

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**20-386/S-032**

**Administrative Documents**

NDA 20-386

Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION  
MERCK RESEARCH LABORATORIES

- |                         |  |
|-------------------------|--|
| 1. Active Ingredient    | Losartan Potassium   |
| 2. Dosage(s)            | 25 mg and 50 mg  |
| 3. Trade Name           | COZAAR   |
| 4. Dosage Form          | Film Coated Tablets  |
| Route of Administration | Oral   |
| 5. Applicant Firm Name  | Merck Research Laboratories                                  |
| 6. NDA Number           | 20-386   |
| 7. Approval Date        | April 14, 1995   |
| 8. Exclusivity          | NCE April 14, 2000<br>New use three years from sNDA approval |

9. Applicable Patent Numbers
- US Patent No. 5,138,069\*  
Expiration Date: August 11, 2009
- US Patent No. 5,153,197\*  
Expiration Date: October 6, 2009
- US Patent No. 5,608,075§  
Expiration Date: March 4, 2014
- US Patent No. 5,210,079\*  
Expiration Date: May 11, 2010

\* Licensed from E.I. DuPont de Nemours and Company  
§ Co-owned by Merck & Co., Inc. with E.I. DuPont de Nemours and Company and The DuPont Merck Pharmaceutical Company (currently known as DuPont Pharmaceutical Company)

## 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 # 20-386

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

- Trade Name: COZAAR
- Active Ingredient(s): Losartan potassium
- Strength(s): 25mg and 50mg
- Dosage Form(s): Film Coated Tablets
- Date  NDA \_\_\_ sNDA filed: December 3, 1993
- Date  NDA \_\_\_ sNDA approved: April 14, 1995

### A. This section should be completed for each individual patent

U.S. Patent Number: 5,138,069

Expiration Date: 8/11/2009

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: E. I. Du Pont de Nemours and Company

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 5,138,069  
covers the composition, formulation and/or method of use of Losartan potassium  
(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.

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**A. This section should be completed for each individual patent**

**U.S. Patent Number:** 5,153,197

**Expiration Date:** 10/06/2009

**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:** E. I. DuPont de Nemours and Company, Wilmington, DE

**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 5,153,197

covers the composition, formulation and/or method of use of losartan potassium

(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.
-

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**A. This section should be completed for each individual patent**

**U.S. Patent Number:** 5,608,075

**Expiration Date:** 03/04/2014

**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, E.I. DuPont de Nemours and Company and The DuPont Merck Pharmaceutical Company both of Wilmington, DE

**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 5,608,075

covers the composition, formulation and/or method of use of Losartan potassium

(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.
-

---

**A. This section should be completed for each individual patent**

**U.S. Patent Number:** US 5,210,079

**Expiration Date:** 05/11/2010

**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:** E. I. DuPont de Nemours and Company, Wilmington, DE

**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 US 5,210,079

covers the composition, formulation and/or method of use of losartan potassium

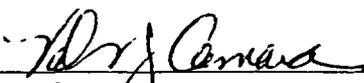
(name of drug product). This product is:

- currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

OR

- the subject of an 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: June 25, 2002

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

IN DUPLICATE

EXCLUSIVITY SUMMARY FOR NDA # 20-386 SUPPL #032

Trade Name: COZAAR

Generic Name: losartan potassium

Applicant Name: Merck and Company, 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.)

SE1

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:

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

Form OGD-011347 Revised 10/13/98

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

d) Did the applicant request exclusivity?

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

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

3 years

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

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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 / X /

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

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 / X /

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 / X / NO / \_\_\_ /

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

NDA# 20-386 \_\_\_\_\_

NDA# \_\_\_\_\_

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 /   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 /  / NO /  /

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

\_\_\_\_\_

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

YES /  / NO /  /

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

YES /  / NO /  /

If yes, explain:

\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /  / NO /  /

If yes, explain:



investigation was relied on:

\_\_\_\_\_

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

\_\_\_\_\_ LIFE Study \_\_\_\_\_

\_\_\_\_\_

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 / X / NO /     / Explain: \_\_\_\_\_

Investigation #2

IND # \_\_\_\_\_ YES /     / NO /     / Explain: \_\_\_\_\_

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: \_\_\_\_\_  
\_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_  
Edward Fromm, Regulatory Health Project Manager

Signature \_\_\_\_\_ Date \_\_\_\_\_  
Douglas C. Throckmorton  
Director, Division of Cardio-Renal Drug Products

cc: Original NDA      Division File      HFD-93 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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Doug Throckmorton  
1/3/03 03:16:04 PM

**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 20-386 Supplement Type (e.g. SE5): SE1 Supplement Number: S-032

Stamp Date: July 26, 2002 Action Date: January 26, 2003

HFD 110 Trade and generic names/dosage form: Cozaar (losartan potassium) Tablets

Applicant: Merck and Co. Therapeutic Class: Angiotensin II Blocker

Indication(s) previously approved: Treatment of hypertension, Treatment of type 2 diabetic nephropathy

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

Number of indications for this application(s): 1

Indication #1: Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

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 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-950/ Terrie Crescenzi

NDA ##-###  
Page 3

**HFD-960/Grace Carmouze**  
(revised 9-24-02)

**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  
301-594-7337**

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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/

-----  
Edward Fromm  
1/17/03 09:02:55 AM

Pursuant to 21 CFR 314.55(c), Merck is requesting a full waiver to the pediatric data requirement for the use of losartan to reduce the risk of cardiovascular morbidity and mortality in pediatric patients with hypertension and LVH. The rationale for this full waiver is that necessary studies are impossible or highly impractical because 1) the number of such patients is very small and 2) the occurrence of stroke and myocardial infarction in such patients is very rare.

LIFE was an outcome study with a composite endpoint of cardiovascular death, myocardial infarction, and stroke. Since stroke and myocardial infarction are rare in pediatric patients with hypertension and LVH [1], it would be impractical or impossible to conduct a study with sufficient power to measure a treatment effect in this population.

Please note that the FDA previously issued a Written Request for pediatric studies for the use of losartan in children with hypertension and that Merck submitted a sNDA fully responding to the WR. The FDA Pediatric Exclusivity Board determined on March 20, 2000, that Merck's sNDA for losartan pediatric studies met the terms of the agency's Written Request.

#### List of References

1. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory Blood Pressure and Left Ventricular Mass Index in Hypertensive Children. *Hypertension* 2002; 39:903-908.

Losartan Potassium  
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.



---

Jeffrey R. Tucker, M.D.  
Director  
Regulatory Affairs

7/25/02

---

Date

At the filing meeting on September 19, 2002, the Division stated that it would not ask for clinical audits of the study sites.

**APPEARS THIS WAY  
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 2003

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: SNDA 20-386/S-032 (Losartan, LIFE Study)

TO: File, NDA

The following are my thoughts on this supplemental NDA to incorporate the LIFE results into losartan labeling; they are, I believe, quite consistent with what the Cardiovascular and Renal Drugs Advisory Committee recommended and the Division believes.

1. Claim

Combined endpoints are a problem; they can imply effects that are not documented or that are even unlikely.

