CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-019 and 029

Administrative/Correspondence

RHPM NDA Efficacy and Labeling Supplement Approval Review
March 4, 2004

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

NDA 20-386/SE5-029

Applicant: Merck and Co.

Classification: SE5 (Peds-related revisions)

Review Classification: Standard (10 month review)

Date of Application: December 21, 2001

Date of AE Letter: October 21, 2002

Date FPL Submitted: February 27, 2004

Date FPL Received: March 1, 2004

User Fee Goal Date: May 1, 2004

Background (Note: Labeling supplement NDA 20-386/S-019 will be approved concurrently with S-029, as Merck, after consultation with the Division, included revisions in the FPL that are acceptable to the Division and allow approval of this supplement as well. The revisions for NDA 20-386/S-019 are, for the most part, identical to those included in the supplement for Hyzaar (losartan potassium/HCTZ)-NDA 20-387/S-015, approved September 30, 2003).

NDA 20-386/SE5-029

An approvable letter was issued on October 21, 2002 for losartan potassium for pediatric-related changes to the **CLINICAL PHARMACOLOGY, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the labeling. After labeling discussions with the firm on January 15 and February 5, 2004, the firm was informed that they could submit Final Printed Labeling (FPL). See my review of changes for this supplement described further below (Review/NDA 20-386-SE5-029).

Pediatric exclusivity was granted for losartan potassium on March 20, 2002.

NDA 20-386/S-019

Merck, in a supplement dated August 25, 1999, submitted updated information for rifampin, fluconazole, and erythromycin to the *Drug Interactions* subsection of the labeling under **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** and changed the subheading "**Use in the elderly**" to "**Geriatric Use**" for this subsection under **PRECAUTIONS.**

The Division issued an approvable letter on April 11, 2000, which asked for final printed labeling with the following revisions:

1. The **CLINICAL PHARMACOLOGY,** *Drug Interactions* subsection should be changed to:

Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and 36% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 50% but increased the AUC of losartan by approximately 30%. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.

2. The **PRECAUTIONS,** *Drug Interactions* subsection should be changed to:

No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreases the concentrations of losartan and its active metabolite. (See **CLINICAL PHARMACOLOGY,** *Drug Interactions*). In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration but increased losartan concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

Merck replied to the approvable letter of April 11, 2000 with the following submission (regarding NDA 20-386/S-019):

In a submission dated November 16, 2001, the sponsor sent in labeling revised to include, with one exception, the changes the Division proposed in the approvable letter of April 11, 2000 and ones agreed to by the Division in verbal and facsimile (July 31, 2001) communications with the sponsor, for the **CLINICAL PHARMACOLOGY,** *Drug Interactions* and **PRECAUTIONS,** *Drug Interactions* subsections of the labeling.

The exception in these revisions, as noted above, was the use of the word "and" instead of "but" in the following sentence (5th sentence, 1st paragraph of the **PRECAUTIONS,** *Drug Interactions* subsection):

Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration but increased losartan concentration.

Dr. Throckmorton said that the word "and" instead of "but" in this sentence was acceptable.

Dr. Throckmorton, in a memo dated April 11, 2003 and in a second approvable letter dated May 20, 2003, asked that the firm submit the following additional information:

> Propose language on the comparative safety and efficacy of losartan based on the RENAAL and LIFE trials. Such comment can be submitted as a part of the response to this approvable action or submitted at a later date, based on a commitment from you that you will provide such a supplement.

Merck, through approvals of supplement S-028 (RENAAL trial-September 17, 2002) and S-032 (LIFE-March 25, 2003) included the requested language in the **Geriatric Use** subsection. Dr. Throckmorton agreed that the revisions were responsive to the second approvable letter for S-019 and were acceptable.

For summary, the revisions to the **CLINICAL PHARMACOLOGY,** *Drug Interactions* and **PRECAUTIONS,** *Drug Interactions* subsections are as follows:

1. Under **CLINICAL PHARMACOLOGY,** *Drug Interactions,* first paragraph has been revised to:

   Losartan, administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan did not affect the pharmacokinetics of oral or intravenous digoxin. There is no pharmacokinetic interaction between losartan and hydrochlorothiazide. Coadministration of losartan and cimetidine led to an increase of about 18% in AUC of losartan but did not affect the pharmacokinetics of its active metabolite. Coadministration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70% following multiple doses. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The AUC of active metabolite following oral losartan was not affected by erythromycin, another inhibitor of P450 3A4, but the AUC of losartan was increased by 30%.

2. Under **PRECAUTIONS,** *Drug Interactions,* the first paragraph has been revised to:

   No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite. (See **CLINICAL PHARMACOLOGY,** *Drug Interactions.*) In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral administration. Fluconazole, and inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration. The pharmacodynamics consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

Merck submitted final printed labeling on February 27, 2004, received February 27, 2004. When compared with the last approved labeling supplement (S-032, March 25, 2003) the following changes were noted:

1. Under **DESCRIPTION**, 4th paragraph, the word "hydroxypropyl methylcellulose" has been changed to "hypromellose".

2. Under **CLINICAL PHARMACOLOGY**, *Pharmacokinetics, General,* the following language below has been relocated from the 4th paragraph in the current labeling and has been inserted in the first paragraph of the revised labeling.

