "(Clonidine hydrochloride) extended release tablets" for the following reasons. Our recommendation is based on the fact that the drug substance that is characterized as active pharmaceutical ingredient with retest date and all related CMC information is clonidine hydrochloride. The ——— **b(4)** has not been characterized to the extent an active pharmaceutical ingredient should be characterized. Moreover, the ——— **b(4)** is part of the drug product manufacturing process; therefore, it **b(4)** should not be part of the established name.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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
10/16/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-500

INFORMATION REQUEST

Tris Pharma, Inc.
Attention: W. Scott Groner
Director, Regulatory Affairs and Compliance
2033 Route 130
Monmouth Junction, NJ 08852

Dear Mr. Groner:

Please refer to your January 13, 2009 new drug application submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Clonidine — extended release tablets.

b(4)

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Adopt at least a specific identification test and its acceptance criteria for clonidine hydrochloride after receipt of the drug substance from the vendor.
2. Provide USP system suitability criteria for the assay method of clonidine hydrochloride, and related substances. Include peak symmetry and resolution factor acceptance criteria as appropriate.
3. Provide USP system suitability criteria for — method of clonidine hydrochloride. Include peak symmetry and resolution factor acceptance criteria as appropriate.

b(4)

Excipients

1. Adopt at least an identification test and its acceptance criteria for each excipient after receipt of the excipient from the vendor.

5. Include content uniformity in the drug product specification with an acceptance criteria based on USP<905>.
6. Adopt a specification for _____ unless justified.
7. The Agency's IVIVC guidance on setting dissolution specification without an IVIVC recommends that the range at any dissolution time point specification is $\pm 10\%$ deviation from the mean dissolution profile obtained from the clinical/bioavailability lots. Based on the evaluation of the dissolution data, the Agency proposes the following specifications for the extended release tablets.

b(4)

Dosage Form	Strength	1 hr	3 hr	6 hr	24 hr
Tablet	0.2mg	NMT			NLT
Tablet	0.3 mg	NMT			NLT

b(4)

D. Analytical Methods and Validation

1. Provide USP system suitability information for the assay of clonidine, related substances, and dissolution assay methods. Include peak symmetry and resolution factor acceptance criteria, as appropriate.
2. Adopt and submit a statistically valid sampling scheme for all test methods for quality control.
3. Provide LOD for compound A and unspecified impurities.

E. Drug Product Stability

1. We understand that your _____

b(4)

Label

1. The established name "clonidine _____ extended release tablets" is not acceptable. Revise the established name to "clonidine hydrochloride extended release tablets".
2. Submit the carton label.
3. Revise the "Description" section of the PI as follows: a) Delete _____ from the list of ingredients. Instead, include the components of the _____ b) Delete _____ description of the _____ along with the chemical structure of the latter.
4. Include the Product Characteristics for _____ in the SPL

b(4)

b(4)

b(4)

DMF

1. DMF _____ was found deficient. Those deficiencies need to be resolved prior to the approval of your application.

b(4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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
09/17/2009

4 Page(s) Withheld

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 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-500

Tris Pharma, Inc.
Attention: W. Scott Groner
Director Regulatory Affairs and Compliance
2033 Route 130, Suite D
Monmouth Junction, NJ 08502

Dear Mr. Groner:

Please refer to your January 13, 2009 new drug application (NDA), received on February 3, 2009 submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Clonidine ER Tablets, 0.2 and 0.3 mg.

b(4)

We also refer to your submissions dated March 6 and April 8, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 3, 2009.

During our filing review of your application, we identified the following potential review issues:

1. Please submit analysis datasets for all your studies, namely 3317, 3390, and 3391.

The datasets should have the following variables:

- SUBJID (Subject ID).
- Treatment group (variable TRT): A, B, C or D.
- Verbatim and MedDRA Preferred Term for all treatment emergent adverse events (TEAEs) and AE that were detected post study withdrawal during follow-up.
- Adverse event start and stop treatment day, and time (as a numeric variable consistent with your REL_TIME).
- Treatment or Study Day and time (in REL_TIME) of study medications. For example, if an AE was detected one day post study drug withdrawal which happened on Day 31, then the Study Day for the onset of AE is Day 32.
- Action taken for AE: none, drug discontinued, etc.
- Treatment Day and REL_TIME of any premature study drug discontinuation when an AE was present at the time of withdrawal.
- The stated reasons for premature study drug discontinuation (AE, patient opted to drop out etc).
- Baseline and ALL subsequent BP and HR measurements.
- Study Day and REL_TIME that correspond to the BP and HR data.
- A variable that categorizes the BP data as pre-study baseline, pre-dose (trough BP), post-dose (anticipated C_{max} BP), standing vs. sitting BP.
- Concomitant blood pressure medications and dosages during screening and during study medication treatment.
- Study codes: 3317, 3390, or 3391, if you are submitting the safety data in a single dataset.