Losartan was more effective than atenolol on its combined endpoint of Total CV mortality plus non-fatal strokes and non-fatal AMI's and was more effective when total mortality is substituted for CV mortality (I know we consider this more conservative but in fact losartan had an advantage on the non-CV deaths of about 18 events, none of them plausibly related to the drug), but had no effect at all on AMI's and no greater effect, compared to atenolol, on CV mortality or morbidity other than stroke. The overall success (vs. an active control that surely had some effect in this trial) is a basis for accepting the study as showing an effect; the question is what effect, and here I would argue we are entitled to look at the components of the endpoint.

In the present case, virtually all the effect is driven by the effect on strokes.

Table 1 shows overall results, the components of the primary endpoint, and overall (not just as primary endpoint) stroke, AMI, and CV mortality rates (note CV mortality includes fatal strokes and AMI's so you can't tell what events are driving it). When you look at cause-specific mortality, however, it is quite clear that almost all of the effect on CV mortality (which is not itself statistically significant, 234 vs. 204,  $p=0.206$ ) comes from the effect on stroke (62 A vs. 40 L), with none from AMI; it isn't really fatal AMI but fatal events identified as CAD and SD (124 A vs. 125 L), and little from "other" (39 L vs. 48 A), the last difference due to 15 L vs. 22 A deaths due to "peripheral vascular disease."

All this leads me to conclude that however we describe the study, the only advantage of losartan comes from its effect on stroke (F+NF) and we should make that clear in labeling.

I want to note one other point. It seems most odd that the majority of what seem to be AMI's seem to have been fatal. Table 1 shows, for losartan, 198 fatal and non-fatal AMI's, with 125 CAD events fatal. If all 125 CAD events were indeed AMI's that would give a 63% mortality. There may, however, be counting errors in those figures. The 125 CAD deaths, e.g., include 81 SD's, which are certainly not all AMI's. This does lead me to ask where the figures for F/NF MI's come from; i.e., what is included?

Table 1  
Results

N	Losartan 4605 events (%)	Atenolol 4588 events (%)	HR (95% CI)	Nominal P
Primary Endpoint <sup>1</sup>	508	588	Adj, 0.869 (0.772-0.970) Unadj 0.854 (0.759-0.962)	p=0.021 p=0.009
CV death	137 (3.0)	154 (3.4)		
AMI	174 (3.8)	168 (3.7)		
Stroke	197 (4.3)	266 (5.8)		
Total Mortality	383 (8.3)	431 (9.4)		
Primary Endpoints with all deaths	670	751		Adjusted p=0.039
Strokes (patients with fatal/NF) <sup>2</sup>	232 (5.0)	309 (6.7)	0.752 (0.634-0.891)	p=0.001
AMI (patients with F/NF) <sup>2</sup>	198 (4.3)	188 (4.1)	1.073 (0.79-1.310)	p=0.491
CV Mortality <sup>2</sup>	204 (4.4)	234 (5.1)	0.886 (0.734-1.069)	p=0.206
Cause Specific CV Mortality				
Stroke	40 (0.9)	62 (1.4)		p=0.032
"AMI" (CAD, SD)	125 (2.7)	124 (2.7)		
Other	39 (0.8)	48 (1.0)		
NF Stroke	192 (4.2)	245 (5.3)		

<sup>1</sup>CV mortality and morbidity (death due to fatal MI, stroke, SD, progressive CHF, and other; morbidity is NF AMI or stroke)

<sup>2</sup>These endpoints are not mutually independent

## 2. Reliance on a single study

The proposed claim, it is critical to note, is not a superiority claim, but an effectiveness claim. The nominal p value of 0.023 for the primary endpoint (or 0.039 for our version using total mortality), is thus very strong evidence of superiority to placebo, given the documented effect on this endpoint of atenolol and, in fact, virtually all antihypertensive treatment. We found similar evidence persuasive for clopidogrel when the CAPRIE study was marginally superior to aspirin (i.e., evidence of effectiveness, not superiority) in a single study.

I do not entirely agree with Dr. Marciniak's conclusion that LIFE can be interpreted favorably enough for a claim under the FD&C Act, even if you believe only that atenolol is not harmful. Certainly the study, having shown superiority to atenolol, is "favorable," but not at a level ordinarily sufficient for approval (i.e., 2 studies or a very strong single study). It is the evidence that atenolol is in fact effective on the LIFE endpoints that makes the case strong. One could, I suppose, argue that all antihypertensives have a favorable effect on stroke, and that this observation also supports reliance on a single study of any particular drug. Indeed, as we develop language for antihypertensive labeling that says, in effect, that they all affect outcomes, I intend to argue that, apart from such a general statement, we should identify the particular drugs that actually have outcome data from at least one study. Aside from various diuretics (mostly at excessive doses), beta blockers, reserpine, nisoldipine, perhaps ramipril (depending on how you interpret HOPE), perhaps amlodipine (depending on how you interpret ALLHAT), most drugs do not have such data. Losartan now does.

3. Labeling for antihypertensives

As noted, the sponsor is not seeking a superiority claim (the single study with non-extreme p value would not generally support that without other evidence), although the description of the study will surely convey the impression of superiority (again see attempts to deal with this for clopidogrel).

What are the implications for labeling? It is hard to think Merck doesn't "deserve" recognition of these results in labeling but to date no antihypertensive drug has an outcome claim (maybe in reality ramipril has one but we didn't think that is what HOPE showed), although some (reserpine, high dose thiazide diuretics, 12.5-25 mg chlorthalidone, based on SHEP, several beta blockers based on STOP, nisoldipine if it came in, amlodipine and lisinpril, based on ALLHAT if someone calculated the known effect of the active control) could probably support such a claim. Our overall labeling plan is to have a general statement, supported both by meta-analyses and individual trial results, that says Rx of elevated BP (combined or isolated systolic) has favorable effects on outcome (surely stroke and CHF, probably mortality and we'll see about AMI, renal function, etc.), together with something about possible differences between treatments in general and in subsets. This would then be followed, I think, by results of hypertension outcome studies involving the particular drug, where those exist.

The present situation may move us somewhat uncomfortably along the second part, and it would be hard to think of a reason not to include LIFE in labeling, making it all the more urgent that we develop the first part.

/S/

Robert Temple, M.D.

cc:  
HFD-101/R Behrman  
HFD-101/R Temple  
drafted:sb/1/7/03;1/21/03  
final:sb/1/31/03  
Filename:Losartan\_MM\_Jan03.doc

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/s/

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Robert Temple  
1/31/03 05:23:49 PM  
MEDICAL OFFICER

RHPM NDA Efficacy Supplement Approval/Labeling Review  
March 20, 2003

Cozaar (losartan potassium) 25, 50 & 100 mg Tablets

NDA 20-386/S-032

**Sponsor:** Merck & Co., Inc.

**Classification:** SE1 (new indication)

**Review Classification:** Priority (6 month review)

**Indication:** Reduction of risk of stroke in \_\_\_\_\_ patients with hypertension and left ventricular hypertrophy

**Date of Application:** July 25, 2002

**Date of AE Letter:** January 24, 2003

**Date FPL Submitted:** March 14, 2003

**Date FPL Received:** March 17, 2003

**User Fee Goal Date:** May 17, 2003

### Background

An approvable letter was issued on January 24, 2003 for losartan potassium for the reduction of the risk of stroke in \_\_\_\_\_ patients with hypertension and left ventricular hypertrophy. After labeling discussions with the firm on January 31, February 10 and 28, 2003, the firm was informed that they could submit Final Printed Labeling (FPL).