   Losartan metabolites have been identified in human plasma and urine. In addition to the active carboxylic acid metabolite, several inactive metabolites are formed. Following oral and intravenous administration of ^{14}C-labeled losartan potassium, circulating plasma radioactivity is primarily attributed to losartan and its active metabolite. *In vitro* studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its metabolites. Minimal conversion of losartan to the active metabolite (less than 1% of the dose compared to 14% of the dose in normal subjects) was seen in about one percent of individuals studied.

3. Under **CLINICAL PHARMACOLOGY**, *Pharmacokinetics, General*, a new (5th) paragraph has been inserted that combines the first sentence below with language currently representing (with some slight revisions) the 5th paragraph of the current labeling:

   The pharmacokinetics of losartan and its active metabolite were also determined after IV doses of each component separately in healthy volunteers. The volume of distribution of losartan and the active metabolite is about 34 liters and 12 liters, respectively. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively. After single doses of losartan administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite. Biliary excretion contributes to the elimination of losartan and its metabolites. Following oral ^{14}C-labeled losartan, about 35% of radioactivity is recovered in the urine and about 60% in the feces. Following an intravenous dose of ^{14}C-labeled losartan, about 45% of radioactivity is recovered in the urine and 50% in the feces.

4. Under **CLINICAL PHARMACOLOGY**, *Special Populations, Pediatric*, the sentence "Losartan pharmacokinetics have not been investigated in patients <18 years of age" has been replaced with tabular Pharmacokinetic (e.g., AUC, Cmax, Tpeak) data comparing adults with children aged 6-16 following multiple dosing of the drug. In addition, the following paragraph was added beneath the table describing the PK differences between adults and children:

   The bioavailability of the suspension formulation was compared with losartan tablets in healthy adults. The suspension and tablet are similar in their bioavailability with respect to both losartan and the active metabolite (see **DOSAGE AND ADMINISTRATION**, *Preparation of Suspension*).

5. Under **CLINICAL PHARMACOLOGY**, *Renal Insufficiency*, the paragraph that reads:

Plasma concentrations of losartan are not altered in patients with creatinine clearance above 30 mL/min. In patients with lower creatinine clearance, AUCs are about 50% greater and they are doubled in hemodialysis patients. Plasma concentrations of the active metabolite are not significantly altered in patients with renal impairment or in hemodialysis patients. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see **WARNINGS**, *Hypotension — Volume-Depleted Patients* and **DOSAGE AND ADMINISTRATION)**

has been changed to:

Following oral administration, plasma concentrations and AUCs of losartan and its active metabolite are increased by 50-90% in patients with mild (creatinine clearance of 50 to 74 mL/min) or moderate (creatinine clearance 30 to 49 mL/min) renal insufficiency. In this study, renal clearance was reduced by 55-85% for both losartan and its active metabolite in patients with mild or moderate renal insufficiency. Neither losartan nor its active metabolite can be removed by hemodialysis. No dosage adjustment is necessary for patients with renal impairment unless they are volume-depleted (see **WARNINGS**, *Hypotension — Volume-Depleted Patients* and **DOSAGE AND ADMINISTRATION**).

Note: This change was made to be consistent with the Hyzaar labeling.

6. Under **CLINICAL PHARMACOLOGY**, Pharmacodynamics and Clinical Effects, the subheading "*Hypertension*" has been changed to "*Adult Hypertension*" and "*Pediatric Hypertension*". Under the heading *of Pediatric Hypertension*, the following language has been included:

The antihypertensive effect of losartan was studied in one trial enrolling 177 hypertensive pediatric patients aged 6 to 16 years old. Children who weighed <50 kg received 2.5, 25 or 50 mg of losartan daily and patients who weighed ≥50 kg received 5, 50 or 100 mg of losartan daily. Children in the lowest dose group were given losartan in a suspension formulation (see **DOSAGE AND ADMINISTRATION**, *Preparation of Suspension*). The majority of the children had hypertension associated with renal and urogenital disease. The sitting diastolic blood pressure (SiDBP) on entry into the study was higher than the 95th percentile level for the patient's age, gender, and height. At the end of three weeks, losartan reduced systolic and diastolic blood pressure, measured at trough, in a dose-dependent manner. Overall, the two higher doses (25 to 50 mg in patients <50 kg; 50 to 100 mg in patients ≥50 kg) reduced diastolic blood pressure by 5 to 6 mmHg more than the lowest dose used (2.5 mg in patients <50 kg; 5 mg in patients ≥50 kg). The lowest dose, corresponding to an average daily dose of 0.07 mg/kg, did not appear to offer consistent antihypertensive efficacy. When patients were randomized to continue losartan at the two higher doses or to placebo after 3 weeks of therapy, trough diastolic blood pressure rose in patients on placebo between 5 and 7 mmHg more than patients randomized to continuing losartan. When the low dose of losartan was randomly withdrawn, the rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan, again suggesting that the lowest dose did not have significant antihypertensive efficacy. Overall, no significant differences in the overall antihypertensive effect of losartan were detected when the patients were analyzed according to age (<, ≥12 years old) or gender. While blood pressure was reduced in all racial subgroups examined, too few non-

White patients were enrolled to compare the dose-response of losartan in the non-White subgroup.