2. Please explain why the CFRs for the study 3317 are blank.
3. Please provide all CFRs (non-blank) for study 3317.
4. For dataset L1003317, under variable "comment", please explain what does BQL mean.
5. For dataset P1003317, please explain what does the variable "period" mean. Specifically, what do values "blank", "1" versus "2" mean for this variable?

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Mr. Devi Kozeli, RAC., Regulatory Project Manager, at (301) 796-1128.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
4/16/2009 10:48:26 AM

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22499 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: █████ (proposed) Established/Proper Name: Clonidine █████ ER Oral Tablet Dosage Form: Oral Suspension Strengths: 0.2 mg and 0.3 mg		
Applicant: Tris Pharma, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 01/13/2009 Date of Receipt: 01/14/2009 Date clock started after UN: 02/03/2009		
PDUFA Goal Date: 12/03/2009		Action Goal Date (if different):
Filing Date: 04/04/2009 Date of Filing Meeting: 03/16/2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only): 3 – New dosage form		
Proposed Indication(s): Treatment of hypertension		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		☐ 505(b)(1) ☒ 505(b)(2)
<i>Refer to Appendix A for further information.</i>		☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐		
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

b(4)

Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s): 102108	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: http://www.fda.gov/ora/compliance_ref/aip.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status Comments:	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☐ YES ☒ NO ☐ YES ☐ NO

<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i> Comments:	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? <i>(NDAs/NDA efficacy supplements only)</i> <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i> Comments:	☐ YES # years requested: ☒ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use <i>(NDAs only)</i>: Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>	☐ Not applicable ☐ YES ☒ NO ☐ YES ☒ NO ☐ YES ☒ NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		☐ YES ☒ NO
If yes, please list below:		
Application No.	Drug Name	Exclusivity Code
If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.		
Format and Content		
Do not check mixed submission if the only electronic component is the content of labeling (COL). Comments:		☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?		
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? <i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> Comments:		☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)		☒ YES ☐ NO
If not, explain (e.g., waiver granted):		

Form 356h: Is a signed form 356h included? <i>If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.</i> Are all establishments and their registration numbers listed on the form? Comments:	☒ YES ☐ NO ☒ YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? Comments:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? Comments:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? Comments:	☐ YES ☒ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? <i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must</i>	☒ YES ☐ NO

<i>sign the certification.</i> Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..." Comments:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>) <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☒ Not Applicable (<i>electronic submission or no CMC technical section</i>) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent. Note: Financial disclosure is required for bioequivalence studies that are the basis for approval. Comments:	☒ YES ☐ NO
Pediatrics	
<u>PREA</u>	
Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PerC prior to approval of the application/supplement.	
Are the required pediatric assessment studies or a full waiver of pediatric studies included? If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? <i>If no, request in 74-day letter.</i> If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) Comments: The sponsor requested a full waiver	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES ☐ NO

<u>BP</u>CA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i> Comments:	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. Comments:	☐ Not applicable ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☐ MedGuide ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i> Comments:	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i> Comments:	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? Comments:	☒ YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>) Comments:	☒ Not Applicable ☐ YES ☐ NO
REMS consulted to OSE/DRISK? Comments:	☒ Not Applicable ☐ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? Comments:	☐ Not Applicable ☒ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. Comments:	☒ Not Applicable ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> Comments:	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? Comments:	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i> Comments:	☐ YES Date(s): ☒ NO
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i> Comments:	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 16, 2009

NDA/BLA #: 22-499

PROPRIETARY/ESTABLISHED NAMES:

APPLICANT: Tris Pharma, Inc.