### Review

Merck submitted final printed labeling on March 14, 2002, received March 17, 2002. When compared with the last approved labeling supplement (S-028, September 17, 2002) the following changes were noted:

1. Under **CLINICAL PHARMACOLOGY**, *Pharmacokinetics, General, Race*, the parenthetical (see also **PRECAUTIONS**, *Race* and **CLINICAL PHARMACOLOGY**, *Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race*) has been added.
2. Under **CLINICAL PHARMACOLOGY**, *Pharmacodynamic and Clinical Effects*, a new subheading entitled *Reduction in the Risk of Stroke* has been added that includes the results of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial.
3. Under **CLINICAL PHARMACOLOGY**, *Pharmacodynamic and Clinical Effects, Nephropathy in Type 2 Diabetic Patients*, Figure 1 and Table 1 have been renamed Figure 4 and Table 2, Table 2 has been renamed Table 3.
4. Under **INDICATIONS AND USAGE**, a new indication beneath the new subheading of *Hypertensive Patients with Left Ventricular Hypertrophy* has been added that reads as follows:

COZAAR is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but there is evidence that this benefit does not apply to Black patients. (see **PRECAUTIONS, Race** and **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke, Race.**)

5. Under **PRECAUTIONS**, a new subsection has been added entitled “*Race*” that reads as follows:

In the LIFE study, Black patients with hypertension and left ventricular hypertrophy had a lower risk of stroke on atenolol than on COZAAR. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study does not provide evidence that the benefits of COZAAR on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects; Reduction in the Risk of Stroke.**)

6. Under **ADVERSE REACTIONS**, a new subheading entitled *Hypertensive Patients with Left Ventricular Hypertrophy* has been added that reads as follows:

In the LIFE study, adverse events with COZAAR were similar to those reported previously for patients with hypertension.

7. Under **DOSAGE AND ADMINISTRATION, Hypertension**, the word “*Hypertension*” has been added to the parentheses in the 2<sup>nd</sup> and 3<sup>rd</sup> paragraphs under this subheading. The parentheses now read: (see **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Hypertension**).

8. Under **DOSAGE AND ADMINISTRATION**, a new subheading entitled “*Hypertensive Patients with Left Ventricular Hypertrophy*” has been added that includes the following information:

The usual starting dose is 50 mg of COZAAR once daily. Hydrochlorothiazide 12.5 mg daily should be added and/or the dose of COZAAR should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response (see **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Reduction in the Risk of Stroke**).

9. Under **DOSAGE AND ADMINISTRATION, Nephropathy in Type 2 Diabetic Patients**, the word “*Nephropathy in Type 2 Diabetic Patients*” has been added to the parenthesis under this subheading. The parenthesis now reads “(see **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Nephropathy in Type 2 Diabetic Patients**)”.

**Comments/Recommendations:**

I will draft an approval letter with labeling for this supplement for Dr. Temple’s signature.

  
\_\_\_\_\_  
Edward J. Fromm  
Regulatory Health Project Manager

dr-ef-3-20-03

RHPM NDA Efficacy Supplement Overview  
January 24, 2003

Cozaar (losartan potassium) Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

**NDA 20-386/SE1-032**

**Applicant:** Merck and Co.

**Classification:** SE1 (new indication)

**Review Classification:** Priority (6 month review)

**Proposed Indication:** Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

**Date of Application:** July 25, 2002

**Receipt Date:** July 26, 2002

**User Fee Goal Date:** January 26, 2003

**Background**

NDA 20-386/S-032 was submitted July 25, 2002, received July 26, 2002, for the new indication of reduction in the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy. The support for this new indication comes from the (LIFE) study, which was a large, multicenter, multinational, randomized, triple-blind, active-controlled study conducted in 9193 hypertensive patients aged 55 to 80 years (mean 67 years) with ECG-documented left ventricular hypertrophy. The goal of the study was to demonstrate the cardiovascular protective effects of Cozaar versus atenolol, over and above the benefits of blood pressure control alone (blood pressure was measured at trough).

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke, and myocardial infarction. The sponsor claims that treatment with Cozaar resulted in a 13.0% risk reduction ( $p=0.021$ ) as compared with atenolol for patients reaching the primary composite endpoint.

The sponsor claims that the benefit of losartan on the primary composite endpoint was generally consistent among multiple pre-specified demographic, geographic, medical history, and disease severity subgroups, as evidenced by the lack of significant treatment-by-subgroup interactions. However, in the predefined subgroup analyses, there was a suggestion of an interaction between ethnic background and treatment ( $p=0.057$ ). Further post hoc analyses revealed a significant qualitative treatment interaction for Blacks versus non-Blacks. Non-Black patients appeared to have lower risk of experiencing an event with losartan, while Black patients appeared to have lower risk with atenolol despite comparable blood pressure reduction among both groups.

Because of the new indication for this class of drugs, the Division asked Merck to present this application before the January 2003 Cardio-Renal Advisory Committee. The Advisory Committee will be asked to primarily address the robustness of the LIFE dataset to support the

new indication as well as comment on the apparent qualitative interaction in the African-American subgroup of this study.

The Cardio-Renal Advisory Committee met on January 6, 2003 to discuss the LIFE supplement and by a vote of 8 for and 2 against said that the LIFE trial would be an adequate basis for approval of losartan plus a **diuretic** to reduce the incidence of fatal and non-fatal stroke only and only in the population specifically studied in the LIFE trial.

The Committee voted, however, 2 for and 8 against to the question of approving losartan as having demonstrated superior efficacy when compared with atenolol in the population studied in LIFE to reduce the incidence of the combination of cardiovascular mortality, MI and stroke.

To the question of the African-American subgroup in the United States and apparent superiority of atenolol to losartan on the primary endpoint, the Committee said that although the subgroup analysis was post-hoc, it appears that atenolol is superior to atenolol and not worse than placebo. They recommended that this finding should be presented in both the **Clinical Trials** section and the **Warnings/Precautions** section of the labeling. In addition, some members said that the Indications section should be written to exclude the use of the product in the Black population.

After internal labeling discussions on January 16 and 22, 2003, we agreed that an approvable letter should issue accompanied by marked-up draft labeling. The marked-up draft labeling will include changes to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the labeling.

#### Meetings

Planning: September 21, 1995

Pre-Advisory Committee Meeting: November 26, 2002

#### **Review**

##### Medical

Division Director: Douglas C. Throckmorton

Conclusion: Approvable, see Dr. Throckmorton's January 22, 2003 memo

##### Medical:

Thomas Marciniak, M.D.

Labeling: See Dr. Marciniak's January 15, 2003 review for his numerous labeling revisions.

