

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-558/S-043

Administrative/Correspondence Reviews

PATENT SUBMISSION FORM

Time Sensitive Patent Information pursuant to 21 C.F.R. §314.53 and/or
Patent Information pursuant to 21 C.F.R. §314.53 and §314.60
for

NDA # 19-558

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: PRINIVIL
- Active Ingredient(s): Lisinopril
- Strength(s): 2.5, 5, 10, 20, 40 mg
- Dosage Form(s): tablet
- Date NDA Filed: April 16, 1986
- Date NDA Approved: December 29, 1987, October 25, 1988 and January 28, 1994

A. This section should be completed for each individual patent

U.S. Patent Number: 4,374,829

Expiration Date: 06/29/2002

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) Y N
2. Drug Product (Composition/Formulation) Y N
3. Method of Use Y N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

**B. The following declaration statement is required if the above listed patent has Composition/
Formulation or Method of Use claims.**

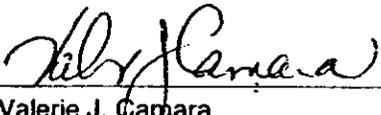
The undersigned declares that United States Patent Number 4,374,829

covers the composition, formulation and/or method of use of lisinopril

(name of drug product). This product is:

- currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act
- OR
- the subject of this application for which approval is being sought.

Respectfully submitted,

By 
Valerie J. Camara
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000 - RY60-30
Rahway, NJ 07065-0907
(732) 594- 3902

Date: July 27, 2001

A copy of the above information should be submitted to the FDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

In accordance with 21 C.F.R. §314.53(d)(4), the applicant shall submit two copies of each submission of patent information to:

Central Document Room
Center For Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Dr.
Rockville, MD 20857

Patent Information

m 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

- | | |
|------------------------------|--|
| 1. Active Ingredient | Lisinopril |
| 2. Dosage(s) | 2.5, 5, 10, 20 and 40 mg |
| 3. Trade Name | PRINIVIL |
| 4. Dosage Form | Tablets |
| Route of Administration | Oral |
| 5. Applicant Firm Name | Merck Research Laboratories |
| 6. NDA Number | 19-558 |
| 7. Approval Date | December 29, 1987, October 25, 1988 and January 28, 1994 |
| 8. Exclusivity | Date First ANDA could be submitted December 29, 1992
Length of Exclusivity Period 5 years |
| 9. Applicable Patent Numbers | US Patent No. 4,374,829
Expiration Date: June 29, 2002* † |

* Pursuant to 35 U.S.C. Section 156, an extension of 676 days has been granted for lisinopril. The patent expiration date is December 29, 2001.

† Pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act [Section 111 of the FDA Modernization Act of 1997 (21 U.S.C. Section 355a)], and the Guidance For Industry issued by FDA in June 1998 and revised in September 1999, pediatric exclusivity attaches to any exclusivity or patent protection that is, or will be, listed in the Orange Book for any drug product containing the same active moiety as the drug studied and for which the party submitting the studies holds the approved NDA. Accordingly, an additional six-month exclusivity period should be applied to US Patent No. 4,374,829 (expiration date December 29, 2001) listed under NDA 19-558 for PRINIVIL (lisinopril) and NDA 19-778 for PRINZIDE (lisinopril-hydrochlorothiazide), as PRINZIDE contains the same active moiety as PRINIVIL, and the NDA for PRINZIDE is also held by Merck.