7. Under **CLINICAL PHARMACOLOGY**, *Reduction in the Risk of Stroke,* the Table #1 for Incidence of Primary Endpoint Events has been changed to Table #2.

8. Under **CLINICAL PHARMACOLOGY**, *Nephropathy in Type 2 Diabetic Patients*, the Table #2 for Incidence of Primary Endpoint Events has been changed Table #3. In addition, Table #3 for Efficacy Outcomes within Demographic Subgroups has been changed to Table #4.

9. Under **PRECAUTIONS**, *Pediatric Use*, the statement "Safety and Effectiveness in pediatric patients have not been established" has been deleted and replaced with the following:

   Antihypertensive effects of COZAAR have been established in hypertensive pediatric patients aged 6 to 16 years. There are no data on the effect of COZAAR on blood pressure in pediatric patients under the age of 6 or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m2 (see **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*, *Special Populations* and *Pharmacodynamics and Clinical Effects*, and **DOSAGE AND ADMINISTRATION**).

10. Under **ADVERSE REACTIONS**, a new subsection entitled "*Pediatric Patients*" has been added with the following language:

    No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

11. Under **DOSAGE AND ADMINISTRATION,** the subheading "*Hypertension*" has been deleted and replaced with the subheadings "*Adult Hypertensive Patients*" and "*Pediatric Hypertensive Patients >6 years of age*". Dosing information for younger children has been included under the *Pediatric Hypertensive Patients >6 years of age* subheading.

    A subsection entitled "*Pharmacodynamics and Clinical Effects*" has been added under *Pediatric Patients >6 years of age* and includes the following language:

    > COZAAR is not recommended in pediatric patients <6 years of age or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m2 (see **CLINICAL PHARMACOLOGY**, *Pharmacokinetics*, *Special Populations*, *Pharmacodynamics and Clinical Effects*, and **PRECAUTIONS**).

    Details of how to make the losartan suspension for children are now detailed under the new subsection, "*Preparation of Suspension (for 200 mL of a 2.5 mg/mL suspension).*

Comments/Recommendations:

I will draft an approval letter for the two supplements with enclosed labeling text for Dr. Throckmorton's signature.

/S/

Edward Fromm

Regulatory Health Project Manager

dr-ef-3-04-04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-386	Efficacy Supplement Type SE-5 Labeling changes in response to our Written Request	Supplement Number 029
Drug: Cozaar (losartan potassium) Tablets, 25, 50, and 100 mg	Applicant: Merck & Co., Inc.	
RPM: E. Fromm	HFD-110	Phone # 594-5332
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	April 27, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid N/A
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (X) Other- Peds Supplement
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) 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.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (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).	( ) 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-October 21, 2002, March 2, 2004
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-October 21, 2002
• Status of advertising (approvals only)	**Not Applicable** ( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) 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)	X (AE letter with marked-up draft labeling)
• Most recent applicant-proposed labeling	NA
• 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)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ Post-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)	NA
❖ Memoranda and Telecons	NA
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other	NA

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary/Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	October 21, 2002-Division Director
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	September 27, 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)*	April 8, 2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	September 19, 2002
❖ 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
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	October 21, 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	X May 22, 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
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	NA
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
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Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(484) 344-2516
Attention:	Dr. Jeffrey Tucker
Company Name:	Merck and Co.
Phone:	(484) 344-7788
Subject:	**Approval Letter and Labeling for NDA 20-386/S-019 and S-029 Cozaar (losartan potassium) Tablets**
Date:	March 11, 2004
Pages including this sheet:	**18**
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

EXCLUSIVITY SUMMARY FOR NDA # 20-386 SUPPL #_SE5-029_____

Trade Name: Cozaar Generic Name: Losartan Potassium

Applicant Name: Merck and Co. HFD # 110

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?
YES /_ __/ NO /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) _SE5_____

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

YES /_X __/ NO /_ __/

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

_____

_____

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

d) Did the applicant request exclusivity?

YES /_X__/ NO /_ __/ ---Applicant requested 6 months of Pediatric Exclusivity

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

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

YES

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

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

YES / X NO /___/

If yes, NDA # 20-386 Drug Name: Cozaar (losartan potassium)

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_____ _____Cozaar (losartan potassium)_____

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 /___/ Not Applicable

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 /_X__/ NO /___/

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

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

YES /___/ NO /_X_/
(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 /_X__/

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 /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: Study P227

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

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

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

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

___Study P227_____ _____

_____ _____

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 # _33,383____ YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____NA____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain ___NA_____

_____ _____

_____ _____

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

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

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

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

/s/

Doug Throckmorton
10/7/02 09:51:57 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-386 **Supplement Type (e.g. SE5):** SE5 **Supplement Number:** 029

Stamp Date: December 21, 2001 **Action Date:** AE-October 21, 2002

HFD 110 **Trade and generic names/dosage form:** Cozaar (losartan potassium) Tablets 25, 50, and 100 mg

Applicant: Merck and Co. **Therapeutic Class:** Angiotensin II receptor Antagonist

Indication(s) previously approved: Hypertension

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

Number of indications for this application(s): Not applicable

Indication #1: _____

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.__1__**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr.__16__**	**Tanner Stage_____**

Comments: Pediatric changes to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE and ADMINISTRATION sections in response to our pediatric Written Request. Peds Exclusivity granted on March 20, 2002.

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 20-386/S-029
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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

/s/

Edward Fromm
3/2/04 09:26:18 AM

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 11/2/99. Application Written Request was made to: NDA/IND#20-386
Timeframe Noted in Written Request for Submission of Studies 11/2/03.
NDA# 20-386 Supplement # 029 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor Merck & Co., Inc.
Generic Name Losartan Trade Name Cozaar
Strength 2.5mg/ml Dosage Form/Route Suspension/oral
Date of Submission of Reports of Studies 12/21/01.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 3/21/02.

Was a formal Written Request made for the pediatric studies submitted?	Y √	N ___
Were the studies submitted after the Written Request?	Y √	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y √	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y √	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y √	N ___
Did the studies fairly respond to the Written Request?	Y √	N ___

SIGNED /S/ _____ DATE 3.20.02

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity ✓ **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
20-386, 20-20-387	5138069	11-Aug-2009
	5153197	6-Oct-2009
	5608075	4-Mar-2014

/S/

SIGNED _____ DATE 3/21/02

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

/s/

Terrie Crescenzi
3/20/02 03:01:04 PM

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 Six-months pediatric market exclusivity
9. Applicable Patent Numbers	US Patent No. 5,138,069* Expiration Date: February 11, 2010 with pediatric market exclusivity US Patent No. 5,153,197* Expiration Date: April 6, 2010 with pediatric market exclusivity US Patent No. 5,608,075§ Expiration Date: September 4, 2014 with pediatric market exclusivity

* 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 Filed: December 3, 1993
- Date NDA Approved: April 14, 1995

A. This section should be completed for each individual patent

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

Expiration Date: 02/11/2010

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. 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.

A. This section should be completed for each individual patent

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

Expiration Date: 04/06/2010

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 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.

A. This section should be completed for each individual patent

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

Expiration Date: 09/04/2014

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.

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: October 15, 2001

A copy of the above information should be submitted to the FDA with the original application or a supplemental NDA (sNDA), or as correspondence to an existing NDA. For patents issued after the NDA or sNDA 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

Losartan Potassium - Pediatric Use
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.

M. C. Elia

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

21-DEC-2001
Date

D/

NOV - 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

NDA 20-386

Merck Research Laboratories
Attention: Jeffrey R. White, M.D.
Sumneytown Pike, BLA-20
West Point, PA 19486

Dear Dr. White:

Reference is made to our July 1, 1999 written request for pediatric studies for Cozaar (losartan potassium) Tablets. We have recently reviewed that written request and have decided to amend it. Please note that the following Written Request supercedes that of July 1, 1999, which is no longer valid.

Changes have been made to the following sections:

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

Strategy

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

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

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

Pediatric Subgroups

Age groups

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

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

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

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

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

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

Racial groups

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

Formulation Issues

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

Dose-ranging Trial

Trial Design

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

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of losartan potassium, with the doses chosen to give blood levels in a range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the

highest approved adult dose.[1] After two weeks of treatment,[2] the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.[3] If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show not effect), but it would be interpretable.

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

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

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

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

Recruiting

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

---

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

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

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

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

Eligibility

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

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

Duration

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

Statistical considerations

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

Pharmacokinetic Trials

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

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

Format of Reports

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

Labeling Changes

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

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

Timing of Submission of Reports

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

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

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

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

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

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

If you have any questions, please contact:

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

Sincerely yours,

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

cc:
Archival NDA
HFD-110/Division file
HFD-110/Project Manager
HFD-101/Office Director
HFD-600/Office of Generic Drugs
HFD-2/MLumpkin
HFD-104/DMurphy
HFD-2/TCrescenzi
Drafted by:sb/10/8/99
Initialed by:
Final:
filename: n20386PedWrit991008doc
PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

Division of Cardio-Renal Drug Products
Medical Officer Review

Name of Drug: Cozaar® Losartan potassium Tablets

Sponsor: Merck Research Laboratory
Date of Submission: December 21, 2001

Type of Submission: Financial statement for the pediatric studies

Reviewer: Abraham M. Karkowsky, M.D., Ph.D.

Summary:

The Financial disclosure information would not impact on the conclusions for the pediatric studies.

Body:

The sponsor submits form #3454, which covers the majority of the investigators in study # 216, #225 and # 227. Two hundred seventy five of the 289 investigators and sub-investigators are included under this form in which the sponsor states that it has not entered into any financial arrangement with these investigators. There were two investigators/sub-investigators that claimed financial interests as well as 12 investigators/sub-investigators, which are no longer at the study site or did not return the disclaimer.

One investigator from the pivotal efficacy study claims significant financial interest [redacted] Mercke & Co. This investigator enrolled 8 patients out of the 176 patients enrolled into the pivotal study. The study was double-blinded so that it is unlikely that this investigator had significant impact on the results. One sub-investigator In the non-pivotal study # 216 claims significant equity interest in Merck [redacted] Since this was a non-pivotal study, there is no reason to assume that this degree of holding with Merck & Co had the potential to alter the conclusions of the development plan.

For the pivotal study # 227, there were nine such sub-investigators from seven sites. Only five subjects out of 177 who were enrolled came from these sites. It is unlikely that these sub-investigators, whose financial forms were missing, altered the outcome of this study.

Two sub-investigators, who did not submit financial disclosure forms, were associated with study # 216. This study evaluated the bioequivalence of an oral solution with the marketed tablet. The study was tangential to establishing the efficacy of the drug in pediatrics. One sub-investigator from study # 225 did not complete the form The study site associated with this investigator enrolled only 3 of the 50 subjects. Consequently, the impact on this investigator on the outcome of the study was minimal.

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

/s/

Abraham Karkowsky
10/2/02 01:13:20 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

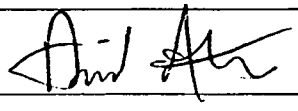
Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Tables C-1 and C-2	
	Losartan Potassium - Pediatric Use	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David Arkowitz	Controller, MRL Financial Services
FIRM/ORGANIZATION: Merck & Co., Inc.	
SIGNATURE: 	DATE: Nov. 13, 2001

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

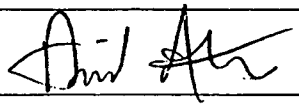
Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Tables C-1 and C-2	
	Losartan Potassium - Pediatric Use	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David Arkowitz	Controller, MRL Financial Services
FIRM/ORGANIZATION: Merck & Co., Inc.	
SIGNATURE: 	DATE: Nov. 13, 2001

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Table D-1 (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study Losartan Potassium - Pediatric Use (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

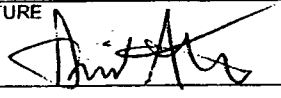
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
David Arkowitz	Controller, MRL Financial Services
FIRM/ORGANIZATION	
Merck & Co., Inc.	
SIGNATURE	DATE
	Nov. 13, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Item 19 Financial Disclosure Information

A. Introduction

In compliance with the U.S. Food and Drug Administration's regulation *Financial Disclosure by Clinical Investigators* published 02-Feb-1998 and revised 31-Dec-1998, the following sections detail the requested information concerning the financial interests of and compensation to investigators participating in the covered clinical studies presented in this application.

Investigators meeting the definition of Clinical Investigator (Part 54.2(d)) were requested to complete and return questionnaires related to their financial interest in Merck & Co., Inc. and proprietary interest in the test product. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR Part 54.4), multiple requests for this information were made, when possible, to Clinical Investigators who did not respond. Please note that Merck & Co., Inc. has not entered into any financial arrangement with our clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (21 CFR 54.2(a)). Merck & Co., Inc. conducted an internal search for all payments that met the definition of "significant payments of other sorts" (21 CFR 54.2(f)) and reported the information, as appropriate.

Data from the Clinical Studies outlined in Tables A-1 and A-2 are presented in this application. The following trials are considered covered clinical studies for the purpose of financial disclosure:

An Open-Labeled, Randomized, Two-Period, Crossover Study to Determine the Relative Bioavailability of Losartan 50-mg Suspension and Losartan 50-mg Tablet Administered Orally as Single Doses (Protocol 216)

For this clinical protocol, the First Patient In (FPI) was 07-Sep-1999 and the Last Patient Out (LPO) was 23-Sep-1999. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of 07-Sep-1999 through 23-Sep-2000 and included, as appropriate. The cut-off date for financial information provided by the investigators was 31-Oct-2001.

An Open-Label Study to Investigate the Pharmacokinetics of Losartan in Hypertensive Children and Infants (Protocol 225)

For this clinical protocol, the First Patient In (FPI) was 16-Jun-2000 and the Last Patient Out (LPO) was 02-Jul-2001. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of 16-Jun-2000 through 31-Jul-2001 and included, as

appropriate. The cut-off date for financial information provided by the investigators was 31-Oct-2001.

A Double-Blind, Randomized Dose-Response Study of Losartan in Children With Hypertension (Protocol 227)

For this clinical protocol, the First Patient In (FPI) was 14-Jul-2000 and the Last Patient Out (LPO) was 31-Aug-2001. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of 14-Jul-2000 through 31-Jul-2001 and included, as appropriate. The cut-off date for financial information provided by the investigators was 31-Oct-2001.

Table A-1 Summary of Covered Clinical Trials as Defined by 21 CFR 54.2(e)

Protocol Number	Protocol Title	FPI	LPO	"Payments of Other Sorts" Range
216	An Open-Labeled, Randomized, Two-Period, Crossover Study to Determine the Relative Bioavailability of Losartan 50-mg Suspension and Losartan 50-mg Tablet Administered Orally as Single Doses	07-Sep-1999	23-Sep-1999	07-Sep-1999 Through 23-Sep-2000
225	An Open-Label Study to Investigate the Pharmacokinetics of Losartan in Hypertensive Children and Infants	16-Jun-2000	02-Jul-2001	16-Jun-2000 Through 31-Jul-2001
227	A Double-Blind, Randomized Dose-Response Study of Losartan in Children With Hypertension	14-Jul-2000	31-Aug-2001	14-Jul-2000 Through 31-Jul-2001

Table A-2 - The following trial is considered a non-covered clinical study for the purpose of financial disclosure:

Table A-2 Summary of Non-Covered Clinical Trials 21 CFR 54.2(e)

Protocol Number	Protocol Title
	Table A-2 is not applicable.

Table A-3 details the total number of investigators in each of the categories that require reporting as defined in 21 CFR 54.2(a,b,c,f). As it is possible for an investigator to meet the definition for more than one category, the number of investigators in each sub-category may not add up to the total number of investigators.

Table A- 3 Summary of Investigators that Meet the Definition of "Clinical Investigator"

Investigator Category	Total Number	Comments
Grand Total Number of Investigators/ Subinvestigators per Protocol and Site	289	Table B-1
Total Number of Investigators/ Subinvestigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site	275	Table C-1
Total Number of Investigators/ Subinvestigators Not Providing Information and Not Certified per Protocol and Site	12	Table C-2 Investigators no longer at site, unable to obtain information (n=6). Investigators not returning requested information (n=6).
Total Number of Investigators/ Subinvestigators Not Certified Due to "Significant Payments of Other Sorts" or Equity Interest (Table D-1) per Protocol and Site	2	Table D-1 Details for payments and equity are detailed for each investigator. The protocols that each investigator participated in are listed.
Total Number of Investigators/ Subinvestigators Receiving Payments Based on the Outcome of the Study per Protocol and Site	0	Merck & Co., Inc. has not entered into any financial arrangements with our clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study.
Total Number of Investigators/ Subinvestigators with Proprietary Interest in the Test Product or Company per Protocol and Site	0	

B. Table of All Clinical Investigators/Subinvestigators

Table B-1 provides the names of all identified clinical investigators and subinvestigators listed by protocol and site number.

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
216-001		NO
		NO
		NO
		NO
		NO
		NO

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
225-001	Hernandez, Oscar Adolfo	NO
		NO
		NO
		NO
		NO
225-002		NO
225-003		NO
		NO
		NO
225-004	Blumer, Jeffrey L.	NO
		NO
		NO
		NO
		NO
		NO
225-005		NO
	Hogg, Ronald J.	NO
		NO
		NO
		NO
225-006		NO
		NO
		NO
		NO
		NO
225-007		NO
		NO
		NO
		NO
		NO
	Tenney, Frank	NO
		NO
225-008		NO
		NO
		NO
		NO
		NO
	Wells, Thomas G.	NO
225-010		NO
		NO
225-012	Cano, Francisco Javier	NO
		NO
		NO
227-001		NO

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
	Loza, Reyner	NO
		NO
227-002		NO
		NO
		NO
		NO
		NO
	Wroblewska-Kaluzewska, Maria	NO
227-003	Achtel, Robert A.	NO
		NO
		NO
		NO
		NO
227-004	Blumer, Jeffrey L.	NO
		NO
		NO
		NO
		NO
		NO
227-006		NO
	Cunningham, Robert	NO
		NO
		NO
		NO
		NO
		NO
227-007		NO
	Eissa, Mona	NO
		NO
		NO
227-008		NO
	Falkner, Bonita	NO
227-010		NO
	Hogg, Ronald J.	NO
		NO
		NO
		NO
227-011		NO
	Hunley, Tracy E.	NO
		NO
		NO
227-013		NO
		NO

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		YES
	Meyers, Kevin	NO
		NO
		NO
		NO
		NO
227-014		NO
	Miller, Kenneth	NO
227-016		NO
		NO
		NO
	Schwartz, George J.	NO
		NO
227-017		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
	Sullivan, Janice E.	NO
		NO
		NO
227-018		NO
		NO
		NO
		NO
		NO
	Siegel, Norman	NO
		NO
227-019		NO
		NO
		NO
		NO
		NO
		NO
	Tenney, Frank	NO
		NO
		NO
227-020		NO
		NO
		NO

Losartan Potassium - Pediatric Use
Financial Disclosure - Item 19

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
	Vergara, Marcela	NO
227-021		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
227-022		NO
		NO
		NO
		NO
		NO
	Wells, Thomas G.	NO
227-025	Cranswick, Noel E.	NO
		NO
		NO
		NO
		NO
227-026		NO
	Lurbe-Ferrer, Amparo	NO
		NO
227-027		NO
	Machado, Livia	NO
		NO
227-029		NO
		NO
		NO
		NO
	Martins, Maymone	NO
		NO
		NO
227-030	Arbus, Gerald S.	NO
		NO
		NO
227-031		NO
	Cote, Jean-Marc	NO
		NO
		NO
		NO
227-032	Cano, Francisco Javier	NO
		NO
227-033		NO

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
	Koch, Vera	NO
		NO
		NO
227-034		NO
		NO
		NO
	Simsolo, Rosa Beatriz	NO
227-035		NO
	Capelli, Horacio	NO
		NO
		NO
		NO
227-036	Briazgounov, Igor	NO
		NO
		NO
		NO
		NO
227-037	Alexandrov, Alexander	NO
227-038		NO
		NO
		NO
		NO
		NO
		NO
	McKinney, Ross E., Jr.	NO
		NO
		NO
227-039		NO
	Thomson, Peter Drummond	NO
227-040		NO
	Rayner, Brian	NO
		NO
		NO
227-041		NO
		NO
	Milford, David Vernon	NO
		NO
227-042		NO
	Holmberg, Christer	NO
		NO
227-043		NO
		NO
	Feber, Janusz	NO
227-044	Kolsky, Alexander	NO

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
227-045		NO
	Rucki, Stepan	NO
227-046		NO
	Proesmans, Willem Christian Josef Jan	NO
		NO
227-048		NO
		NO
		NO
		NO
		NO
		NO
227-049	Daniels, Stephen R.	NO
		NO
227-050		NO
		NO
	Sakihara, Graciela	NO
		NO
227-051		NO
		NO
		NO
		NO
		NO
	Gitomer, Jeremy J.	NO
227-052	Campos, Alfonso	NO
		NO
		NO
		NO
		NO
		NO
		NO
227-053	Bartosh, Sharon M.	NO
		NO
		NO
		NO
		NO
227-054		NO
		NO
	Molina, Carmen	NO
		NO
		NO
227-056		NO
	Podracka, Ludmila	NO
		NO

Table B-1 Table of All Investigators/Subinvestigators for the Covered Clinical Trials

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
227-057		NO
	Torro-Domenech, Maria Isable	NO
227-058		NO
		NO
	Rokicki, Wladyslaw	NO
227-061	Cea-Crespo, Jose Maria	NO
227-062		NO
	Hernandez, Oscar Adolfo	NO
		NO
		NO
227-064	Burdmann, Emmanuel Almeida	NO
		NO
		NO
		NO
		NO
227-065		NO
		NO
	Van de Walle, Johan Jules Gustaaf	NO

C. Form FDA 3454 – Certification: Financial Interest and Arrangements of Clinical Investigators

Certification for the financial interests of investigators/subinvestigators participating in the covered clinical studies is attached; this information is reflective of the requirements outlined in 21 CFR Part 54.4(a)(1).

Table C-1 lists all investigators/subinvestigators who have met the certification criteria regarding an absence of financial arrangements as defined in 21 CFR 54.2.

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
216-001	
225-001	Hernandez, Oscar Adolfo

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
225-002	
225-003	
	Koch, Vera
225-004	Blumer, Jeffrey L.
225-005	
	Hogg, Ronald J.
225-006	
225-007	
225-008	
225-010	
225-012	Cano, Francisco Javier
227-001	
227-002	

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
	Wroblewska-Kaluzewska, Maria
227-003	Achtel, Robert A.
227-004	Blumer, Jeffrey L.
227-006	Cunningham, Robert
227-007	Eissa, Mona
227-008	Falkner, Bonita
227-010	Hogg, Ronald J.
227-011	Hunley, Tracy E.
227-013	Meyers, Kevin

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
227-014	
227-016	
	Schwartz, George J.
227-017	
	Sullivan, Janice E.
227-018	
	Siegel, Norman
227-019	
	Tenney, Frank
227-020	
	Vergara, Marcela
227-021	
	Valentini, Rudolph P.
227-022	

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
	Wells, Thomas G.
227-025	Cranswick, Noel E.
227-026	Lurbe-Ferrer, Amparo
227-027	
227-029	Martins, Maymone
227-030	
227-031	Cote, Jean-Marc
227-032	Cano, Francisco Javier
227-033	Koch, Vera
227-034	Simsolo, Rosa Beatriz
227-035	Capelli, Horacio

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
227-036	Briazgounov, Igor
227-037	Alexandrov, Alexander
227-038	McKinney, Ross E., Jr.
227-039	Thomson, Peter Drummond
227-040	Rayner, Brian
227-041	Milford, David Vernon
227-042	Holmberg, Christer
227-043	Feber, Janusz
227-044	Kolsky, Alexander
227-045	Rucki, Stepan
227-046	Proesmans, Willem Christian Josef Jan
227-048	

Table C-1 Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2

Protocol/Site	Investigator/Subinvestigator
	Norwood, Victoria Fay
227-049	
227-050	
	Sakihara, Graciela
227-051	
227-052	Campos, Alfonso
227-053	Bartosh, Sharon M.
227-054	
	Molina, Carmen
227-056	
	Podracka, Ludmila
	Podracky, Juraj
227-057	
	Torro-Domenech, Maria Isable
227-058	
227-061	Cea-Crespo, Jose Maria
227-062	
	Hernandez, Oscar Adolfo

Table C-1	**Table of All Investigators/Subinvestigators Who are Certified by Merck & Co., Inc. Regarding the Absence of Financial Arrangements as Defined in 21 CFR 54.2**
Protocol/Site	**Investigator/Subinvestigator**
227-064	Burdmann, Emmanuel Almeida
227-065	
	Van de Walle, Johan Jules Gustaaf

Table C-2 lists all investigators/subinvestigators who did not provide the requested financial information by the cut-off date and includes the reason that this information could not be provided. In compliance with the regulatory requirement for the Sponsor to demonstrate "due diligence" (21 CFR Part 54.4), multiple requests for this information were made, when possible, to Clinical Investigators who did not respond.

