

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**19-777/S-044**

**Administrative/Correspondence**

## **13 PATENT INFORMATION**

### **13.1 Patent Information**

The Patent information to support this supplemental new drug application is incorporated by reference into this section from NDA 19-777 (Item 13 Patent Information) for Zestril<sup>®</sup> (lisinopril) Tablets and correspondence sent to the Division of Cardio-Renal Drug Products dated 01 May 1989 regarding extension of the patent life of US Patent No. 4,374,829 to December 29, 2001.

The Patent information to support this supplemental new drug application is also incorporated by reference into this section from NDA 19-888 (Item 13 Patent Information) for Zestoretic<sup>®</sup> (lisinopril/hydrochlorothiazide) Tablets and correspondence sent to the Division of Cardio-Renal Drug Products dated 01 May 1989 regarding extension of the patent life of US Patent No. 4,374,829 to December 29, 2001.

EXCLUSIVITY SUMMARY FOR NDA # 19-777 SUPPL # SE5-044

Trade Name Zestril Generic Name lisinopril

Applicant Name AstraZeneca Pharmaceuticals LP HFD # 110

Approval Date If Known July 1, 2003

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

a) Is it an original NDA?  
YES /\_\_\_/ NO /X/

b) Is it an effectiveness supplement?  
YES /X/ NO /\_\_\_/

If yes, what type? (SE1, SE2, etc.) SE5

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 /X/ 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.

\_\_\_\_\_  
\_\_\_\_\_

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 /\_X\_/

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 /\_X\_/ NO /\_\_\_/

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /\_X\_/ NO /\_\_\_/

If yes, NDA # 19-558. Drug Name Prinivil (lisinopril).

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /\_\_\_/ NO /\_\_\_/

IF THE ANSWER TO QUESTION 3 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#

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. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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:

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(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.



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 /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ 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: \_\_\_\_\_  
\_\_\_\_\_

Alisea Sermon, Pharm.D.

June 25, 2003  
Date

Signature Title: Regulatory Health Project Manager

Douglas C. Throckmorton, M.D.  
Signature of Office/  
Signature Title: Division Director

June 25, 2003  
Date

Form OGD-011347 Revised 10/13/98  
cc: Original NDA          Division File

HFD-610 Mary Ann Holovac

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

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Alisea Sermon  
7/1/03 09:42:10 AM

Doug Throckmorton  
7/1/03 11:36:54 AM

**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: NDA 19-777 Supplement Type (e.g. SE5): SE5 Supplement Number: 044

Stamp Date: September 5, 2001 Action Date: \_\_\_\_\_

HFD 110 Trade and generic names/dosage form: Zestril (lisinopril) Tablet

Applicant: AstraZeneca Pharmaceuticals LP Therapeutic Class: Antihypertensive

Indication(s) previously approved: Hypertension, Heart Failure, Acute Myocardial Infarction

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Hypertension

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies: 1 month to 16 years

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. 1 yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 16 Tanner Stage \_\_\_\_\_

**Comments: Pediatric studies submitted in response to our 11/2/99 Written Request and 3/26/01 Written Agreement. Proposed labeling changes to the CLINICAL PHARMACOLOGY, PRECAUTIONS/Pediatric Use, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections.**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*if studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*if studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
71-594-7337**

**ITEM 16 - CERTIFICATION STATEMENT**

Re: Zestril (lisinopril) Tablets NDA 19-777: supplemental NDA

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP, that we did not use and will not use in connection with this application, the services of any person in any capacity debarred under section 306 (a) or (b)

Sincerely,

Lindy M. Lancaster for

Anthony Rogers

Vice President, Regulatory Affairs



**OFFICES OF DRUG EVALUATION  
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT  
ACTION PACKAGE CHECKLIST**

NDA# 19-777/S-044

Drug: Zestril (lisinopril) Tablet, 2.5, 5, 10, 20, 30, 40 mg

Applicant: AstraZeneca Pharmaceuticals LP

Chem/Ther/Other Types: SE5

CSO/PM: Quynh Nguyen

Phone: 4-5311

HFD-110

USER FEE GOAL DATE: September 5, 2002

DATE CHECKLIST COMPLETED: July 5, 2002

Arrange package in the following order (include a completed copy of this CHECKLIST): Check or Comment