BACKGROUND: This application is a 505(b)(2) NDA. The sponsor, Tris Pharma, Inc., is seeking approval to market Clonidine ~~_____~~ ER Oral Suspension, eq. to 0.1 mg clonidine hydrochloride per mL. The primary reference list drug (RLD) is Catapres® Tablets and the secondary RLD is Catapres-TTS®, both manufactured by Boehringer Ingelheim.

b(4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Devi Kozeli	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Clinical	Reviewer:	Nancy Xu	Y
	TL:	Abraham Karkowsky	
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Robert Kumi	Y
	TL:	Rajnikanth Madabushi	N
Biostatistics	Reviewer:	Steve Bai	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Charles Resnick	Y
	TL:	Charles Resnick	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Amit K. Mitra	Y
	TL:	Kasturi Srinivasachar	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES:

505(b)(2) filing issues? If yes, list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO

Electronic Submission comments List comments:	☒ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason: This drug is not the first in its class
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
- Establishment(s) ready for inspection? - Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ Not Applicable ☒ YES ☐ NO
Sterile product?	☐ YES ☒ NO

If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)	☐ YES ☐ NO
FACILITY (BLAs only) Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Devi Kozeli, RAC. GRMP Timeline Milestones: Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☐	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22500

ORIG-1

TRIS PHARMA INC

CLONIDINE ^r ER
ORAL TABLETS

b(4)

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

/s/

DEVI KOZELI

11/30/2009

This Filing review was originally completed on 04/04/09



Department of Health and Human Services

Public Health Service

Food and Drug Administration

Rockville, MD 20857

MAR 19 2009

W. Scott Groner
Director, Regulatory Affairs and Compliance
Tris Pharma, Inc.
2033 Route 130, Suite D
Monmouth Junction, NJ 08852

RE: Tris Pharma, Inc., Small Business Waiver Request 2009.028 for a New Drug Application, NDA 22-500 for Clonidine — Extended Release Tablets b(4)

Dear Mr. Groner:

This responds to your letter¹ received December 16, 2008, requesting a waiver of an application user fee under the small business waiver provision, section 736(d)(1)(D)² of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2009.028). You request a waiver of the fiscal year (FY) 2009³ human drug application fee for new drug application (NDA) 22-500 for Clonidine — Extended Release Tablets.⁴ For the reasons described below, the Food and Drug Administration (FDA) grants the Tris Pharma, Inc. (Tris) request for a small business waiver of the application fee for NDA 22-500 for Clonidine — Extended Release Tablets (Clonidine — ER). b(4)

According to your waiver request, Tris has fewer than 500 employees including employees of any other affiliate companies. You state that Tris has one prescription product, a nutritional supplement, delivered for introduction into interstate commerce. The product, MyKidz Iron FL, is manufactured for a marketing partner, NextWave Pharmaceuticals. You do not believe that this product qualifies as a prescription drug product; therefore, you state Tris does not have a prescription drug product introduced or delivered for introduction into interstate commerce. You do not expect to introduce a prescription drug product within the next 12 months. You expected to submit your application for Clonidine — ER to the Agency on December 31, 2008. b(4)

Under section 736(d)(4) of the Act,⁵ a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate⁶ submits to the FDA for review. The

¹ Your letter was dated December 15, 2009, which we presume was a typographical error.

² 21 U.S.C. 379h(d)(1)(D).

³ FY 2009 = October 1, 2008, through September 30, 2009.

⁴ According to the FDA review division, the NDA number you provided (101635) is actually the investigational new drug application (IND) number. The appropriate assigned NDA number for this application is NDA 22-500.

⁵ 21 U.S.C. 379h(d)(4).

⁶ "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(11)).

small business waiver provision entitles a small business to a waiver when the business meets the following criteria:

- (1) The business must employ fewer than 500 persons, including employees of its affiliates.
- (2) The business does not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce.
- (3) The marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Tris's request for a small business waiver for its NDA 22-500, Clonidine ~~ER~~, is based on the following findings:

b(4)

- The Small Business Administration (SBA) determined and stated in its letter dated February 4, 2009, that Tris is a small business with the following affiliates: Ketan Mehta, Smith Mehta, and BVM Holdings, Inc.
- SBA also confirmed that Tris and its affiliates have fewer than 500 employees.
- According to FDA records, Tris does not have any other products that have been approved under human drug applications and introduced or delivered for introduction into interstate commerce.
- The marketing application for NDA 22-500 is the first human drug application, within the meaning of the Act, to be submitted to FDA by Tris or its affiliates.

Consequently, your request for a small business waiver of the application fee for NDA 22-500 is granted. We have notified the FDA Office of Financial Management (OFM) of this waiver decision.

FDA records show that Tris submitted the full NDA 22-500 on January 14, 2009, and FDA was notified on February 3, 2009, of an application fee payment of \$623,600. We have asked the Office of Financial Management (OFM) to issue a refund of the \$623,600 for NDA 22-500, User Fee ID Number 3008979 that you submitted for the review of the application. If you do not receive a check for that amount within 30 days of the date of this letter, please contact Edmund Mendez, OFM, at 301-827-9341.