Conclusion: Approval; Dr. Marciniak states in his review, that the "LIFE study demonstrates adequately that antihypertensive regimens including losartan are superior to ones including atenolol for reducing the composite endpoint of death, myocardial infarction, and stroke in hypertensive patients with left hypertrophy. The endpoint is a vital one and the magnitude of the treatment effect is reasonable (about a 10% risk reduction) such that a single trial is acceptable for supporting the new indication." He notes however, that the treatment effect of the losartan/hydrochlorothiazide regimen is primarily on the endpoint of stroke and therefore he believes that the new indication for this drug should read "an antihypertensive regimen including losartan and

hydrochlorothiazide is superior to one including atenolol and hydrochlorothiazide in reducing the incidence of stroke in non-black hypertensive patients 55 years of age or older with left ventricular hypertrophy." He adds that "other data sources" should be used to help address the issue of whether losartan's effect for this indication is reversed in blacks.

**Statistical:** John Lawrence, Ph.D.  
**Labeling:** None  
**Conclusion:** Dr. Lawrence states in his December 10, 2002 review that "based on one randomized (LIFE) study losartan appears to be superior to atenolol in reducing the rate of the composite endpoint Stroke/MI/CV Death in the overall population studied. There appears to be a difference in this effect among races (blacks vs. non-blacks) and there is no evidence of the superiority of losartan in blacks.

Biopharmaceutics

**Reviewer:** Elena Mishina, Ph.D.  
**Labeling:** None  
**Conclusion:** At the filing meeting on September 19, 2002, it was determined that a Biopharmaceutics review was not needed for this application.

Chemistry No full review (see Environmental Assessment)

Pharmacology

**Reviewer:** Anthony Proakis, Ph.D.  
**Labeling:** None  
**Conclusion:** At the filing meeting on September 19, 2002, it was determined that a Pharmacology review was not needed for this application. Please also see Dr. Proakis' October 17, 2002 memo.

Safety Update: There have been no safety updates since the original submission of July 26, 2002.

Patent info: Included in package

Pediatric info: Waiver granted for this indication

DSI: At the filing meeting on September 19, 2002, the Division stated that it would not ask for clinical audits of the study sites.

Debarment Certification: Included in package

Exclusivity Summary: Included in package

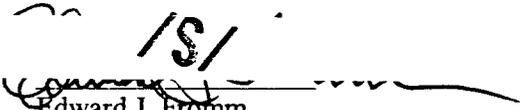
Environmental Assessment: Sponsor granted Categorical Exclusion

Financial Disclosure: acceptable, see Dr. Karkowsky's January 24, 2003 memo.

OPDRA Tradename Review: Not needed, the firm did not change the trade or generic name for this new indication.

DDMAC: No formal comments have been received to date

Comments: I will draft an approvable letter with marked-up draft labeling for Dr. Temple's signature.

*ISI*  
  
Edward J. Fromm  
Regulatory Health Project Manager

dr-ef-1-24-03

41 pages redacted from this section of  
the approval package consisted of draft labeling

DDMAC

As of March 6, 2003, DDMAC has not completed a review of this submission.

APPEARS THIS WAY  
ON ORIGINAL



Douglas C. Throckmorton, M.D.  
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857  
Tel (301) 594-5365, FAX (301) 594-5494

### Memorandum

**DATE:** 1.22.03

**FROM:** Douglas C. Throckmorton, M.D., Director  
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

**TO:** Robert Temple, M.D., Director  
Office of Drug Evaluation One (ODE-1)

**SUBJECT:** NDA 21-386/S-032,  
**NAME OF DRUG:** Cozaar (losartan hydrochloride)  
**SPONSOR:** Merck and Company

#### DOCUMENTS USED FOR MEMO:

1. LIFE Medical Review, including draft labeling, by Thomas Marciniak, M.D., dated 1.15.03.
2. LIFE Statistical Review by John Lawrence, Ph.D., dated 12.05.02.
3. Environmental Assessment by Florian Zelinski, Ph.D., dated 10.25.02.

#### CONCLUSIONS

This memorandum constitutes the Divisional memorandum for the approvability of losartan to reduce the incidence of stroke in patients with hypertension and left ventricular hypertrophy (LVH) on electrocardiogram. There were no Clinical Pharmacology, Pharm/Tox, or Chemistry reviews performed as none were needed for this supplemental submission. No deficiencies have been identified save that of agreement on the labeling.

#### BACKGROUND

The LIFE trial has been reviewed in depth by Drs. Marciniak and Lawrence and the reader is referred there for details of the trial design and outcomes. Aside from the issues related to describing the clinical outcomes in labeling, no deficiencies were noted in the submission related to Chemistry, Clinical Pharmacology, or Pharmacology/Toxicology. I think there are two issues to grapple with in this application, and these are dealt with below: how to describe the clinical effect measured in the trial, and how to deal with the unanticipated qualitative interaction with race seen in the trial.

#### What Did LIFE Find?

LIFE was designed to compare the effects of two drugs, losartan and atenolol, on hard clinical endpoints (CV death, MI, stroke), in a population with hypertension and left ventricular hypertrophy (LVH). The latter inclusion, in my view, served to increase the incidence of events in the trial population (similar to the function that proteinuria or a history of MI have served in other large trials). In this high-risk population, the expectation (my priors if you will) were that both drugs had a positive effect in this population relative to placebo, but that no difference between the two drugs would be observed, absent a differential effect on blood pressure.

The trial was well-designed and executed, and while small differences in blood pressure between the two groups were observed, there is little cause to believe that any observed treatment differences could be laid solely to this effect. In the end, losartan (used in a regimen combined with HCTZ) reduced the incidence of the primary endpoint significantly compared to atenolol in the overall population ( $p=0.02$ ). Given the prior expectations about the effect of the active comparator (atenolol) versus an imputed placebo, the Advisory Committee felt (and I agree) that 'beating' atenolol in this trial with regard to a relevant clinical endpoint would be the equivalent of a robust treatment effect ('two trials worth') and certainly sufficient to support labeling. So does this mean that the LIFE trial results represent a robust demonstration of an effect on the combined primary endpoint? No.

The primary endpoint was a composite, and as detailed in the reviews of Drs. Marciniak and Lawrence, the result for the primary endpoint was driven more or less exclusively by an effect on stroke (both fatal and non-fatal as you point out in your memo). So, while I agree that a robust treatment effect has been demonstrated with regard to stroke, the other components (death, MI) appeared to have been more or less equally affected by both treatments. Again, with my priors, this means that had a placebo been present in this trial, both would have 'beaten' it more or less to the same degree, but that such a demonstration falls short of the level of evidence needed to, say, insert the outcome language for these components of the endpoint into labeling.

The Divisional recommendation to you is that the effect of losartan on stroke is highly relevant and should be inserted into the label within the indications section to reflect the strength of this finding. The effect of losartan on the primary endpoint should be included in the Clinical Trials section, but only in the context of data on the relevant contributions of the three components of the endpoint, and with language that makes it clear where the primary effect was (on stroke).

#### **Is The Interaction With Race In LIFE A Chance Occurrence?**

As discussed extensively by others, the outcomes observed in LIFE were quite different for non-Black and Black patients. Simply, losartan 'beat' atenolol in non-Black population and atenolol 'beat' losartan in the Black population. The superiority of atenolol was consistent among the sub-groups of the Black population when examined, despite the small numbers in these groups and the unstable point estimates they normally as associated with. Such a finding is vanishingly rare in my experience in the Center, and the Division's collective memory has not identified another clear example (the BEST trial is perhaps the closest). Could this have occurred by chance? It is highly unlikely, in my view. First, as ably reviewed by the Biometricians (whose support to the Division in this matter was superlative), the likelihood of finding a nominally significant interaction is low in the first place due to low sensitivity of such tests. Additionally, while it is not uncommon for the point estimate for one of the many subset analyses the sponsors typically conduct to be 'qualitatively' different (that is, to see an inversion of the risk ratio), to have both the risk ratio reversed and to have the outer bound of the 95% confidence intervals not overlap for the overall population and the subset is very rare. Add to this the nebulous/ non-quantifiable observation that there does appear to be a (largely quantitative) interaction with race for other cardiovascular effects (*e.g.*, hypertension), and I conclude that the observation is both relevant and persuasive.

The next issue to whether or not we have sufficient data to determine whether losartan is in fact deleterious in Blacks (that is, worse than placebo). Here, the sponsor has provided analyses that suggest that while this cannot be excluded, their best estimate of losartan's effects still place it as overall advantageous relative to placebo in Black patients. We have no other data from outcome trials to draw on in this regard directly for angiotensin receptor blockers, and given the uncertainty of this estimate I suggest that the label remain silent on the efficacy of losartan relative to placebo in the Black population. The label should describe the overall effect of losartan in LIFE relative to atenolol as being driven by the non-Black population and should separately summarize the LIFE data in Blacks and non-Blacks.

As a final point, this outcome with regard to race provides strong support to the efforts we've made in recent years to improve the labeling of these drugs with regard to race, gender and age. Where no adequate data exist, this should be clearly reflected in the label.

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/s/

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Doug Throckmorton  
1/24/03 07:54:39 AM  
MEDICAL OFFICER

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FOOD AND DRUG ADMINISTRATION**



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**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** **Confirmation of Labeling Telecon for  
NDA 20-386/S-032  
Cozaar (losartan potassium) Tablets**

**Date:** February 4, 2003

**Pages including this sheet:** 2

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

Please let me know that you received this. Thanks!

Confirmation of Telecon

Drug: Cozaar (losartan potassium)-LIFE Supplement  
Application: NDA 20-386/S-032  
Sponsor: Merck & Co.

Date Confirmation Faxed: February 4, 2003

T-Con Date: February 10, 2003, 8:00-9:30 A.M.

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research  
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director  
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader  
Thomas Marciniak, M.D., HFD-110, Medical Officer  
George Chi, Ph.D, HFD-710, Division of Biometrics I  
James Hung, Ph.D., HFD-710, Statistician/Team Leader  
John Lawrence, Ph.D., HFD-710, Statistician  
Edward Fromm, HFD-110, Regulatory Health Project Manager

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**Date:** February 4, 2003

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**Phone:** 301-594-5332  
**Fax:** 301-594-5494

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**Date:** January 23, 2003

**Pages including this sheet:** 2

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**Phone:** 301-594-5332

**Fax:** 301-594-5494

Please let me know that you received this. Thanks!

Confirmation of Telecon

Drug: Cozaar (losartan potassium)-LIFE Supplement  
Application: NDA 20-386/S-032  
Sponsor: Merck & Co.

Date Confirmation Faxed: January 23, 2003

T-Con Date: January 31, 2003, 1:30-2:30 P.M.

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research  
Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director  
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader  
Thomas Marciniak, M.D., HFD-110, Medical Officer  
James Hung, Ph.D., HFD-710, Statistician/Team Leader  
John Lawrence, Ph.D., HFD-710, Statistician  
Edward Fromm, HFD-110, Regulatory Health Project Manager

Our telephone # is (301) 827-3477 or you can supply a call-in number if you have consultants.

Thanks,

Ed

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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** Confirmation of Labeling Telecon for  
NDA 20-386/S-032  
Cozaar (losartan potassium) Tablets

**Date:** January 23, 2003

**Pages including this sheet:** 2

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck & Co.

**Phone:** (484) 344-7788

**Subject:** Draft Questions for Cozaar (losartan potassium) for  
January 2003 Cardio-Renal Advisory Committee  
Meeting  
NDA 20-386/S-032

**Date:** December 18, 2002

**Pages including this sheet:** 4

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

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**Subject:** Draft Questions for Cozaar (losartan potassium) for  
January 2003 Cardio-Renal Advisory Committee  
Meeting  
NDA 20-386/S-032

**Date:** December 18, 2002

**Pages including this sheet:** 4

**From:** Edward Fromm  
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**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** **Confirmation of Meeting for  
NDA 20-386/S-32  
Cozaar (losartan potassium) Tablets**

**Date:** November 12, 2002

**Pages including this sheet:** 2

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

### Confirmation of Meeting

Drug: Cozaar (losartan potassium) for type 2 Diabetic Nephropathy  
Application: NDA 20-386/S-032  
Sponsor: Merck & Co.  
Subject: Pre-Advisory Committee Meeting

Date Requested: November 8, 2002  
Date Confirmation Faxed: November 12, 2002

Meeting Date & Time: November 26, 2002, 1:00-3:00 P.M.

Meeting Location: Conference room "F", 5<sup>th</sup> floor, 1451 Rockville Pike, Rockville, Md 20852

#### FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader  
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader  
Thomas Marciniak, M.D., HFD-110, Medical Officer  
James Hung, Ph.D., HFD-110, Statistician/Team Leader  
John Lawrence, Ph.D., HFD-110, Statistician  
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist  
Charles Anello, Sc.D., HFD-700, Office of Biostatistics  
George Chi, Ph.D., HFD-710  
Edward Fromm, HFD-110, Regulatory Health Project Manager

Please submit your draft briefing book at least 2 weeks prior to the meeting.

Thanks,

Ed

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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeff Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** Minutes of Meeting w/FDA, Nov. 26, 2002  
Cozaar (losartan potassium)  
NDA 20-386/S-032

**Date:** January 21, 2003

**Pages including this sheet:** 6

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

## **Minutes of a Meeting between Merck and the FDA**

Date: November 26, 2002

Sponsor: Merck & Co., Inc.

Subject: NDA 20-386/S-032  
Cozaar (losartan potassium) Tablets

Indication: Reduction in the Risk of Cardiovascular Morbidity and Mortality in Hypertensive Patients with Left Ventricular Hypertrophy

Purpose: Pre-Advisory Committee Meeting

### FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader  
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader  
Thomas Marciniak, M.D., HFD-110, Medical Officer  
Robert O'Neill, Ph.D., HFD-700, Director, Office of Biostatistics  
James Hung, Ph.D., HFD-110, Statistician/Team Leader  
John Lawrence, Ph.D., HFD-110, Statistician  
Charles Anello, Sc.D., HFD-700, Office of Biostatistics  
George Chi, Ph.D., HFD-710, Director, Division of Biometrics  
Edward Fromm, HFD-110, Regulatory Health Project Manager

### Merck

Michael Elia, Ph.D., Senior Director, Regulatory Affairs  
Dennis Erb, Ph.D., Executive Director, Regulatory Affairs  
Jeffrey Tucker, M.D., Director, Regulatory Affairs  
Bonnie Goldman, M.D., Senior Vice President, Global Strategic Regulatory Development  
Brian White-Guay, M.D., Vice President, Global Regulatory Affairs  
Douglas Greene, M.D., Executive Vice President, MRL Clinical Sciences & Product Development  
Marie Dray, Executive Director, Regulatory Agency Relations  
Betsy Fallen, Manager, Worldwide Regulatory Coordination  
Laura Demopoulos, M.D., Executive Director, Clinical Research  
Barry Gertz, M.D., Ph.D., Senior Vice President, Clinical Sciences  
Jon Edelman, M.D., Senior Director, Clinical Development  
William Keane, M.D., Vice President, Clinical Development  
George Klinger, Manager, Clinical Development  
Raymond Bain, Ph.D., Vice President, Biostatistics & Research Decision Sciences  
Kathy Harris, Ph.D., Associate Director, Scientific Staff  
Steven Snapinn, Ph.D., Senior Director, Scientific Staff  
Donald Black, M.D., Vice President, GSRD Therapeutic Area  
Gregory Reaves, Vice President, Communication & Research Policy

## **Background**

Merck, on July 25, 2002, submitted an efficacy supplement for losartan potassium for reduction in the risk of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy. The firm was given a priority review for this supplement.

The Division asked Merck to present their data for this new indication at the January 2003 Cardio-Renal Advisory Committee Meeting. The firm agreed to present before the Committee and requested feedback on a draft background package for the meeting as well as the review of the application to date by the Division.

## **Meeting**

Merck opened the meeting by noting that they have submitted questions to the Division for our assessment of the application to date and have asked for any revisions we may suggest to the draft background package for the Advisory Committee meeting. Dr Throckmorton replied that although the statistical and medical reviews have not been completed for the application, he has started to draft questions for the Advisory Committee members to answer. The Division has reviewed the firm's questions for today's meeting and is happy to provide the sponsor feedback in anticipation of the Advisory Committee meeting.

## Questions

1. The primary hypothesis of the LIFE study was that, compared with atenolol, losartan would reduce the incidence of cardiovascular morbidity and mortality in patients with essential hypertension and left ventricular hypertrophy. The primary endpoint was a composite of cardiovascular morbidity and mortality, as measured by the combined incidence of cardiovascular mortality, fatal and nonfatal stroke, and fatal and nonfatal myocardial infarction. Treatment with losartan resulted in a 13% decrease (Hazard Ratio [HR]: 0.869 [95% CI 0.772 to 0.979],  $p=0.021$  in the relative risk (adjusted for baseline Framingham risk score and LVH) of the primary composite compared with atenolol.

- a) Does the FDA agree that the atenolol-based antihypertensive regimen had a benefit in reducing cardiovascular morbidity and mortality in the LIFE population?

Dr. Throckmorton replied that there is evidence to suggest that beta-blockers are helpful in reducing mortality and morbidity but nevertheless, the sponsor will need to generate a robust dataset to support this argument. This dataset will need to quantify the benefit of beta-blockers (not just atenolol) versus placebo. Merck noted that the population studied in the LIFE trial has not been studied in a comparable population to date. Dr. Throckmorton said there were probably several small studies conducted with a population similar to the LIFE study that could be used to calculate an order of magnitude of effect for the beta-blocker vs. placebo interaction.

- b) Would the FDA consider as supportive information, a putative placebo-type analysis that showed a losartan-based regimen (i.e., losartan plus other antihypertensives as necessary to control blood pressure) to be superior to no antihypertensive treatment?

Merck said the intent of the question was to try to generate an indirect comparison of the effect of losartan versus placebo by pooling the results of the beta-blocker and placebo analyses and those from LIFE trial (losartan versus atenolol). Dr. Lawrence said this type of analysis would be very complicated and would be difficult to interpret. Dr. Throckmorton reiterated that a

putative placebo-type analysis of atenolol or beta-blockers in a population similar to the LIFE trial would be most helpful.

2. The components of the primary composite endpoint were defined as cardiovascular mortality, fatal and nonfatal stroke and fatal and nonfatal myocardial infarction. Each component was evaluated separately using an approach that counted all patients who experienced a component in the analysis of that endpoint; in each analysis patients were counted only once. A test for heterogeneity among the components was pre-planned.

- a) Does the FDA agree with our approach to the analyses of the components of the composite endpoint?

Dr. Hung said it was important to describe what percentage of events make up the primary endpoint. Dr. O'Neill said that he was unsure when looking at the data, how the individual components contribute to the composite endpoint through the entire (4 year) duration of the study. Hazard rates should therefore also be defined (e.g., by curves) for each component as a progression of time for the entire study.

3. The test for heterogeneity among the components of the primary composite endpoint was statistically significant ( $p=0.023$ ). The reduction in the risk of cardiovascular death by 11% (HR: 0.866 [95% CI 0.734 to 1.069],  $p=0.206$ ) was not significant, but was directionally consistent with the benefit of losartan on the primary composite endpoint. Losartan was associated with a significant 25% reduction in the risk of fatal and nonfatal stroke (HR: 0.752 [95% CI 0.634 to 0.891],  $p=0.001$ ). The incidence of myocardial infarction (fatal and nonfatal) (HR: 1.073 [95% CI 0.879 to 1.310],  $p=0.491$ ) was not statistically significantly different between the treatment groups.

- a) Given that the study compared two antihypertensive treatments with different mechanisms of action, does the FDA agree that the observed heterogeneity among the components of the composite endpoint in the LIFE study is understandable?

Dr. Throckmorton said we have not finalized our thinking on this subject but said the sponsor may want to comment further on the relationship between stroke and myocardial infarction at the Advisory Committee Meeting. Tests for heterogeneity that are positive for the composite endpoint are not always sensitive and should not be viewed as conclusive.

- b) Does the FDA agree that stroke reduction observed in the LIFE study is not a chance occurrence?

Dr. Throckmorton noted that the overall primary endpoint result appears robust, although stroke is certainly driving the composite endpoint.

4. Does the FDA agree that the LIFE study supports the proposed indication?
5. Does the FDA agree that the LIFE study supports an indication for losartan to reduce the risk of stroke in hypertensive patients with LVH?

Dr. Throckmorton said, in response to questions #4 and 5, that we would not be able to comment on them until the reviews have been completed and advice received from the Advisory Committee members on this application.