- |     |   |                  |                                 |          |
|-----|---|------------------|---------------------------------|----------|
| 1.  | ACTION LETTER with supervisory signatures<br>Are there any Phase 4 commitments?   | AP<br>Yes        | AE X<br>No X                    | NA       |
| 2.  | Have all disciplines completed their reviews?<br>If no, what reviews are still in draft?  | Yes X            | No                              |          |
| 3.  | LABELING (package insert and carton and container labels).<br>(If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)   | Draft X<br>Final | Revised Draft                   |          |
| 4.  | Package inserts of the last 3 drugs approved that are of similar pharmacologic class.   | X                |                                 |          |
| 5.  | CLINICAL INVESTIGATOR FINANCIAL DISCLOSURE  | X                | (medical officer's review only) |          |
| 6.  | PATENT INFORMATION  | X                |                                 |          |
| 7.  | EXCLUSIVITY CHECKLIST   | X                |                                 |          |
| 8.  | PEDIATRIC PAGE (all NDAs)   | X                |                                 |          |
| 9.  | DEBARMENT CERTIFICATION (Copy of applicant's certification [all NDAs submitted after 1992]).  |                  |                                 | X        |
| 10. | Statement on status of DSI's AUDIT OF MAJOR CLINICAL STUDIES<br>If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.<br>If no audits were requested, include a memo explaining why.   |                  |                                 | NA       |
| 11. | REVIEWS [If more than 1 review for any 1 discipline, separate reviews with a sheet of: colored paper. Any conflicts between reviews must have resolution documented.]:<br>DIVISION DIRECTOR'S MEMO X<br>GROUP LEADER'S MEMO<br>MEDICAL REVIEW X<br>SAFETY UPDATE REVIEW NA<br>STATISTICAL REVIEW X<br>BIOPHARMACEUTICS REVIEW X<br>PHARMACOLOGY REVIEW (include pertinent IND reviews) X<br>Statistical Review of Carcinogenicity Study(ies) NA<br>CAC Report/Minutes NA<br>CHEMISTRY REVIEW X<br>Labeling and Nomenclature Committee Review Memorandum NA<br>Date EER completed (attach signed form or CIRTS printout) NA<br>FUR needed FUR requested NA<br>Have methods been validated? NA<br>Environmental Assessment Exclusion? X<br>If no exclusion, Review/FONSI<br>MICROBIOLOGY REVIEW (see chemistry review)<br>What is the status of the monograph? NA |                  |                                 |          |
| 12. | CORRESPONDENCE and FAXes  |                  |                                 | NA       |
| 13. | Minutes of Meetings including Telecons and Memoranda<br>Date of End-of-Phase 2 Meeting<br>Date of pre-IND Meeting   | NA<br>NA<br>NA   |                                 |          |
| 14. | ADVISORY COMMITTEE MEETING MINUTES<br>or, if not available, 48-hour Info Alert or pertinent section of transcript   | NA               |                                 |          |
| 15. | FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS   |                  |                                 | NA       |
| 16. | If approval letter, has ADVERTISING MATERIAL been reviewed?<br>If no and this is an AP with draft labeling letter, has advertising material already been requested?   |                  |                                 | NA<br>NA |
| 17. | INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)  |                  |                                 | NA       |
| 18. | INTEGRATED SUMMARY OF SAFETY (from NDA)   |                  |                                 | NA       |

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

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**Transmitted to FAX Number:** (302) 886-2822