EXCLUSIVITY SUMMARY FOR NDA # 19-558 SUPPL # 043

Trade Name Prinivil Generic Name lisinopril

Applicant Name Merck & Co., Inc. HFD # 110

Approval Date If Known _____

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 /___/

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 / / 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 / /

Appears This Way
On Original

Appears This Way
On Original

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

NDA# 19-558 Prinivil (lisinopril)

2. Combination product. N/A

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 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 / X / 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 / X / 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 / X / 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 /_X_ /

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:

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 / ___ /

Investigation #2

IND # _____ YES / ___ /

(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 / X /

If yes, explain: _____

Alisea Sermon, Pharm.D. 5/30/03
Signature Date
Title: Project Manager

Douglas C. Throckmorton, M.D. 5/30/03
Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

/s/

Alisea Sermon
5/29/03 03:43:44 PM

Doug Throckmorton
5/29/03 09:42:58 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: NDA 19-558 Supplement Type (e.g. SE5): SE5 Supplement Number: 043

Stamp Date: September 24, 2001 Action Date: _____

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

Applicant: Merck & Co., Inc. 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}

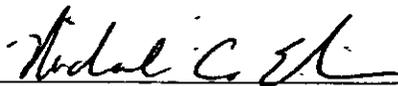
Regulatory Project Manager

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

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
1-594-7337

Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

 _____ 24SEPT2001

Michael C. Elia, Ph.D., DABT
Director, Regulatory Affairs

Date

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,

Cindy M. Lancaster for

Anthony Rogers

Vice President, Regulatory Affairs



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

NDA# 19-558/S-043 Drug: Prinivil (lisinopril) Tablet, 2.5, 5, 10, 20, 40 mg

Applicant: Merck & Co., Inc. Chem/Ther/Other Types: SE5

CSO/PM: Quynh Nguyen Phone: 4-5311 HFD-110

USER FEE GOAL DATE: July 25, 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
Are there any Phase 4 commitments? | AP
Yes | AE X
No X | NA |
| 2. | Have all disciplines completed their reviews?
If no, what reviews are still in draft? | Yes X | No | |
| 3. | LABELING (package insert and carton and container labels).
(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
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
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
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.]:
DIVISION DIRECTOR'S MEMO X
GROUP LEADER'S MEMO
MEDICAL REVIEW X
SAFETY UPDATE REVIEW NA
STATISTICAL REVIEW X
BIOPHARMACEUTICS REVIEW X
PHARMACOLOGY REVIEW (include pertinent IND reviews) X
Statistical Review of Carcinogenicity Study(ies) NA
CAC Report/Minutes NA
CHEMISTRY REVIEW X
Labeling and Nomenclature Committee Review Memorandum NA
Date EER completed (attach signed form or CIRTS printout) NA
FUR needed FUR requested NA
Have methods been validated? NA
Environmental Assessment Exclusion? X
If no exclusion, Review/FONSI
MICROBIOLOGY REVIEW X
What is the status of the monograph? NA | | | |
| 12. | CORRESPONDENCE and FAXes | | | NA |
| 13. | Minutes of Meetings including Telecons and Memoranda
Date of End-of-Phase 2 Meeting
Date of pre-IND Meeting | NA
NA
NA | | |
| 14. | ADVISORY COMMITTEE MEETING MINUTES
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?
If no and this is an AP with draft labeling letter, has advertising material already been requested? | | | NA
NA |
| 17. | INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA) | | | NA |
| 18. | INTEGRATED SUMMARY OF SAFETY (from NDA) | | | NA |

Nguyen, Quynh

From: Cropp, Cheryl
ant: Wednesday, June 05, 2002 2:11 PM
fo: 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

RHPM Review of Draft Labeling

Applications: NDA 19-558/SE5-043
Prinivil (lisinopril) Tablet, 2.5, 5, 10, 20, 40 mg

Applicant: Merck & Co, Inc.