6. The treatment benefit of losartan on the primary composite endpoint was generally consistent among multiple pre-specified demographic, geographic, medical history, and disease severity subgroups, as evidenced by the lack of significant treatment-by-subgroup interactions. However, in the predefined subgroup analyses, there was a suggestion of an interaction between ethnic background and treatment ( $p=0.057$ ). Further post hoc analyses revealed a significant qualitative treatment interaction for Blacks versus non-Blacks. Non-Black patients appeared to have lower risk of experiencing an event with losartan, while Black patients appeared to have lower risk with atenolol despite comparable blood pressure reduction among both groups.
  - a) Does the FDA agree that the findings are generally consistent in the demographic, geographic, disease history and disease severity subgroups as evidenced by the lack of significant treatment-by-treatment subgroups interaction?

Dr. Throckmorton said that he is unsure if there is a treatment interaction with the Black subgroup in the study but said our statisticians would address this subject at the Advisory Committee meeting. He added that other trials with beta-blockers such as BEST (Beta-Blocker Evaluation of Survival Trial) did not seem to have these qualitative interactions and therefore the sponsor should explore trials with beta-blockers to see if there is a pattern to them.

- b) Does the FDA agree that the findings of the LIFE study in Black patients should be reflected in the product label?

Merck said their intent at the present time is to include the Black subgroup results and asked if the Agency agrees with this approach. Dr. Throckmorton said he cannot answer their question at this time but noted that he would try to keep the subgroup problems focused into one question for the Advisory Committee members to consider.

7. Sitting trough systolic blood pressure at the end of the follow-up or last visit before a primary endpoint, whichever occurred first, fell by 30.2 mm Hg in the losartan group and 29.1 mm in the atenolol groups (treatment difference  $p=0.015$ ); sitting diastolic blood pressure was reduced by 16.6 mm Hg in the losartan group and 16.8 mm Hg in the atenolol group.
  - a) Does the FDA agree that the differences in blood pressure are unlikely to account for all of the benefits observed in the LIFE study?

Dr. Throckmorton said we are unable to answer this question at the present time but the sponsor should make arguments for the differences observed in the LIFE study.

8. Does the Agency have any comments or concerns about our background document?

Dr. Throckmorton said the two main issues are:

- 1) Generating a robust dataset to justify and quantify atenolol/beta-blockers effect on reducing morbidity and mortality versus placebo.
- 2) Explore the possible qualitative interactions in subgroups in trial involving beta-blockers.

9. Does the FDA plan to make a presentation at the Advisory Committee Meeting?

As mentioned earlier, the Agency's statisticians will make a presentation regarding the subgroups interactions in the LIFE study.

10. What will be the Agency's (primary reviewers') position in their briefing document to the Advisory Committee?

Dr. Marciniak (medical reviewer) said he expects to complete his review by December 6, 2002 and noted that he is uncertain whether a small difference in blood pressure effect between the atenolol and losartan treatment regimens could account for the favorable outcomes on morbidity and mortality in the losartan group. What really is needed is ABPM data from both treatment groups. Merck said they have a limited amount (about 30 patients) of ABPM data for both groups and will submit them to the Division shortly. Dr. Throckmorton said these data would be helpful but because of the small numbers of patients, difficult to interpret.

Dr. Marciniak said the sponsor might want to explore further the heterogeneity of the dataset with respect to Black and White patients in the study. For example, explain the treatment difference in the study between Black and White patients in the United States or the effect of the baseline differences of Black patients that received losartan versus Black patients that received atenolol.

Dr. Throckmorton noted that although we would be unable to share our reviews with the sponsors, any questions on data or analyses the reviewers might have with the application would be communicated to the sponsor as they arise.

11. What does the FDA consider to be the key questions for the Advisory Committee members to discuss?

Please see question #8.

#### Summary of Main Action Items

Dr. Throckmorton said the sponsor's briefing document was acceptable and suggested that they might want to expand it with the following information:

- 1) Generate a robust dataset to justify and quantify atenolol/beta-blockers effect on reducing morbidity and mortality versus placebo.
- 2) Explore the possible qualitative interactions in subgroups in trials involving beta-blockers.

Merck said they would submit any available ABPM data for the LIFE study as soon as possible.

Minutes Preparation:

/S/  
Edward Fromm

Concurrence:

/S/ (L.R.O.)  
Douglas C. Throckmorton, M.D.

dr/ef-12/3/02/-1/21/03

Rd: JHung-12/9/03  
GChi-1/8/03  
CAnello-1/8/03  
JLawrence-1/8/03  
R'ONeill-1/9/03  
AKarkowsky-1/16/03  
NStockbridge-1/17/03

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**Subject:** Minutes of Meeting w/FDA, Nov. 26, 2002  
Cozaar (losartan potassium)  
NDA 20-386/S-032

**Date:** January 21, 2003

**Pages including this sheet:** 6

**From:** Edward Fromm

**Phone:** 301-594-5332

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**Minutes of a Meeting Between Merck Research Laboratories and the FDA**

Date: September 21, 1995

Application: IND [REDACTED]  
Cozaar (losartan) Tablets

Sponsor: Merck Research Laboratories

**Participants:**FDA

Robert Temple, M.D., HFD-100, Director, Office of Drug Evaluation 1  
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products  
Shaw Chen, M.D., Ph.D., HFD-110, Supervisory Medical Officer  
Charles Ganley, M.D., HFD-110, Medical Officer  
Maryann Gordon, M.D., HFD-110, Medical Officer  
James Hung, Ph.D., HFD-713, Statistician  
David Roeder, HFD-110, Regulatory Health Project Manager

Merck

Jon Edelman, M.D., Clinical Development  
John Flaherty, M.D., Clinical Development  
Steve Snappin, Ph.D., Statistician  
Bill Grossman, M.D., Clinical Research  
Charles Sweet, Ph.D., Clinical Development  
Bonnie Goldmann, M.D., Regulatory Affairs  
Larry Bell, Ph.D., Regulatory Affairs  
Marie Dray, Regulatory Affairs

**Background**

Merck requested a meeting to discuss their protocol entitled "Losartan Intervention for Endpoint Reduction in Hypertension" (LIFE). This is a randomized, triple-blind, multi-center, active control trial in patients with hypertension and left ventricular hypertrophy (LVH). The purpose of this study is to show the effect of losartan on cardiac mortality and morbidity in this patient population.

**Meeting**

The sponsor began by presenting the rationale for their study design. This presentation included their rationale for studying LVH as it relates to the effects of angiotensin II on cardiac muscle as well as a discussion of the inclusion criteria, duration of study, sample size, and titration scheme.

The sponsor then referred to a question raised by Dr. Ganley about their inclusion of patients with isolated systolic hypertension (ISH). Dr. Ganley clarified his question, saying that he is

concerned that they are studying two separate populations. Dr. Lipicky concurred, pointing out that ISH is believed to be pathophysiologically different than essential hypertension. In response to an assurance from the sponsor that they will analyze the results to ensure that there are no significant differences between the two groups, he said that the trial is not powered to detect a difference. He was concerned that people would assume that the two groups responded similarly without convincing data to support that assumption.

Dr. Temple looked more favorably on the sponsor's proposal. He stated that it would be useful to get data on ISH patients. He acknowledged that there could be some ambiguity in a study designed this way, but the traditional approach of selecting patients based on their diastolic blood pressure was also flawed. He noted that something would be missed either way the trial was designed, so, even with our reservations, the sponsor's combined approach would be acceptable.