**Attention:** Ms. Judy Firor

**Company Name:** AstraZeneca Pharmaceuticals LP

**Phone:** (302) 886-7539

**Subject:** Zestril

**Date:** 7/2/03

**Pages including this sheet:** 41

**From:** Alisea Sermon  
**Phone:** 301-594-5334  
**Fax:** 301-594-5494

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU.**

**RHPM Review of Final Printed Labeling  
NDA 19-777/042&SE5-044**

**Date of Submission:** June 12, 2003  
**FPL Submitted:** June 13, 2003  
**Date of Review:** June 20, 2003  
**Sponsor Name:** AstraZeneca Pharmaceuticals LP  
**Product(s) Name:** Zestril (lisinopril)

**Evaluation:**

These supplemental new drug applications provide for FPL revised to add changes to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE** and **DOSAGE AND ADMINISTRATION** sections of the labeling in accordance with our July 25, 2002 approvable letter for Zestril (lisinopril) pediatric efficacy supplement (S-044) and revised safety information (S-042).

The final printed labeling also includes revisions in response to our approval letters dated October 17, 2002 and January 22, 2003 that provided for changes to the **WARNINGS/Head and Neck Angioedema** and **Intestinal Angioedema** subsections.

**Recommendation:**

The FPL is identical to the labeling changes described in the approvable letter dated July 25, 2002 and the approval letter received by Merck for Prinivil (lisinopril) dated May 29, 2003.

An approval letter should issue for this supplemental new drug application.

Alisea Sermon, Pharm.D.  
Regulatory Project Manager

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

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Alisea Sermon :  
7/2/03 08:14:21 AM  
CSO

**RHPM Review of Draft Labeling**

**Application:** NDA 19-777/SLR-042 and SE5-044  
Zestril (lisinopril) Tablet, 2.5, 5, 10, 20, 30, 40 mg

**Applicant:** AstraZeneca Pharmaceuticals LP

**Document Date:** July 17, 2000 and January 23, 2002 (SLR-042)  
November 2, 2001 (SE5-044)

**Receipt Date:** July 19, 2000 and January 24, 2002 (SLR-042)  
November 5, 2001 (SE5-044)

**Background:** Supplemental application SLR-042 was submitted to include revised safety information per 21 CFR 314.70(b). In the cover letter, the sponsor referred to the February 17, 1999 approval letter for Prinivil (lisinopril) Tablets (NDA 19-558/S-036) sent to Merck Research Laboratories, stating that the proposed changes in SLR-042 are identical to the changes approved for NDA 19-558/S-036. Please refer to Ms. Sandy Birdsong's RHPM Review of Draft Labeling dated December 3, 2001 in DFS for the review of labeling supplement SLR-042.

Supplemental application SE5-044 provides for the submission of pediatric study reports, submitted in fulfillment of a Written Request dated November 2, 1999 and Written Agreement dated November 1, 2001. Pediatric exclusivity was granted on November 19, 2001. Based on data included in the supplemental application, the sponsor proposes revisions to the **CLINICAL PHARMACOLOGY, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections.

**Review:** For SE5-044, the sponsor has submitted draft labeling revised as follows:

1. Under **CLINICAL PHARMACOLOGY**, the following subsection has been added at the end of this section:

**Pediatric Patients**

**L**

U

J

2. Under **PRECAUTIONS**, the **Pediatric Use** subsection has been changed from:

**Pediatric Use:** Safety and effectiveness in pediatric patients have not been established.

to:

U

J

3. Under **ADVERSE REACTIONS**, the following subsection has been added before the **Clinical Laboratory Test Findings** subsection:

U

J

4. Under **DOSAGE AND ADMINISTRATION**, the following subsections

U

J

The following changes were noted since the last approved package insert (approved February 7, 2000/SE1-037):

1. Minor editorial corrections were made, e.g. capitalizations of letters and spelling corrections.
2. Under **DOSAGE AND ADMINISTRATION**, in the table under **Dosage Adjustment in Renal Impairment**, " $\geq 10 \leq 30$ " under the "Creatinine Clearance mL/min" column has been changed to ">10 <30."
3. Under **DOSAGE AND ADMINISTRATION/Heart Failure**, the word "daily" has been removed in the first sentence of the second paragraph. This sentence has been changed from:

"The usual effective dosage range is 5 to 40 mg per day administered as a single daily dose."

to

"The usual effective dosage range is 5 to 40 mg per day administered as a single dose."