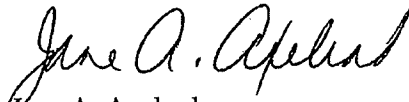
If FDA refuses to file the application or if Tris withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Tris should contact this office at least 90 days before it expects to resubmit its marketing application to determine whether Tris continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

Tris Pharma, Inc.
Waiver Request 2009.028
Page 3

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-796-3602.

Sincerely,

A handwritten signature in cursive script, reading "Jane A. Axelrad".

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

Tris Pharma, Inc.
Waiver Request 2009.028
Page 4

BCC:

M. Jones/B. Friedman/A. Jones

Chron file

Tris waiver file

HFD-110 – Project Manager for NDA 22-500, Devi Kozeli

HFM-110 C. Vincent/R. Eastep

HF-60 E. Mendez, H. Chaves (Refund Pending/RECORD ON PAYMENT AND ARREARS LIST)

HFV-3 T. Forfa

HFV-100 D. Newkirk

Drafted: B. Friedman 2/10/2009

CDER Application Check: Another application N22-499 also submitted same day as N22-500

B. Friedman 2/10/2009

CBER Application Check: C. Vincent: 2/10/2009

Edited: O. Pritzlaff 3/10/2009

Reviewed: J. Axelrad 3/17/2009

aj 3/19/09

Date: 3/18/09



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-500

Tris Pharma, Inc.
Attention: W. Scott Groner
Director Regulatory Affairs and Compliance
2033 Route 130, Suite D
Monmouth Junction, NJ 08502

Dear Mr. Groner:

Please refer to your new drug application (NDA) submitted on January 13, 2009, under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Clonidine ~~_____~~ ER Tablets, 0.2 and 0.3 mg. **b(4)**

You were notified in our letter dated February 3, 2009, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of February 3, 2009.

The review priority classification for this application is standard (S).

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed, under section 505(b) of the Act, on April 4, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 3, 2009.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Devi Kozeli, RAC., Regulatory Project Manager, at 301-796-1128.

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC.
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
2/6/2009 04:02:00 PM

PDUFA Clock Restart

(This form must be completed upon applicant removal from the arrears list.)

Applicant: Tris Pharma, Inc

Date Firm Removed From Arrears List (Payment Date): February 3, 2009

NDA #	Supplement (S) or Reviewable Unit (RU) #
22500	

PROJECT MANAGER: Devi Kozeli, RAC.

HFD-110

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/s/

Devi Kozeli
2/4/2009 03:15:09 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-500

Tris Pharma, Inc.
Attention: W. Scott Groner
Director Regulatory Affairs and Compliance
2033 Route 130, Suite D
Monmouth Junction, NJ 08502

Dear Mr. Groner:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Clonidine ER Tablets, 0.2 and 0.3 mg **b(4)**

Date of Application: January 13, 2009

Date of Receipt: January 14, 2009

Our Reference Number: NDA 22-500

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 70963
Charlotte, NC 28272-0963

Checks sent by a courier should be addressed to:

Wachovia Bank
Attn: Food and Drug Administration, Lockbox 70963
1525 West WT Harris Blvd., Room NC0810
Charlotte, NC 28262

NOTE: Please include the User Fee I.D. Number, the Application number, and the FDA P.O. Box number (P.O. Box 70963) on the enclosed check. It would be helpful if you included the user fee cover sheet (Form FDA 3397) with your payment.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

NDA 22-500
Page 2

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other questions, please call Bev Friedman or Mike Jones at 301-594-2041.

If you have any questions, please call Devi Kozeli, RAC., Regulatory Project Manager, at 301-796-1128.

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC.
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
2/3/2009 06:44:48 AM

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2010 See Instructions for OMB Statement, below.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PREScription DRUG USER FEE COVERSHEET
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm		
1. APPLICANT'S NAME AND ADDRESS TRIS PHARMA INC W Scott Groner 2033 Route 130, Suite D Monmouth Junction NJ 08852 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER N101635	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? ☐ YES ☒ NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: ☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION ☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
2. TELEPHONE NUMBER 732-940-0358	3. PRODUCT NAME Clonidine — ER Tablets	6. USER FEE I.D. NUMBER PD3008979
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. ☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) ☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE ☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act ☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO		
OMB Statement: Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Food and Drug Administration CDER, HFD-94 CDER, HFD-99 12420 Parklawn Drive, Room 3046 1401 Rockville Pike Rockville, MD 20852 Rockville, MD 20852-1448		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Principal Regulatory Affairs Manager	DATE 12/31/08
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$623,600.00		
Form FDA 3397 (03/07)		

b(4)

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