Document Date: September 24, 2001

Receipt Date: September 25, 2001

Background: This supplemental application provides for the submission of pediatric study reports, submitted in fulfillment of a Written Request dated November 2, 1999 and Written Agreement dated March 26, 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: 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:

C

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:

Pediatric Use

Antihypertensive effects of PRINIVIL have been established in hypertensive pediatric patients aged _____ to 16 years. _____

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

- []
4. Under **DOSAGE AND ADMINISTRATION**, the following subsections have been added at the end of this section:

Pediatric Hypertensive Patients

The usual recommended starting dose is 0.07 mg/kg (up to 5 mg) once daily. Dosage should be adjusted according to blood pressure response. Doses above 0.61 mg/kg (or in excess of 40 mg) have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY, _____

PRINIVIL is not recommended . _____ in pediatric

[]

Preparation of Suspension (for 200 mL of a 1.0 mg/mL suspension)

Add 10 mL of Purified Water USP to a polyethylene terephthalate (PET) bottle containing ten 20-mg tablets of PRINIVIL and shake for at least one minute. Add 30 mL of Bicitra®** diluent and 160 mL of Ora-Sweet SF™*** to the concentrate in the PET bottle and gently shake for several seconds to disperse the ingredients. The suspension should be stored at or below 25°C (77°F) and can be stored for up to four weeks. Shake the suspension before each use.

□]
***Trademark of Paddock Laboratories, Inc.

There are no other changes since the last approved package insert (approved August 7, 2001/S-038).

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:

Clinical Study: In a clinical study involving 115 hypertensive pediatric patients to 16 years of age, patients who weighed <50 kg received either 0.625, 2.5, or 20 mg of lisinopril daily and patients who weighed ≥50 kg received either 1.25, 5, or 40 mg of lisinopril daily.

2. Under **PRECAUTIONS**, the *Pediatric Use* section should be rewritten as follows:

Pediatric Use

Antihypertensive effects of PRINIVIL have been established in hypertensive pediatric patients aged 6 to 16 years. There are no data on the use of PRINIVIL in □] in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m² □]

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: "

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

In his June 13, 2002 biopharmaceutics review, Dr. Robbie recommended the following changes to the sponsor's proposed language:

1. The proposed description of the pharmacokinetics of lisinopril should be moved to the **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism** section and should be modified to read "Pharmacokinetics of lisinopril was studied in pediatric hypertensive patients between 1 and 6 years. Steady state peak plasma concentrations occurred within 6 hours and the extent of absorption based on urinary recovery was about 28%, which are similar to adults. The typical value of lisinopril oral clearance in a child weighing 30 kg is 10 L/h, which increases in proportion to weight."

(Note: Per a July 19, 2002 discussion with Dr. Robbie, he stated that the first sentence should read: " "

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 correction should be made:

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.

It was noted that parts of this labeling differed in content from the labeling for NDA 19-777/Zestril (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 this supplement requesting final printed labeling revised as indicated above.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager

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

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

/s/

Quynh Nguyen
9/5/02 06:19:17 PM
CSO

57 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

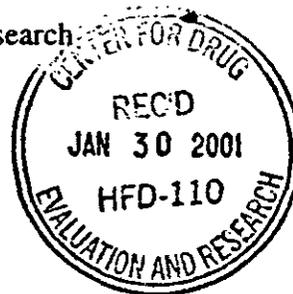
Michael C. Elia, Ph.D., DABT
Director
Regulatory Affairs

Merck & Co., Inc
BLA-20
PO. Box 4
West Point PA 19486
Tel 610 397 3180
215 652 5000
Fax 610 397 2516
Email michael_elia@merck.com



January 29, 2001

Robert Temple, M.D. – Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-40
1451 Rockville Pike
Rockville, MD 20852



Dear Dr. Temple:

NDA 19-558 PRINIVIL® (Lisinopril) Tablets

PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES

Please refer to the revised Written Request for pediatric studies on lisinopril issued by FDA to Merck on November 2, 1999. Please also refer to our Proposed Written Agreement (WA) submitted on June 21, 2000, the telephone conversations between Dr. Stephen Fredd of FDA and Dr. Michael C. Elia of Merck Research Laboratories, a Division of Merck & Co., Inc., on August 9 and 10, 2000 and October 18, 2000, and the draft Written Agreement sent from FDA to Merck on August 10, 2000. Reference is also made to the January 5, 2001 submission of Merck's proposed Written Agreement and the subsequent conversations on January 16 and 25, 2001 between Drs. Fredd and Elia regarding revisions to be made to our proposed WA. These revisions have been incorporated into our new, proposed WA (see below). Reference is also made to NDA 19-777 for ZESTRIL® (LISINOPRIL) Tablets, owned by AstraZeneca Pharmaceuticals LP.; [

1.