4. The package insert has been changed to reflect the trademark statement and the new ownership. The change in NDA sponsorship was submitted to the Agency on February 2, 2000. These changes were included in the July 18, 2001 Annual Report.

In his November 19, 2001 medical review, Dr. Stockbridge recommended the following changes to the sponsor's proposed language:

1. Under **CLINICAL PHARMACOLOGY**, the first two paragraphs should be rewritten as follows:

[

]

[

]

2. \_\_\_\_\_ the Pediatric Use section should be rewritten as follows:

Pediatric Use

[

]

Dr. Stockbridge wrote in his November 19, 2001 review that the other labeling changes proposed by the sponsor were "adequate." Per a July 17, 2002 conversation with Dr. Stockbridge, he stated that the statement in his review "Under DOSAGE AND ADMINISTRATION, the sponsors propose the following: [

\_\_\_\_\_ ] should be ignored since the statement was not actually included in the sponsor's proposed labeling.

In his June 19, 2002 biopharmaceutics review, Dr. Gobburu recommended the following changes to the sponsor's proposed language:

1. [

]

2. The Clinical Study portion of sponsor proposed label should include the following sentence. [

In his July 11, 2002 chemistry review under "Evaluation of Labeling Information," Dr. Zimmerman noted the following:

"The directions for preparation provide adequate steps to allow this suspension dosage form to be easily prepared.

The labeling of the drug product as a suspension is justified since not all of the tablet excipients are fully dissolved even though the active drug moiety is known to be easily dissolved.

Concerning the shake time, it has been shown that the tablets quickly dissolve within 30 seconds. The recommended shake time of one minute is considered to offer a good time margin for complete dissolution to take place."

Minor editorial errors in the package insert were noted in this draft labeling submission. Per July 17 and 19, 2002 conversations with Dr. Stockbridge, he agreed that the following editorial corrections should be made:

1. Throughout the package insert, the font style of the section or subsection words in the parenthetical and non-parenthetical references should be made consistent with that of the actual section or subsection headers, e.g., the word "WARNINGS" in the phrase "(See WARNINGS)" should be changed to bold font style.
2. Under WARNINGS/Fetal/Neonatal Morbidity and Mortality, in the first sentence of the sixth paragraph, the spelling of the word "hyperkaliemia" should be corrected to "hyperkalemia."
3. Under DOSAGE AND ADMINISTRATION, in the table under Dosage Adjustment in Renal Impairment, ">10 <30" under the "Creatinine Clearance mL/min" column should be restored to " $\geq 10 \leq 30$ ."
4. Under DOSAGE AND ADMINISTRATION/Heart Failure, the word "daily" should be restored in the first sentence of the second paragraph so that it reads as follows: "The usual effective dosage range is 5 to 40 mg per day administered as a single daily dose."

It was noted that parts of this labeling differed in content from the labeling for NDA 19-558/Prinivil (lisinopril) Tablet. Per a July 25, 2002 conversation, Drs. Throckmorton and Stockbridge agreed that the labeling should be consistent for both NDA 19-558/Prinivil and NDA 19-777/Zestril, except for the information pertaining to the ATLAS trial from NDA 19-777/Zestril.

#### **Comments/Recommendations:**

An approvable letter should issue for both these supplements (SLR-042 and SE5-044) requesting final printed labeling revised as indicated above.

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager

qn/7-3-02/7-18-02/7-22-02/7-25-02

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/s/

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Quynh Nguyen  
9/5/02 06:25:49 PM  
CSO

96 page(s)  
of draft labeling was  
redacted from the  
approval package

**Nguyen, Quynh**

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**From:** Cropp, Cheryl  
**ent:** Wednesday, June 05, 2002 2:11 PM  
**To:** Nguyen, Quynh  
**Cc:** Chong, Barbara; Haffer, Andrew  
**Subject:** Pediatric Efficacy Supplements for Lisinopril

Hello Quynh,

I have completed my review of Lisinopril (NDA 19-558/SE5-043 and 19-777/SE5-044). I have no comments or issues with the proposed labeling. Please let me know if you have any questions and/or concerns.

Sincerely,

Cheryl Cropp, Pharm.D., BCPS  
DDMAC



NDA 19-777

AstraZeneca Pharmaceuticals LP  
Attention: Ms. Cindy Lancaster  
1800 Concord Pike  
P. O. Box 8355  
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

Reference is made to your request for a Written Agreement dated June 28, 2001, and our amended Written Request dated November 2, 1999, for pediatric studies of lisinopril. We are issuing this Written Agreement pursuant to your request. For ease of reference, we are providing the page number and paragraph heading in the amended Written Request letter that pertain to the agreements.

The Food and Drug Administration and AstraZeneca Pharmaceuticals LP agree to the following:

1. Clarification of Bullet 3 under "Strategy" – page 1.

AstraZeneca Pharmaceuticals LP proposes to provide safety data on lisinopril from:

- the controlled dose-ranging study and the pharmacokinetic studies;
- a retrospective medical chart review of 80 to 100 pediatric patients in a pediatric nephrology practice treated with lisinopril to describe adverse events, effects on blood pressure and doses used;
- a review of all available safety information in pediatric patients from postmarketing surveillance and the literature.

2. Clarification of "Dose-ranging Trial – Trial Design" – page 3.

AstraZeneca Pharmaceuticals LP intends to include in the dose-ranging trial a randomized withdrawal phase to ensure the study should be interpretable (i.e., Trial C in the Written Request).

3. Clarification of "Dose-ranging Trial – Eligibility" – page 4.

In the dose-ranging trial, AstraZeneca Pharmaceuticals LP proposes to include approximately 10-30% African-American patients and >25% female patients.

4. Clarification of "Dose-ranging Trial – Statistical Considerations" – page 4.

The dose-ranging trial will be designed with at least 80% power (at the p=0.05 statistical significance level) to detect a treatment effect in the randomized withdrawal phase.

5. Clarification of "Format of Reports" – page 4.

Case report forms from the pharmacokinetic and dose-ranging studies submitted electronically will be annotated with the names of the SAS variables used. AstraZeneca Pharmaceuticals LP intends to submit a report with data definition tables to allow navigation through the SAS transport files. All data points entered onto the case report forms that pertain to the study will be included as a variable in the data definition tables, although some text fields considered supportive to the data will not be included.

If you have any questions, please contact:

Ms. Sandra Birdsong  
Regulatory Project Manager  
(301) 594-5334

Any changes to this agreement should be made in writing by consensus under a separate correspondence. Alterations to this document without consensus are not valid.

    |S|

Steven J. Miller, Ph.D.  
Executive Director, Regulatory Affairs  
AstraZeneca Pharmaceuticals LP

    |S|

Robert Temple, M.D.  
Director, Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Robert Temple  
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Four Years from  
the Date of this Letter NOV - 2 2003

NDA 19-777

Zeneca Pharmaceuticals  
A Business Unit of Zeneca, Inc.  
Attention: Mr. Robert J. Orzolek  
1800 Concord Pike  
P.O. Box 15437  
Wilmington, DE 19850-5437

Dear Mr. Orzolek:

Reference is made to our December 23, 1998 written request for pediatric studies for Zestril (lisinopril) Tablets. We have recently reviewed that written request and have decided to amend it. Please note that the following Written Request supercedes that of December 23, 1998, which is no longer valid.

Changes have been made to the following sections:

1. The third bullet under "strategy,"
2. The fourth and fifth bullet under "age groups,"
3. The second sentence under "recruiting,"
4. "Format of Reports," and
5. The date the reports are due
6. Timing of Submission of Reports

### Strategy

The requested data will provide guidance for the use of lisinopril to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial, and an open treatment phase following the trial or other comparable database, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of lisinopril on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

## **Pediatric Subgroups**

### Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1 - 24 months),
- pre-school children (age 2 - 6 years),
- school-age children (age 6 - 12 years or  $\leq$  Tanner Stage 3), preferred group for effectiveness study, and
- adolescents ( $>$  12 years or  $>$  Tanner Stage 3 - 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide "children" into "pre-school" and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

### Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure a mixture of black and non-black patients.