The sponsor then discussed their selection of a comparator agent. Their goal was to select an agent with antihypertensive effects similar to losartan that also had a perceived benefit on mortality and is effectively used in combination with diuretics. They also wanted to use the agent for which there is a single worldwide formulation.

Regarding the endpoints, the sponsor proposed a combined primary endpoint of cardiac mortality (coronary heart disease and other cardiac deaths from stroke, aortic aneurysm, PVD, and CHF) and cardiac morbidity (MI and stroke). Dr. Temple suggested that they use total mortality as their primary endpoint instead of just cardiac mortality. Since most deaths in a trial such as this are cardiovascular in nature, the interpretation of results would be much simpler if they just counted all deaths. Dr. Ganley added that if they counted total mortality and cardiac mortality separately, they could have problems if the non cardiac deaths went the wrong way.

Dr. Ganley questioned the sponsor's use of CHF as a secondary endpoint. Since atenolol's effect on CHF in this population is unknown, and could be adverse, these results would be difficult to interpret. Beating atenolol in this population is no guarantee that losartan would beat placebo. He was also had ethical concerns regarding the treatment of subjects that have CHF. According to the protocol, they will not be treated with ACE inhibitors until they reach the primary endpoint, which in the case of CHF patients would be hospitalization. Since treatment with ACE inhibitors prior to hospitalization could benefit these patients, he recommended that they revise their protocol so that these patients have the option of receiving ACE inhibitors prior to hospitalization. The sponsor agreed to discuss the matter with their steering committee.

Dr. Ganley said that to avoid having to submit reports of underlying disease-related events, they should request a waiver of the requirements to report serious and unexpected adverse reactions in the course of the study. They would need to identify disease-related events that would not need reporting except at end-study. We will send them a letter advising them on how to report these adverse reactions.

The sponsor asked what would happen if their trial showed an overall positive effect on the combined endpoint but was neutral on mortality. Could they describe the study in the labeling? Dr. Temple said that a persuasive overall effect would be a basis for a claim, but how to describe results of studies with combined endpoints is often a problem, one that, however, must always be worked out. The firm also asked if one positive trial could be sufficient for a labeling claim.

Dr. Temple responded that the answer was result-dependent. A robust (low p-value) finding with no problems or inconsistencies and internal consistency could be sufficient. He suggested that the sponsor should try to avoid stopping the study too soon. A way to avoid problems would be to stop only for a mortality difference. Morbidity endpoints are often reevaluated later and results could change.

The study will evaluate many secondary endpoints. Dr. Lipicky said that if the primary endpoint is not positive ( $p \leq 0.05$ ) we would almost certainly not consider the results of the secondary endpoints to be a basis for a claim. The sponsor agreed that if this were the case they would consider it to be a negative study, but they thought results might be placed in the CLINICAL PHARMACOLOGY section of the labeling. FDA staff disagreed, noting that implied claims unsupported by data cannot legally be put into the CLINICAL PHARMACOLOGY section.

Dr. Hung noted that it was not clear from their submission whether the primary analysis would be Cox regression or log rank analysis. He recommended that if it were Cox regression, they should pre-specify the covariates. The firm responded that the primary analysis will be a log rank without covariates. Additional analyses with covariates will also be done.

Dr. Hung also noted that the protocol provides for an interim analysis by the DSMB that would allow them to modify the protocol. He asked that they clarify their description of this provision, since it was somewhat vague.

Dr. Ganley suggested that they submit the randomization code and a blank case report form to the Division. Dr. Lipicky noted that this is a useful precaution in large trials such as this.

  
-----  
David Roeder  
Regulatory Health Project Manager

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RD: JHung/10-11095  
SChen/10-11-95  
CGanley/10-13/95  
RTemple/10-20-95

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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** **AP Letter and Labeling for NDA 20-386/S-032**  
(supersedes previous-March 25, 2003 AP letter for  
this supplement)

**Date:** March 25, 2003

**Pages including this sheet:** 18

**From:** Edward Fromm

**Phone:** 301-594-5332

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\*\*\*\*\* -CARDIO RENAL - \*\*\*\*\* 301 594 5494-\*\*\*\*\*

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



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

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1451 Rockville Pike  
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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** AP Letter and Labeling for NDA 20-386/S-032  
(supersedes previous-March 25, 2003 AP letter for this supplement)

**Date:** March 25, 2003

**Pages including this sheet:** 18

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

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**Transmitted to FAX Number:** (484) 344-2516

**Attention:** Dr. Jeffrey Tucker

**Company Name:** Merck and Co.

**Phone:** (484) 344-7788

**Subject:** **Approvable Letter and Revisions to the Labeling  
for NDA 20-386/S-032  
Cozaar (losartan potassium) Tablets**

**Date:** January 24, 2003

**Pages including this sheet:** 7

**From:** Edward Fromm

**Phone:** 301-594-5332

**Fax:** 301-594-5494

**\*\*Please let me know that you received this\*\*\*\*Thanks!!**

MODE = MEMORY TRANSMISSION

START=JAN-24 17:52

END=JAN-24 17:54

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STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-386	Efficacy Supplement Type SE-1 (Reduction of risk for CV death, stroke and myocardial infarction)	Supplement Number 032
Drug: Cozaar (losartan potassium) Tablets, 25, 50, and 100 mg		Applicant: Merck & Co., Inc.
RPM: E. Fromm	HFD-110	Phone # 594-5332
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		May 17, 2003
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (X) No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM-January 24, 2003
<b>General Information</b>	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-January 24, 2003
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
Marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
Outgoing correspondence (i.e., letters, E-mails, faxes)	X
Oranda and Telecons	X
Types of Meetings	
• Planning meeting (indicate date)	September 21, 1995
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Pre-Advisory Committee	November 26, 2002

❖ Advisory Committee Meeting	
• Date of Meeting	January 6, 2003
• 48-hour alert	Quick Minutes
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Division Director-January 24, 2003
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	January 15, 2002
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	None
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	December 10, 2002
❖ Biopharmaceutical review(s) (indicate date for each review)	NA
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NA
• Bioequivalence studies	NA
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	NA
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	NA
• Review & FONSI (indicate date of review)	X November 1, 2002
• Review & Environmental Impact Statement (indicate date of each review)	NA
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: NA ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed NA ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X-See Dr. Proakis' October 17, 2002 memo
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NA
❖ CAC/ECAC report	NA

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: February 29, 2004.

## USER FEE COVER SHEET

### See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.  
Sumneytown Pike, BLA-10  
P.O. Box 4  
West Point, PA 19486

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N020386

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

\_\_\_\_\_  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

( 484 ) 344-2383

3. PRODUCT NAME

COZAAR™ (losartan potassium)

6. USER FEE I.D. NUMBER

4386

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

Food and Drug Administration  
CDER, HFD-94  
and 12420 Parkdown Drive, Room 3046  
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE  
Bonnie J. Goldmann, M.D.  
Senior Vice President

DATE

25 July 2002