[conduct of pediatric studies for lisinopril by Merck with the intent of satisfying the requirements of Section 505A of the Federal Food, Drug and Cosmetic Act (the Act) and thereby qualifying lisinopril-containing products for an additional six month period of marketing exclusivity in the U.S. [

] for the purpose of qualifying for pediatric exclusivity under Section 505A of the Act. In accordance with the Agency's position as described by Dr. Fredd on October 18, 2000, [

] s.

Pursuant to Section 505A of the Act, 21 U.S.C. 355a and FDA's *Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act*," Merck hereby proposes to enter into a Written Agreement for pediatric studies on lisinopril. Our intention in proposing this Written Agreement is to clarify several items in the Written Request and to reach agreement on what will be necessary to meet our study objectives.

Proposed Written Agreement:

The items below refer to the relevant sections of the Written Request, issued November 2, 1999.

Merck & Co., Inc. and the Food and Drug Administration agree to the following:

1. Clarification of Bullet 3 under "Strategy"

Merck proposes to provide safety data on lisinopril from:

- the controlled dose-ranging and 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"

Merck intends to include in the dose-ranging trial a randomized withdrawal phase to ensure the study is interpretable (i.e., Trial C in the Written Request).

3. Clarification of "Dose-ranging Trial - Eligibility"

In the dose-ranging trial, Merck proposes to include approximately 10-30% African-American patients and 25-50% female patients.

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

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.

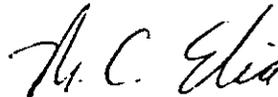
5. Clarification of "Format of Reports"

Case report forms from the pharmacokinetic and dose-ranging studies submitted electronically will be annotated with the names of the SAS variables used. Merck 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.

Robert Temple, M.D. – Director
NDA 19-558 PRINIVIL® (Lisinopril) Tablets
Page 3

If you have any questions or need additional information, please contact Michael C. Elia, Ph.D., DABT (610-397-3180) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,



Michael C. Elia, Ph.D., DABT
Director
Regulatory Affairs

q:\baf\521\nda lett\rev wa 012901

Federal Express #1

Desk Copy:

Raymond J. Lipicky, M.D., Director, WOC2, HFD-110 - Federal Express #2
Stephen B. Fredd, Deputy Director for Policy, WOC2, HFD-110 - Federal Express #2
Sandra Birdsong, Regulatory Health Project Manager, WOC2, HFD-110
Federal Express #2

cc:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No. 0910-0036
Expiration Date March 31, 2003
See OMB Statement on page 2

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Merck & Co., Inc.	DATE OF SUBMISSION 1-29-01
TELEPHONE NO (include Area Code) 610-397-3180	FACSIMILE (FAX) Number (include Area Code) 610-397-2516
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): P.O. Box 4 Sumneytown Pike, BLA-20 West Point, PA 19486	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 19-558		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lisinopril	PROPRIETARY NAME (trade name) IF ANY PRINIVIL™	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (S)-1-[N ² -(1-carboxy-3-phenylpropyl)-L-valeryl]-L-proline dihydrate	CODE NAME (if any)	
DOSAGE FORM Tablet	STRENGTHS 2.5, 5, 10, 20, 40 mg	ROUTE OF ADMINISTRATION Oral
(PROPOSED) INDICATION(S) FOR USE Hypertension		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)
IF AN NDA IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug Holder of Approved Application
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION _____
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)
REASON FOR SUBMISSION <i>Proposed Written Agreement for Pediatric Studies</i>
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary) include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1	index		
2	Labeling (check one)	<input type="checkbox"/> Draft Labeling	<input type="checkbox"/> Final Printed Labeling
3	Summary (21 CFR 314.50 (c))		
4	Chemistry section		
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)		
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)		
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)		
5	Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)		
6	Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)		
7	Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))		
8	Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)		
9	Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)		
10	Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)		
11	Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)		
12	Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)		
13	Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))		
14	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))		
15	Establishment description (21 CFR Part 600, if applicable)		
16	Debarment certification (FD&C Act 306 (k)(1))		
17	Field copy certification (21 CFR 314.50 (k)(3))		
18	User Fee Cover Sheet (Form FDA 3397)		
19	Financial Information (21 CFR Part 54)		