### **Formulation Issues**

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailability compared to the marketed product.

### **Dose-ranging Trial**

#### **Trial Design**

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of lisinopril is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of lisinopril, with the doses chosen to give blood levels in a range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose.<sup>1</sup> After two weeks of treatment,<sup>2</sup> the trial would be analyzed by looking for a significantly positive slope

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<sup>1</sup> Doses would usually be derived from adult doses scaled by body surface area, but there should be, from PK data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.

of the placebo-corrected change in blood pressure from baseline as a function of dose.<sup>3</sup> If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show no effect), but it would be interpretable.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful.<sup>4</sup> In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close follow-up and withdrawal to open-label treatment at the discretion of their physicians. The analysis of Trial C would be a slope analysis for the first phase, but then (if the first phase revealed a flat dose-response curve) an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a positive dose response (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower on active treatment). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of lisinopril and then randomly withdrawn to lower doses (including placebo), with the same close follow-up, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

#### Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must also be included, and at least 50% of the patients in the trial should be 6 – 12 years old or  $\leq$  Tanner Stage 3 or younger. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with lisinopril or other therapy should be neither required nor disqualifying.

#### Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

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<sup>2</sup> The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

<sup>3</sup> In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

<sup>4</sup> When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

#### Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

#### Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional ( $P=0.05$ ) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

#### **Pharmacokinetic Trials**

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [[www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm), under Clinical/Pharmacological (Draft)].

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to lisinopril and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life,  $C_{max}$ , and  $t_{max}$  in pediatric subjects of the various age groups.

#### **Format of Reports**

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. You may submit this report with essential data in electronic form, with a case report form annotated with the names of the SAS variables used.

#### **Labeling Changes**

The results of the completed studies may be used in the labeling of your drug product to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population<sup>5</sup> that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product is approved.

#### **Timing of Submission of Reports**

Reports of the above studies must be submitted to the Agency on or before four years from the date of this letter. Please remember that pediatric exclusivity only adds to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies.

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<sup>5</sup> For example, pediatric patients with hypertension secondary to advanced renal disease.

When submitting the reports, please clearly mark your submission **“SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED”** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

Director  
Office of Generic Drugs  
HFD-600, Metro Park North II  
7500 Standish Place  
Rockville, MD 20855-2773

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely yours,

Robert Temple, M.D.  
Director  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDA

HFD-110/Division file

HFD-110/Project Manager

HFD-101/Office Director

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-2/TCrescenzi

Drafted by: sb/10/8/99

Initialed by:

Final:

filename: n19777PedWrit991008doc

PEDIATRIC WRITTEN REQUEST LETTER  
INFORMATION REQUEST (IR)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 19-777/S-044

AstraZeneca Pharmaceuticals LP  
Attention: Ms. Cindy M. Lancaster  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Dear Ms. Lancaster:

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

Name of Drug Product: Zestril (lisinopril) Tablets

NDA Number: 19-777

Supplement number: S-044

Date of supplement: November 2, 2001

Date of receipt: November 5, 2001

Unless we notify you within 60 days of the receipt 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 January 4, 2002 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Cardio-Renal Drug Products, HFD-110  
Attention: Division Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardio-Renal Drug Products, HFD-110  
Attention: Division Document Room  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any questions, please call:

**Ms. Sandra Birdsong**  
**Regulatory Project Manager**  
**(301) 594-5334**

Sincerely yours,

**Natalia A. Morgenstern**  
**Chief, Project Management Staff**  
**Division of Cardio-Renal Drug Products**  
**Office of Drug Evaluation I**  
**Center for Drug Evaluation and Research**

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/s/

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Natalia Morgenstern  
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