Table C-2	**Table of All Investigators/Subinvestigators Not Providing Information and Not Certified**	
Protocol/Site	**Investigator/Subinvestigator**	**Reason**
216-001		Investigator no longer at site / Cannot certify. Forms sent on 05-30-2000.
216-001		Investigator no longer at site / Cannot certify. Forms sent on 05-30-2000.
225-007		Investigator no longer at site / Cannot certify. Forms sent on 10-23-2000.
227-006		Did not return form with requested information. Forms sent on 06-04-2001; 08-07-2001.
227-013		Investigator no longer at site / Cannot certify. Forms sent on 01-30-2001; 04-24-2001.
227-018		Did not return form with requested information. Forms sent on 07-18-2000; 11-27-2000; 05-21-2001; 08-07-2001.
227-018		Investigator no longer at site / Cannot certify. Forms sent on 07-18-2000; 11-27-2000; 05-21-2001.
227-019		Did not return form with requested information. Forms sent on 08-15-2001; 11-05-2001.
227-019		Did not return form with requested information. Forms sent on 08-15-2001; 11-05-2001.
227-030	Arbus, Gerald S.	Investigator no longer at site / Cannot certify. Forms sent on 05-24-2001.
227-038		Did no return form with requested information. Forms sent on 03-02-2001; 11-05-2001.
227-054		Did not return form with requested information. Forms sent on 09-10-2001; 11-05-2001.

D. Form FDA 3455 – Disclosure: Financial Interests and Arrangements of Clinical Investigators

Disclosure of the financial interests of investigator/subinvestigators participating in the covered clinical studies is attached; this information is reflective of 21CFR Part 54.4(a)(3).

Table D-1 lists all investigators/subinvestigators who have met the disclosure criteria regarding financial interests as defined in 21 CFR 54.2(a,b,c,f).

Please note that Merck & Co., Inc. has not entered into any financial arrangement with our clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study (21 CFR 54.2(a)).

Table D-1 Table of All Investigators/Subinvestigators Who Hold Financial Interests Requiring Disclosure

Protocol/Site	Investigator/Subinvestigator	Financial Interest/Steps Taken to Minimize Bias
216-001	—	Equity interest in Merck —
227-014	—	— in "Significant Payments of Other Sorts"; bias minimized through trial design, i.e. double-blind, multicenter study sites.

RHPM NDA Efficacy Supplement Overview
October 21, 2002

Cozaar (losartan potassium) Tablets, 25, 50 and 100 mg for the treatment of hypertension in response to our Pediatric Written Request

NDA 20-386/SE5-029

Applicant: Merck and Co., Inc.

Classification: SE5

Review Classification: Standard (10 month & 12 month)

Indication: Treatment of hypertension in children aged 1 month to 16 years

Date of Application: December 21, 2001

Receipt Date: December 21, 2001

User Fee Goal Dates: 10 month: October 21, 2002
12 month: December 21, 2002

Background

Merck has submitted this efficacy supplement in response to our Pediatric Written Request of July 1, 1999, and later amended on November 2, 1999. The sponsor conducted one primary, randomized, double-blind, dose-response efficacy study (P227) along with an open-label pharmacokinetic study. The sponsor proposed changes to the **CLINICAL PHARMACOLOGY**, **PRECAUTIONS**, and **DOSING** and **ADMINISTRATION** sections of the labeling.

The Pediatric Exclusivity Board granted 6 months exclusivity for losartan potassium on March 20, 2002.

Review

Medical	
Division Director:	Douglas C. Throckmorton
Conclusion:	Approvable
Labeling:	See Dr. Throckmorton's October 21, 2002 memo detailing his labeling suggestions to the **CLINICAL PHARMACOLOGY, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the labeling.
Medical	Abraham Karkowsky, M.D., Ph.D.
Conclusion:	Approvable; see Dr. Karkowsky's September 27, 2002 review for his suggested changes to the **CLINICAL PHARMACOLOGY, PRECAUTIONS, ADVERSE REACTIONS**, and **DOSING AND ADMINISTRATION** sections of the labeling.

Statistical	Jasmine Choi, M.S.
Conclusion:	Approvable; The reviewer states that "both parametric and nonparametric tests showed statistically significant positive dose-response relationship of losartan treatment in pediatric patients".

Biopharmaceutics:	
Reviewer:	Elena Mishina, Ph.D
Conclusion:	Approvable; see Dr. Mishina's September 19, 2002 review for her suggested changes to the **CLINICAL PHARMACOLOGY** and **DOSING AND ADMINISTRATION** sections of the labeling

Chemistry:	
Reviewer:	Ramshara Mittal, Ph.D.
Conclusion:	Approvable
Labeling:	In his October 21, 2002 review, Dr. Mittal suggested changes, under **DOSAGE AND ADMINISTRATION** to the heading "*Preparation of Suspension*" and to the instructions for shaking the suspension.

Patent info: Included in package

Debarment Certification: Included in package

Exclusivity Summary: Included in package

Environmental Assessment: A Finding of No Significant Impact (FONSI); see May 20, 2002 Environmental Assessment review.

Financial Disclosure: Included in package

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

Comments: The Division is suggesting labeling changes to the **CLINICAL PHARMACOLOGY, PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections. I will draft an approvable letter with marked-up draft labeling for Dr. Throckmorton's signature.

/S/

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-10-21-02

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

/s/

Edward Fromm
10/23/02 02:21:55 PM
CSO

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

The Worldwide Clinical Summary is reproduced exactly as it appears in the Clinical and Statistical Documentation

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