20. OTHER (Specify) *Proposed Written Agreement for Pediatric Studies*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

- 1 Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820
- 2 Biological establishment standards in 21 CFR Part 600.
- 3 Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
- 4 In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
- 5 Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
- 6 Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
- 7 Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Michael C. Elia</i>	TYPED NAME AND TITLE Michael C. Elia, Ph.D., DABT Director, Regulatory Affairs	DATE <i>1-29-01</i>
--	--	------------------------

ADDRESS (Street, City, State, and ZIP Code) Sumneytown Pike, P.O. Box 4, BLA-20 West Point, PA 19486	Telephone Number (610) 397-3180
--	--------------------------------------

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	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.
--	--

Michael C. Elia, Ph.D., DABT
Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel: 610 397 3180
215 652 5000
Fax: 610 397 2516
Email: michael_elia@merck.com

January 05, 2001

LEGON COPY

Robert Temple, M.D. – Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-40
1451 Rockville Pike
Rockville, MD 20852



Dear Dr. Temple:

**NDA 19-558 PRINIVIL® (Lisinopril) Tablets
PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**

Please refer to the revised Written Request for pediatric studies on lisinopril issued by FDA to Merck on November 2, 1999. Please also refer to our Proposed Written Agreement submitted on June 21, 2000, the telephone conversations between Dr. Stephen Fredd of FDA and Dr. Michael C. Elia of Merck Research Laboratories, a Division of Merck & Co., Inc., on August 9 and 10, 2000 and October 18, 2000, and the draft Written Agreement sent from FDA to Merck on August 10, 2000. Reference is also made to NDA 19-777 for ZESTRIL® (LISINOPRIL) Tablets, owned by AstraZeneca Pharmaceuticals LP. ☐

☐

☐

☐ with the intent of satisfying the requirements of Section 505A of the Federal Food, Drug and Cosmetic Act (the Act) and thereby qualifying lisinopril-containing products for an additional six month period of marketing exclusivity in the U.S. ☐

☐ In accordance with the Agency's position as described by Dr. Fredd on October 18, 2000. ☐

☐

Pursuant to Section 505A of the Act, 21 U.S.C. 355a and FDA's *Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act*, Merck hereby proposes to enter into a Written Agreement for pediatric studies on lisinopril. Our intention in proposing this Written Agreement is to clarify several items in the Written Request and to reach agreement on what will be necessary to meet our study objectives.

Proposed Written Agreement:

The items below refer to the relevant sections of the Written Request, issued November 2, 1999.

Merck & Co., Inc. and the Food and Drug Administration agree to the following:

1. Clarification of "Dose-ranging Trial - Eligibility"

In the dose-ranging trial, Merck proposes to include approximately 10-30% African-American patients and 25-50% female patients.

2. Clarification of Bullet 3 under "Strategy"

Merck proposes to provide safety data on lisinopril from:

- the controlled dose-ranging and pharmacokinetic studies. Note that safety data from the open-label extension portion of the dose-ranging trial will not be provided in the initial sNDA; these data will be provided as an information amendment to the IND when available.
- a review of all available safety information on pediatric patients from postmarketing surveillance of both PRINIVIL® (Lisinopril) Tablets and ZESTRIL® (LISINOPRIL) Tablets (i.e., a combined analysis), and
- a literature review on the use of lisinopril in pediatric patients.

3. Clarification of "Dose-ranging Trial - Trial Design"

Merck intends to include in the dose-ranging trial a randomized placebo withdrawal phase to ensure the study is interpretable (i.e., Trial C in the Written Request).

4. Clarification of "Dose-ranging Trial - Eligibility"

In the dose-ranging trial, Merck proposes to include approximately 10-30% African-American patients and 25-50% female patients.

5. Clarification of "Dose-ranging Trial - Statistical Considerations"

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 placebo withdrawal phase.

6. Clarification of "Format of Reports"

Case report forms from the pharmacokinetic and dose-ranging studies submitted electronically will be annotated with the names of the SAS variables used. Merck 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.

Robert Temple, M.D. – Director
NDA 19-558 PRINIVIL® (Lisinopril) Tablets
Page 3

If you have any questions or need additional information, please contact Michael C. Elia, Ph.D., DABT (610-397-3180) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,



Michael C. Elia, Ph.D., DABT
Director
Regulatory Affairs

q/antell/elia/letters/FDA1501.doc

Federal Express #1

Attachment: Merck submission to NDA 19-558, dated June 21, 2000, E

J

Desk Copy w/Attachment:

Raymond J. Lipicky, M.D., Director, WOC2, HFD-110 - Federal Express #2

Stephen B. Fredd, Deputy Director for Policy, WOC2, HFD-110 - Federal Express #2

Sandra Birdsong, Regulatory Health Project Manager, WOC2, HFD-110 - Federal Express #2

cc:

J

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0335
Expiration Date: March 31, 2003
See OMB Statement on page 2

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Merck & Co., Inc.

DATE OF SUBMISSION

1-3-03

TELEPHONE NO. (Include Area Code)

610-397-3180

FACSIMILE (FAX) Number (Include Area Code)

610-397-2516

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

P.O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-558

ESTABLISHED NAME (e.g., Proper name, USPI/USAN name)

Lisinopril

PROPRIETARY NAME (trade name) IF ANY

PRINIVIL™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
(S)-1-[N²-(1-carboxy-3-phenylpropyl)-L-tyrosyl]-L-proline dihydrate

CODE NAME (If any)

DOSAGE FORM

Tablet

STRENGTHS

2.5, 5, 10, 20, 40 mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

Hypertension

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

CBE

CBE-30

Prior Approval (PA)

REASON FOR SUBMISSION

Proposed Letter Agreement for Pediatric Studies

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary) Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or if not when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

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3	Summary (21 CFR 314.50 (c))
4	Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
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6	Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
7	Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
8	Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
9	Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
10	Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
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13	Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
14	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
15	Establishment description (21 CFR Part 600, if applicable)
16	Debarment certification (FD&C Act 306 (k)(1))
17	Field copy certification (21 CFR 314.50 (k)(3))
18	User Fee Cover Sheet (Form FDA 3397)
19	Financial information (21 CFR Part 54)

20. OTHER (Specify) *Proposed Indication Agreement for Pediatric Studies*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA if this application is approved. I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

- 1 Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
- 2 Biological establishment standards in 21 CFR Part 600.
- 3 Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
- 4 In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
- 5 Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
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If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Michael C. Eha</i>	TYPED NAME AND TITLE Michael C. Eha, Ph.D., DABT Director, Regulatory Affairs	DATE 1-5-01
ADDRESS (Street, City, State, and ZIP Code) Sumneytown Pike, P.O. Box 4, BLA-20 West Point, PA 19486		Telephone Number (610) 397-3180

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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 data submitted herein contains trade secrets, or privileged or confidential information, the property of Merck & Co., Inc. and government agencies are not authorized to make it public without written permission from Merck.

Michael C. Eia, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Tel 610 397 3180
215 652 5000
Fax 610 397 2516

June 21, 2000



Robert Temple, M.D. – Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
WOC2, HFD-40, Room 6014
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Temple:

**NDA 19-558 PRINIVIL® (Lisinopril) Tablets
PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**

Please refer to the revised Written Request for pediatric studies on lisinopril issued by FDA to Merck on November 2, 1999. Please also refer to NDA 19-777 for ZESTRIL® (lisinopril) Tablets, owned by AstraZeneca Pharmaceuticals LP; [

[

] with the intent of satisfying the requirements of Section 505A of the Federal Food, Drug and Cosmetic Act (the Act) and thereby qualifying lisinopril-containing products for an additional six month period of marketing exclusivity in the U.S.

Pursuant to Section 505A of the Act, 21 U.S.C. 355a and FDA's *Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act*, Merck hereby proposes to enter into a Written Agreement for pediatric studies on lisinopril. Our intention in proposing this Written Agreement is to clarify several items in the Written Request and to reach agreement on what will be necessary to meet our study objectives. In addition, we seek written agreement from the FDA that pediatric studies using lisinopril in the form of Merck's PRINIVIL® will satisfy the requirements for lisinopril under Section 505A of the Act for — Merck's —
lisinopril-containing products.

Proposed Written Agreement:

The items below refer to the relevant sections of the Written Request, issued November 2, 1999.

Merck & Co., Inc. and the Food and Drug Administration agree to the following:

1. Clarification of "Strategy"

[

2. Clarification of Bullet 3 under "Strategy"

Merck proposes to provide safety data on lisinopril from:

- the controlled dose-ranging and pharmacokinetic studies.
- a review of all available safety information on pediatric patients from postmarketing surveillance of both PRINIVIL® (lisinopril) Tablets and ZESTRIL® (lisinopril) Tablets (i.e., a combined analysis), and
- a literature review on the use of lisinopril in pediatric patients.

3. Clarification of "Dose-ranging Trial - Trial Design"

Merck intends to include in the dose-ranging trial a randomized placebo withdrawal phase to ensure the study is interpretable (i.e., Trial C in the Written Request).

4. Clarification of "Dose-ranging Trial - Eligibility"

In the dose-ranging trial, Merck proposes to include approximately 10-30% African-American patients and 25-50% female patients.

5. Clarification of "Dose-ranging Trial - Statistical considerations"

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 placebo withdrawal phase.

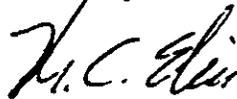
Robert Temple, M.D. - Director
NDA 19-558 PRINIVIL® (Lisinopril) Tablets
Page 3

6. Clarification of "Format of Reports"

Case report forms from the pharmacokinetic and dose-ranging studies submitted electronically will be annotated with the names of the SAS variables used. Merck 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 or need additional information, please contact Michael C. Elia, PhD, (610-397-3180) or, in my absence, Bonnie J. Goldmann, MD (610-397-2383).

Sincerely,



Michael C. Elia, PhD
Director
Regulatory Affairs

q/antell/cha/letters/FDA62100.doc

Federal Express #1

Attachment:

Desk Copy w/Attachment:

Ms. Sandra Birdsong, HFD-110, WOC2 - Federal Express #1

cc w/attachment:

Federal Express #2



NDA 19-558

MICHAEL C. ELIA

APR 03 2001

REGULATORY AFFAIRS

Merck and Company, Inc.
Attention: Michael C. Elia, Ph.D.
P. O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Elia:

Reference is made to your request for a Written Agreement dated January 29, 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 Merck and Company agree to the following:

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

Merck 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.

Merck 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, Merck 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.

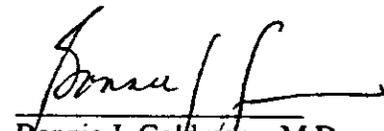
5. Clarification of "Format of Reports" – page 4.

Case report forms from the pharmacokinetic and dose-ranging studies submitted electronically will be annotated with the names of the SAS variables used. Merck 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 Health 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.



Bonnie J. Goldmann, M.D.
Vice President, Regulatory Affairs
Merck & Co., Inc.

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

/s/

Rachel Behrman
3/26/01 11:38:52 AM

Information and data submitted herein contains trade secrets, or privileged or confidential information, the property of Merck & Co., Inc. and government agencies are not authorized to make it public without written permission from Merck.

3 Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

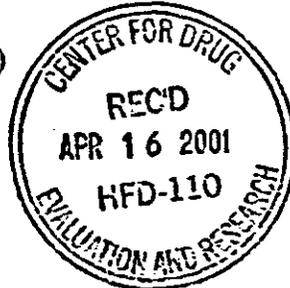
Michael C. Elia, Ph.D., DABT
Director
Regulatory Affairs

April 12, 2001

These copies are
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not desk copies

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486
Tel 610 397 3180
215 652 5000
Fax 610 397 2516
Email: michael_elia@merck.com

Robert Temple, M.D, Director
HFD-40, Room 6014
Office of Drug Evaluation I (CDER)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852



Dear Dr. Temple:

NDA 19-558: PRINIVIL™ Tablets (Lisinopril)
Fully Executed Written Agreement

DATE
N-PG

Reference is made to the above NDA, to Merck's original request for a Written Agreement dated December 10, 1998, and to the revised Written Request for lisinopril pediatric studies dated November 2, 1999. Reference is also made to the Merck Proposed Written Agreement submitted to the Agency January 29, 2001. Additional reference is made to the copy of the final Written Agreement, dated March 26, 2001, that was received from the Agency electronically signed by Rachel Behrman, M.D. (FDA) for Robert Temple, M.D. (FDA). One original, signed by Bonnie Goldmann, M.D. (MRL), is enclosed.

If you have any questions or need additional information, please contact Michael C. Elia, Ph.D., DABT (610-397-3180) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Michael C. Elia, Ph.D., DABT
Director, Regulatory Affairs

q:\bafallen\lisinopril\finwritt agree.doc

Enclosure : Original Executed Written Agreement
Federal Express #1

Desk Copy: Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852
c/o
Raymond J. Lipicky, M.D. - Director
Division of Cardio-Renal Drug Products
w/CD
Federal Express #2

Ms. Sandra L. Birdsong - Consumer Safety Officer
w/Enclosure
WOC2, HFD-110, Room 5024
Federal Express #3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Merck & Co., Inc.

DATE OF SUBMISSION

4-12-01

TELEPHONE NO. (Include Area Code) 610-397-3180

FACSIMILE (FAX) Number (Include Area Code) 610-397-2516

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

P.O. Box 4
Sumneytown Pike, BLA-20
West Point, PA 19486

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-558

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)
Lisinopril

PROPRIETARY NAME (trade name) IF ANY
PRINIVIL™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)
(S)-1-[N²-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate

CODE NAME (If any)

DOSAGE FORM:
Tablet

STRENGTHS:
2.5, 5, 10, 20, 40 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:

Hypertension

APPLICATION INFORMATION

APPLICATION TYPE
(check one)

- NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION *Fully Executed Written Agreement*

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

**Information and data submitted herein contains trade secrets,
or privileged or confidential information,
the property of Merck & Co., Inc. and government agencies
are not authorized to make it public without
written permission from Merck**

Food and Drug Administration
Rockville MD 20857

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

NDA 19-558

Merck & Co., Inc.
Attention: Jeffrey R. White, M.D.
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. White:

Reference is made to our December 23, 1998 written request for pediatric studies for Prinivil (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.¹ After two weeks of treatment,² the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.³ 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.⁴ 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.

¹ 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.

² 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.

³ 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.

⁴ 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.

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.

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, 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 population⁵ 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.

⁵ For example, pediatric patients with hypertension secondary to advanced renal disease.

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. 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: n19558PedWrit991008doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

7 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling