CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-387/S-013, 015 & 027

Administrative Documents

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 # 20-387

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

- Trade Name: HYZAAR
- Active Ingredient(s): Losartan potassium and Hydrochlorothiazide
- Strength(s): 50 mg/12.5 mg and 100 mg/25 mg
- Dosage Form(s): Film Coated Tablets
- Date ✓ NDA __ sNDA filed: December 10, 1993
- Date ✓ NDA __ sNDA approved: April 28, 1995

A. This section should be completed for each individual patent

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

Expiration Date: 8/11/2009

Type of Patent - indicate all that apply:

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

Name of Patent Owner: E. I. Du Pont de Nemours and Company, 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 5,138,069
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: 10/6/2009

Type of Patent - indicate all that apply:

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

Name of Patent Owner: E. I. DuPont de Nemours and Company, Wilmington, DE

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

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

The undersigned declares that United States Patent Number 5,153,197

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

(name of drug product). This product is:

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

  OR

- __ the subject of this application for which approval is being sought.

A. This section should be completed for each individual patent

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

Expiration Date: 3/4/2014

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: September 19, 2002

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

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

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

IN DUPLICATE

NDA 20-387

Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Losartan Potassium and Hydrochlorothiazide
2. Dosage(s)	50 mg/ 12.5mg and 100 mg/ 25 mg
3. Trade Name	HYZAAR
4. Dosage Form	Film Coated Tablets
Route of Administration	Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	20-387
7. Approval Date	April 28, 1995
8. Exclusivity	New use three years from sNDA approval
9. Applicable Patent Numbers	US Patent No. 5,138,069* Expiration Date: August 11, 2009 US Patent No. 5,153,197* Expiration Date: October 6, 2009 US Patent No. 5,608,075§ Expiration Date: March 4, 2014

* 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)

EXCLUSIVITY SUMMARY FOR NDA # 20-387 SUPPL #027

Trade Name: Hyzaar Generic Name: losartan potassium/hydrochlorothiazide

Applicant Name: Merck and Company, Inc. HFD # 110

Approval Date If Known:

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /___/ NO /_X__/

b) Is it an effectiveness supplement?

YES /_X__/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE1_

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

YES /_X__/ NO /___/

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

_____

_____

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

_____

_____

Form OGD-011347 Revised 10/13/98

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

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

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

e) Has pediatric exclusivity been granted for this Active Moiety?. **Yes** (to losartan)

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

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

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

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

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_X__/ NO /___/

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

NDA= _20-386_____ _____

NDA# _____ _____

NDA= _____ _____

2. Combination product.

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

YES /_X__/ NO /___/

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

NDA# _20-386 __losartan potassium_____

NDA# _11-835 ___hydrochlorothiazide_____

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:**

____P232 & P228_____

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	**IND #_33,383_____**	**YES /___/**	**NO /__X_/**
Investigation #2	IND #_____	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"):

_____P232 & P228_____ ___

_____

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: _____

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

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

YES /___/ NO /_X__/

If yes, explain: _____

Signature Date
Edward Fromm, Regulatory Health Project Manager

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

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

Exclusivity sheet to be put into DFS for signing by Dr. Throckmorton after Approval.

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-387 Supplement Type (e.g. SE5): SE1 Supplement Number: 027

Stamp Date: September 24, 2002 Action Date: November 16, 2003

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

Applicant: Merck and Co. Therapeutic Class: Angiotensin II receptor blocker

Indication(s) previously approved: Hypertension

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

Number of indications for this application(s): one

Indication #1: (Severe HTN) Hyzaar is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

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

X 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
X Disease/condition does not exist in children
X Too few children with disease to study
☐ There are safety concerns
☐ Other:

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study

- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other:_____

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

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

Other:_____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze

(revised 9-24-02)

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

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
9/26/03 05:35:37 PM

Losartan Potassium/HCTZ First-Line for Severe Hypertension
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.

JrATucl

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

9/24/02

Date

At the filing meeting on November 1, 2002, the Division stated that it would not ask for clinical audits of the study sites.

RHPM NDA Efficacy and Labeling Supplement Approval Review
September 26, 2003

Hyzaar (losartan potassium/hydrochlorothiazide) 50/12.5 & 100/25 mg Tablets

NDA 20-387/SE1-027

Applicant: Merck and Co.

Classification: SE1 (new indication)-NDA 20-387/S-027

Review Classification: Standard (10 month review)

Indication: Hyzaar is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients.

Date of Application: September 24, 2002

Date of AE Letter: July 25, 2003

Date FPL Submitted: September 16, 2003

Date FPL Received: September 16, 2003

User Fee Goal Date: November 16, 2003

Background (Note: Labeling supplements NDA 20-387/S-013 & 015 will be approved concurrently with S-027 as Merck, after consultation with the Division, included revisions in the FPL that are acceptable to the Division and allow approval of these supplements as well).

NDA 20-387/SE1-027

An approvable letter was issued on July 25, 2003 for losartan potassium/hydrochlorothiazide for the initial treatment of hypertension so severe that the short-term risk of inadequate blood pressure control exceeds the excess risk of beginning the components, losartan and hydrochlorothiazide, together. After labeling discussions with the firm on August 4 and 18th, 2003, 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 20-387-SE1-027).

NDA 20-387/S-013

Merck submitted a "Changes Being Effected" supplement on April 1, 1999 for the following changes to the labeling:

1. **CLINICAL PHARMACOLOGY,** *Pharmacodynamics and Clinical Effects, Losartan Potassium*: the information on cough has been relocated to the **ADVERSE REACTIONS** section. In addition, the following sentence has been added beneath the information on

cough: "Cases of cough, including positive re-challenges, have been reported with the use of losartan in post-marketing experience."

2. **CLINICAL PHARMACOLOGY,** *Pharmacodynamics and Clinical Effects, Losartan Potassium*: In the fifth paragraph, the sentence "Black patients, however, had notably smaller responses to losartan monotherapy." has been replaced with "COZAAR was effective in reducing blood pressure regardless of race, although the effect was somewhat less in black patients (usually a low-renin population)."

3. **ADVERSE REACTIONS,** *Post-Marketing Experience*: "Respiratory: Dry cough (see above) has been reported with losartan" has been added.

Comments/Recommendations: The above labeling changes were similar to those approved for the Cozaar monotherapy (NDA 20-386/S-011 & 013, August 31, 1998) and were acceptable to the Division. However, the sponsor did not submit 20 copies of final printed labeling and therefore it was decided to request this labeling in an approvable letter that also included NDA 20-386/S-019 and NDA 20-387/S-015. The approvable letter was issued on April 11, 2000.

Because of continuing disagreements between the sponsor and the Division regarding supplements NDA 20-386/S-019 & NDA 20-387/S-015, which proposed changes to the **Geriatric** sections of the labeling, I suggested, in a telephone conversation with Merck on April 29, 2003, that the sponsor send in FPL separately for NDA 20-387/S-013. The Division formalized this conversation in a letter to Merck dated May 20, 2003. Merck asked, in lieu of a separate submission for S-013, if they could include the corrected language when sending FPL for NDA 20-387/S-027. I said this was acceptable and a review of the FPL submitted September 16, 2003 found the changes as described above with the following minor exception:

1. The word "Losartan" has been inserted for "COZAAR" in the second sentence of the fifth paragraph under **CLINICAL PHARMACOLOGY,** *Pharmacodynamics and Clinical Effects, Losartan Potassium.*

NDA 20-387/S-015

The sponsor, in supplements dated August 25, 1999, submitted updated information for rifampin, fluconazole, and erythromycin to the *Drug Interaction* section of the labeling under **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** and added to **PRECAUTIONS,** a *Geriatric Use* subsection, in response to 21 CFR 201.57(f)(10).

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.

3. The *Geriatric Use* subsection should be revised as follows:

Clinical Studies of DRUG Name did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Merck replied to the approvable letter of April 11, 2000 with the following submissions:

1. In a submission dated August 2, 2001, they stated since there were data on more than 100 patients 65 years and over, the type "B" paragraph under CFR 201.57 was applicable. Therefore they asked the Division to reconsider the following language for the **Geriatric Use** subsections Hyzaar (Note: the following proposed language was just a reiteration of what was submitted earlier in NDA 20-387/S-015):

[

]

2. 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.

It is worth noting that Merck continued to include the "type B" paragraph for the **Geriatric Use** subsection in this submission.

Dr. Throckmorton, in a memo dated April 11, 2003, said that that a second approvable letter should issue for NDA 20-387/S-015 with the following revisions and rationale:

1. Submission of adequate data in support of your proposed labeling change, including data comparing the adverse event profile and efficacy of Hyzaar in patients with hypertension for the elderly population (≥65 years old), patients <65 years old and the total population with hypertension. Your letter of August 2, 2001 correctly points out that an arbitrary number can provide a guideline, but certainly it can never be a satisfactory single mechanism for determining appropriate language on the safety and efficacy of a product in the Geriatric population. Adequate data specific to the population and product are required.

2. Our proposed language for Hyzaar under **PRECAUTIONS**/*Geriatric Use* is as follows:

   Clinical studies of Hyzaar did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

   Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

A second approvable letter issued on May 20, 2003 asking for the above changes for NDA 20-387/S-015. The FPL submitted for NDA 20-387/S-027 contained the above changes for the *Geriatric Use* subsection and thus the major obstacle blocking approval of this supplement has been lifted. Merck did add the reference parenthetical (see **CLINICAL PHARMACOLOGY**, *Special Populations*) after the second paragraph above so that the second paragraph of this subsection now reads:

Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (see **CLINICAL PHARMACOLOGY**, *Special Populations*).

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

1. Under CLINICAL **PHARMACOLOGY,** *Drug Interactions, Losartan Potassium*, 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, Losartan Potassium*, 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.

Review-NDA 20-387/S-027

Merck submitted final printed labeling on September 16, 2003, received September 16, 2003. When compared with the last approved labeling supplement (S-024, November 7, 2002) the following changes were noted:

1. Under **DESCRIPTION**, 7th paragraph, the word "hydroxypropyl methylcellulose" has been changed to "hypromellose".

2. Under **CLINICAL PHARMACOLOGY**, *Pharmacokinetics, General, Losartan Potassium, Renal Insufficiency*, this subsection has been revised as follows:

   Losartan: 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 the 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.

Hydrochlorothiazide: Following oral administration, the AUC for hydrochlorothiazide is increased by 70 and 700% for patients with mild and moderate renal insufficiency, respectively. In this study, renal clearance of hydrochlorothiazide decreased by 45 and 85% in patients with mild and moderate renal impairment, respectively.

The usual regimens of therapy with HYZAAR may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment. loop diuretics are preferred to thiazides, so HYZAAR is not recommended. (See **DOSAGE AND ADMINISTRATION**).

3. Under **CLINICAL PHARMACOLOGY**, a new subsection has been inserted entitled "*Severe Hypertension (Sitting Diastolic Blood Pressure [SiDBP] ≥110 mmHg)*" with the following language:

The safety and efficacy of HYZAAR as initial therapy for severe hypertension (defined as a mean SiDBP ≥ 110 mmHg confirmed on 2 separate occasions off all antihypertensive therapy) was studied in a 6-week double-blind, randomized, multicenter study. Patients were randomized to either losartan and hydrochlorothiazide (50-12.5 mg, once daily) or to losartan (50 mg, once daily) and followed for blood pressure response. Patients were titrated at 2-week intervals if their SiDBP did not reach goal (<90 mmHg). Patients on combination therapy were titrated from losartan 50 mg/hydrochlorothiazide 12.5 mg to losartan 50 mg/hydrochlorothiazide 12.5 mg (sham titration to maintain the blind) to losartan 100 mg/hydrochlorothiazide 25 mg. Patients on monotherapy were titrated from losartan 50 mg to losartan 100 mg to losartan 150 mg, as needed. The primary endpoint was a comparison at 4 weeks of patients who achieved goal diastolic blood pressure (trough SiDBP<90 mmHg).

The study enrolled 585 patients, including 264 (45%) females, 124 (21%) blacks, and 21 (4%) ≥ 65 years of age. The mean blood pressure at baseline for the total population was 171/113 mmHg. The mean age was 53 years. After 4 weeks of therapy, the mean SiDBP was 3.1 mmHg lower and the mean SiSBP was 5.6 mmHg lower in the group treated with HYZAAR. As a result, a greater proportion of the patients on HYZAAR reached the target diastolic blood pressure (17.6% for HYZAAR, 9.4% for losartan; p=0>0.006). Similar trends were seen when the patients were grouped according to gender, race or age (<, ≥ 65). (**Note:** the "17.6% for HYZAAR in the above sentence was reduced from 17.8% in previous versions of labeling due to Ms. Choi noticing that one subject in the HZAAR arm was concomitantly receiving a beta-blocker. This subject was removed from this analysis and not only causes the above number to be reduced slightly but also is responsible for the 29.8% number in the following sentence (see also Dr. Desai's e-mail dated August 26, 2003).

After 6 weeks of therapy, more patients who received the combination regimen reached target diastolic blood pressure than those who received the monotherapy regimen (29.8% versus 12.5%, respectively).

During the study period, there were no reported cases of syncope in either treatment group. There were 2 (0.6%) and 0 (0.0%) cases of hypotension reported in the group treated with HYZAAR and the group treated with losartan, respectively. The overall pattern of adverse events reported for patients treated with HYZAAR as initial therapy was similar to the adverse event profile for patients treated with losartan as initial therapy. For information on the specific adverse events observed during the study period, see **ADVERSE REACTIONS**, *Severe Hypertension*.

4. The **INDICATIONS AND USAGE** section has been revised to:

HYZAAR is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy of hypertension, except when the hypertension is severe enough that the value of achieving prompt blood pressure control exceeds the risk of initiating combination therapy in these patients (see **CLINICAL PHARMACOLOGY**, *Pharmacodynamics and Clinical Effects*, and **DOSAGE AND ADMINISTRATION**).

5. Under **ADVERSE REACTIONS**, a new subsection entitled "*Severe Hypertension*" has been inserted after the *Geriatric Use* subsection and reads as follows:

Severe Hypertension: In a clinical study in patients with severe hypertension (SiDBP $\geq$ 110 mmHg), the overall pattern of adverse events reported through six weeks of follow-up was similar in patients treated with HYZAAR as initial therapy and in patients treated with losartan as initial therapy. There were not reported cases of syncope in either treatment group. There were 2 (0.6%) and 0 (0.0%) cases of hypotension reported in the group treated with HYZAAR and the group treated with losartan, respectively. There were 3 (0.8%) and 2 (1.2%) cases of increased serum creatinine (> 0.5 mg/dL) in the group treated with HYZAAR and the group treated with losartan respectively during the same time period. (See **CLINICAL PHARMACOLOGY**, *Pharmacodynamics and Clinical Effects, Severe Hypertension*).

6. Under **DOSAGE AND ADMINISTRATION**, a new subheading entitled "**Hypertension**" has been added. In addition, a new subsection entitled "**Severe Hypertension**" has been added that includes the following language:

Severe Hypertension

The starting dose of HYZAAR for initial treatment of severe hypertension is one tablet of HYZAAR 50-12.5 once daily (See **CLINICAL PHARMACOLOGY**, *Pharmacodynamics and Clinical Effects*). For patients who do not respond adequately to HYZAAR 50-12.5 after 2 to 4 weeks of therapy, the dosage may be increased to one tablet of HYZAAR 100-25 once daily. The maximum dose is one tablet of HYZAAR 100-25 once daily. HYZAAR is not recommended as initial therapy in patients with hepatic impairment (see **WARNINGS**, *Impaired Hepatic Function*) because the appropriate 25 mg starting dose of losartan cannot be given. It is also not recommended for use as initial therapy in patients with intravascular volume depletion (e.g., patients treated with diuretics, see **WARNINGS**, *Hypotension-Volume-Depleted Patients*).

Comments/Recommendations:

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

/S/

Edward Fromm
Regulatory Health Project Manager

dr-ef-9-26-03

RHPM NDA Efficacy Supplement Overview
July 24, 2003

Hyzaar (losartan potassium/hydrochlorothiazide) for the Initial Treatment of Severe Hypertension

NDA 20-387/SE1-027

Applicant: Merck and Co.

Classification: SE1 (new indication)

Review Classification: Standard (10 month review)

Proposed Indication: Initial treatment of severe hypertension (SiDBP>110 mmHg). It is also proposed for the treatment of hypertension when initial treatment with losartan or hydrochlorothiazide alone does not result in adequate control of blood pressure.

Date of Application: September 24, 2002

Receipt Date: September 25, 2002

User Fee Goal Date: July 25, 2003

Background

NDA 20-387/S-027 was submitted September 24, 2002, received September 25, 2002, for the new indication of initial treatment of severe hypertension (SiDBP>110 mmHg). It is also proposed for the treatment of hypertension when initial treatment with losartan or hydrochlorothiazide alone does not result in adequate control of blood pressure. The support for this new indication comes from two completed studies. Study P232 was an active control study of patients with SiDBP>110 mm Hg and was the pivotal study.

The second study (P228), was a placebo controlled trial comparing the efficacy of Hyzaar (100/25) and Hyzaar (50/12.5) to placebo. A majority (2/3) of the patients in P228 had SiDBP<110 mm Hg at baseline.

After an internal meeting on July 11, 2003, we agreed that an approvable letter should issue accompanied by marked-up draft labeling. The marked-up draft labeling will include changes to the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS**, and **DOSAGE AND ADMINISTRATION** sections of the labeling.

Meetings

Planning (telecon): June 19, 2000
Pre-NDA Meeting: August 21, 2002

Review

Medical
Division Director: Douglas C. Throckmorton, M.D.

Conclusion:	Approvable, see Dr. Throckmorton's memo is pending
Medical	
Group Leader:	Norman Stockbridge, M.D., Ph.D.
Labeling:	Dr. Stockbridge has suggested revisions to the **CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS** section of the labeling.
Conclusion:	Approvable, Dr. Stockbridge stated in his May 9, 2003 review that studies 232 and 228 demonstrated that patients with severe hypertension could attain blood control sooner and with about the same adverse event profile as monotherapy (losartan) alone.
Medical	
Medical Officer:	Mehul Desai, M.D.
Labeling:	Although Dr. Desai does not believe the application is approvable, he did suggest labeling revisions to the **CLINICAL PHARMACOLOGY** section of our mark-up of the draft labeling.
Conclusion:	Not approvable; Dr. Desai states in his review, that the approval of this supplement, could affect the traditional, titration approach to hypertension. He notes further that "changing the approach to treatment of hypertension without showing that it leads to improved long-term compliance, improved outcomes, or increased safety does not seem optimal."
Statistical:	Jasmine Choi, M.S.
Labeling:	Ms. Choi suggested revisions to the **CLINICAL PHARMACOLOGY** section of the labeling
Conclusion:	Approvable, Ms. Choi notes in her review that "Losartan plus hydrochlorothiazide combination therapy group had a significantly higher percentage of patients who achieved goal blood pressure (sitting diastolic blood pressure <90 mmHg) at Week 4 compared to Losartan monotherapy group. She notes further that "the number of patients who achieved the goal a Week 6 and other supportive analyses also confirmed that Losartan plus hydrochlorothiazide combination therapy had a significantly better antihypertensive effect than Losartan monotherapy.
Biopharmaceutics	
Reviewer:	Elena Mishina, Ph.D
Labeling:	Dr. Mishina suggested changes to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the labeling.
Conclusion:	Approvable, with labeling changes as noted above.
Chemistry	No full review (see Environmental Assessment)
Pharmacology	
Reviewer:	Anthony Proakis, Ph.D.
Labeling:	None
Conclusion:	At the filing meeting on November 1, 2002, it was determined that a Pharmacology review was not needed for this application. Please also see Dr. Proakis' January 7, 2003 memo.

Safety Update: There have been no safety updates since the original submission of September 24, 2002.

Patent info: Included in package

Pediatric info: Not applicable

DSI: At the filing meeting on November 1, 2002, the Division stated that it would not ask for clinical audits of the study sites.

Debarment Certification: Included in package

Exclusivity Summary: Included in package

Environmental Assessment: Sponsor granted FONSI.

Financial Disclosure: acceptable, see page 12 of Dr. Desai's Medical Review.

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

DDMAC: In an e-mail dated July 23, 2003, DDMAC said they did not have comments regarding the Hyzaar labeling.

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

Edward J. Fromm
Regulatory Health Project Manager

dr-ef-7-24-03

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

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-387	Efficacy Supplement Type SE-1 (Initial Treatment of severe HTN)	Supplement Number 027
Drug: Hyzaar (losartan potassium/HCTZ) 50-12.5 & 100-25 mg Tablets	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	November 16, 2003
❖ 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	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ 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-September 26, 2003, July 24, 2003
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-July 25, 2003
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(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)	NA
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	NA
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC-August 4, 2003
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ 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)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• Planning meeting (indicate date)	June 19, 2000 (telecon)
• Pre-NDA meeting (indicate date)	August 21, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	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)*	Division Director-August 1, 2003
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	May 5, 2003
❖ 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 9, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	April 10, 2003
❖ 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)*	NA
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	NA
• Review & FONSI *(indicate date of review)*	X November 1, 2002
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: NA ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed NA ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X-See Dr. Proakis' January 7, 2003 memo
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(484) 344-2516
Attention:	Dr. Jeff Tucker
Company Name:	Merck and Co.
Phone:	(484) 344-7788
Subject:	**Approval Letter & Labeling for NDA 20-387 Supplements-013, 015 & 027**
Date:	September 30, 2003
Pages including this sheet:	17
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

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FDA/CDER/HFD-110
5600 Fishers Lane
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:	**Approvable Letter for NDA 20-387/S-027 Hyzaar (losartan potassium/HCTZ) Tablets**
Date:	July 25, 2003
Pages including this sheet:	**16**
From:	**Edward Fromm**
Phone:	**301-594-5311**
Fax:	**301-594-5494**

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

********** -COMM. JOURNAL- ********** DATE JUL-25-2003 ***** TIME 16:20 *********

MODE = MEMORY TRANSMISSION START=JUL-25 16:17 END=JUL-25 16:20

FILE NO.=408

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

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5600 Fishers Lane
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:	**Approvable Letter for NDA 20-387/S-027 Hyzaar (losartan potassium/HCTZ) Tablets**
Date:	July 25, 2003
Pages including this sheet:	**16**
From:	**Edward Fromm**
Phone:	**301-594-5311**
Fax:	**301-594-5494**

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

Minutes of a Telecon between Merck and the FDA

Date: January 24, 2003

Sponsor: Merck & Co., Inc.

Subject: NDA 20-387/S-027, Hyzaar (Losartan Potassium/Hydrochlorothiazide) Tablets

Purpose: To Discuss the Feasibility of Presenting Hyzaar for the Initial Treatment of Severe Hypertension before the May, 2003 Cardio-Renal Advisory Committee

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Mehul Desai, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-710, Statistician/Team Leader
Jasmine Choi, M.S., HFD-710, Statistician
Edward Fromm, HFD-110, Regulatory Health Project Manager

Merck

Jeffrey Tucker, M.D., Director, Regulatory Affairs, Domestic
Michael Elia, Ph.D., Senior Director, Regulatory Affairs, Domestic
Bonnie Goldman, M.D., Senior Vice President, Global Strategic Regulatory Development
Ray Bain, Ph.D., Vice President, Biostatistics & Research Decision Sciences
Laura Demopoulos, M.D., Executive Director, Clinical Research
Christina Salerno, Medical Program Coordinator, Cardio/Hypertension/Renal
Steven Snapinn, Ph.D., Senior Director, Scientific Staff, Clinical Biostatistics & Research Data Systems
Robin Mukherje, Ph.D., Senior Biometrician, Biostatistics, Clinical Biostatistics & Research Data Systems
Betsy Fallen, Manager, Worldwide Regulatory Regulatory Coordination

Background

Hyzaar (losartan potassium/hydrochlorothiazide) is currently marketed for the treatment of hypertension. Merck submitted a supplement (S-027, dated September 24, 2002) requesting approval of a proposed indication for Hyzaar for its use as a first-line treatment for patients with severe hypertension. The telecon today is to discuss the possibility of presenting Hyzaar before the May 2003 Cardio-Renal Advisory Committee.

Telecon

Advisory Committee Meeting

Dr. Throckmorton opened the telecon by noting that, after discussions with Dr. Temple regarding Hyzaar and the May 2003 Advisory Committee Meeting, we he have decided not to ask Merck to present Hyzaar for the indication of first-line treatment of patients severe hypertension before the Advisory Committee. We feel that we have enough information about the new indication to make an informed judgement without the Committee's advice.

Review Issues

Dr. Desai asked for additional clarification on the number of patients uptitrated at different timepoints in the trial. For example, how many patients were uptitrated to losartan 100/HCTZ 25 mg at week 2 and at week 4 of the trial? The sponsor said they would submit the data asked for as soon as it is available.

Ms. Choi noted that about 10 % of the patients who completed the study did not have measurements at the 4 week timepoint and asked what the rationale was for this omission. The sponsor said they would submit an explanation detailing why those measurements were not collected.

Minutes Preparation: /S/
Edward Fromm

Concurrence: /S/
Douglas C. Throckmorton, M.D.

dr/ef-1/24/03-1/27/03

Rd: JChoi-1/24/03
JHung-1/24/03
MDesai-1/24/03

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US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
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: **Confirmation of Telecon for NDA 20-387/S-027 Hyzaar (losartan potassium/hydrochlorothiazide) Tablets**

Date: January 16, 2003

Pages including this sheet: **2**
From: **Edward Fromm**
Phone: **301-594-5332**
Fax: **301-594-5494**

Confirmation of Telecon

Drug:	Hyzaar (losartan potassium/hydrochlorothiazide) for Initial Treatment of Severe Hypertension
Application:	NDA 20-387/S-027
Subject:	May 2003 Cardio-Renal Advisory Committee Meeting
Sponsor:	Merck & Co.
Date Confirmation Faxed:	January 16, 2003
T-Con Date:	January 24, 2003, 8:00-8:30 A.M.

FDA Participants:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Deputy Division Director
Mehul Desai, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-710, Statistician/Team Leader, Office of Biometrics I
Jasmine Choi, M.S., HFD-710, Statistician, Office of Biometrics I
Edward Fromm, HFD-110, Project Manager

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

Thanks,

Ed

********** -COMM. JOURNAL- ********** DATE JAN-16-2003 ***** TIME 15:39 *******

MODE = MEMORY TRANSMISSION START=JAN-16 15:38 END=JAN-16 15:39

FILE NO.=162

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5600 Fishers Lane
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: **Confirmation of Telecon for**
NDA 20-387/S-027
Hyzaar (losartan potassium/hydrochlorothiazide)
Tablets

Date: January 16, 2003

Pages including this sheet: **2**

From: **Edward Fromm**
Phone: **301-594-5332**
Fax: **301-594-5494**

E FROM

JUN 23 2000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(610) 397-2516
Attention:	Dr. Michael Elia
Company Name:	Merck and Co.
Phone:	(610) 397-3180
Subject:	**Minutes of Telecon, June 19, 2000**
Date:	6/23/00
Pages including this sheet:	3
From:	**Edward Fromm**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

PLEASE NOTIFY US OF ANY SIGNIFICANT DIFFERENCES IN UNDERSTANDING YOU MAY HAVE REGARDING THE MEETING OUTCOMES (AS REFLECTED IN THE MINUTES).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

cc: NDA 20-387
HFD-110
HFD-110/Efromm
HFD-110/SMatthews

Minutes of a Telephone Conference Call between Merck and the FDA

Date: June 19, 2000

Application: NDA 20-387
Hyzaar (losartan/hydrochlorothiazde) Tablets

Sponsor: Merck and Co.

Subject: Revised protocol for Hyzaar as a first-line treatment of severe hypertension

FDA participants

Douglas Throckmorton, M.D., HFD-110, Medical Officer
Edward Fromm, HFD-110, Consumer Safety Officer

Merck

Laura Demopolous, M.D., Clinical Research
Michael Elia, Ph.D., Regulatory Affairs

Background

Merck met with the Division on May 18, 2000 to discuss a study that would be supportive of an indication for Hyzaar as a first-line treatment for severe hypertension. At that meeting, the Division suggested modifications to the firm's proposed study. Merck sent to the Division, on June 6, 2000, a revised protocol which included many of the Division's recommendations. The firm requested a teleconference with the Division to get its feedback on the revised protocol.

Telecon

Dr. Throckmorton began the telecon by noting that he and Mr. Fromm had discussed with Dr. Temple on June 16, 2000 the firm's revised protocol. Dr. Temple had asked them to tell the firm that he thought its revised protocol was reasonable but that he also had several areas of concern. These are:

- making distinctions about treatment based on severity of blood pressure would be a change in the way the Agency has labeled anti-hypertensives. The proposed initial use of the combination is also a change from the usual step-care recommendation. This may be reasonable (trying the single drug may just waste time) but safety needs to be well assured.

- the WARNINGS, DOSAGE and ADMINISTRATION, and other sections of the labeling may have to be adjusted to reflect the use in severe hypertensive patients.

Dr. Temple had said that there did not appear to be enough safety exposure for patients taking Hyzaar as currently proposed (i.e., 340 patients) in the revised protocol. Dr. Temple thought it was usually certain that the combination would control blood pressure longer and more often than losartan alone. The main issue was whether initiation with the combination product produced adverse events, notably excessive blood pressure fall. He suggested that the firm double the size of its safety base for Hyzaar; he said that this information could come from sources other than patients enrolled in this protocol, it could come, for example, from the NDA itself. The firm asked if this

meant that the safety database should be expanded to 680 patients. Dr. Throckmorton said, that in his opinion, the company should concentrate on showing adequate power to detect a smaller change (e.g., 2% at 80% power) in the incidence of adverse events than what was outlined in their June 6, 2000 submission (see Table 1, page 3).

Merck asked the Division if they should focus on first-dose cardiovascular adverse events from Hyzaar when compiling their safety database. Dr. Throckmorton said that these were important as well as renal complications from exposure to Hyzaar. The firm noted that the study protocol for Hyzaar requires that serum creatinine measurements be taken at baseline, week 4 and 6.

Dr. Throckmorton noted that the 150 mg maximal dose proposed for the losartan arm of the study is acceptable.

Dr. Throckmorton asked the company why 110 mm Hg was chosen as the diastolic blood pressure cutoff for severe hypertension. The firm said that 110 mm Hg was chosen based on Joint National Council (JNC) VI guidelines.

Merck asked the Division if one, single, adequately designed trial that was successful on efficacy and showed minimal adverse events would be adequate to support an indication for Hyzaar for first-line use in patients with severe hypertension. Dr. Throckmorton said he believed it would but emphasized that Dr. Temple would make the final decision on what would be included in the labeling, and where in labeling such information would appear.

Conclusion

The Division suggested that Merck expand its safety exposure database for Hyzaar so as to provide enough power to detect small changes in the incidence of important adverse events, notably excessive falls in blood pressure. Merck said that they would do a sample size reestimation to provide adequate power on safety for Hyzaar.

Minutes Preparation: /S/
Edward Fromm

Concurrence: /S/ 6-23-00
Douglas Throckmorton, M.D.

drafted: 6-20-00/6-22-00

rd: DThrockmorton-6/20/00
RTemple-6/22/00

cc: NDA 20-387
HFD-110
HFD-101/RTemple
HFD-110/DThrockmorton
HFD-110/EFromm/SMatthews

MESSAGE CONFIRMATION

06/23/00 15:24
ID=FDA CDER DCRDP

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number: (610) 397-2516

Attention: Dr. Michael Elia

Company Name: Merck and Co.

Phone: (610) 397-3180

Subject: **Minutes of Telecon, June 19, 2000**

Date: 6/23/00

Pages including this sheet: 3

From:

NDA REGULATORY FILING REVIEW & MINUTES

NDA 20-387/S-027, Hyzaar (losartan potassium/HCTZ) Tablets, 50-12.5 and 100-25 mg

Applicant: Merck & Co, Inc.

Date of Application: September 24, 2002
Date of Receipt: September 25, 2002
Date of Filing Meeting: November 1, 2002
Filing Date: November 24, 2002

Indication requested: Initial treatment of severe hypertension (SiDBP≥110 mmHg)

Type of Application: Full NDA _____ Supplement ____X_____
(b)(1) ____X_____ (b)(2) _____

Therapeutic Classification: ___Standard____ _____
Resubmission after a withdrawal or refuse to file __NA_____
Chemical Classification: (1,2,3 etc.)__6___
Other (orphan, OTC, etc.)___NA_____

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NO

If the application is affected by the application integrity policy (AIP), explain. NO

User Fee Status: Paid ____X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) __NA_____
Form 3397 (User Fee Cover Sheet) submitted: YES___X___ NO_____
User Fee ID#____4421_____
Clinical data? YES ___X____ NO _____ Referenced to NDA# _____
Date clock started after UN ____NA_____

User Fee Goal date: ___July 25, 2003_____

Action Goal Date (optional) ___July 25, 2003_____

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.
- Submission complete as required under 21 CFR 314.50? YES
- If electronic NDA, does it follow the Guidance? YES
  If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Techinical Document, does it follow the guidance? NA
- Patent information included with authorized signature? YES

- Exclusivity requested? YES; If yes, ___3____years

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? NO (requested waiver for all age groups)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

List referenced IND numbers: IND 33,383

End-of-Phase 2 Meeting? NO

Pre-sNDA Meeting(s)? August 21, 2002

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? NA

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? ?

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
  If no, did sponsor submit a complete environmental assessment? NA
  If EA submitted, consulted to Nancy Sager (HFD-357)? NA

- Establishment Evaluation Request (EER) package submitted? NA

- Parenteral Applications Consulted to Sterile Products (HFD-805)? NA

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 1, 2002

BACKGROUND

Merck has submitted this efficacy supplement for a new indication for the use of Hyzaar for the initial treatment of severe hypertension (SiDBP≥ 110 mmgHg). The sponsor has also submitted data demonstrating the futility of monotherapy to treat patients with severe hypertension.

At the present time, there have been no other angiotensin II antagonists approved for this new indication.

ATTENDEES:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Mehul Desai, M.D., HFD-110, Medical Officer
Elena Mishina, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Anthony Proakis, Ph.D., HFD-110, Pharmacologist
Edward Fromm, HFD-110, Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer	Completion Date
Medical:	Mehul Desai, M.D.	March 30, 2003
Secondary Medical:	TBD	
Statistical:	Jasmine Choi, M.S.	March 30, 2003
Pharmacology:	Anthony Proakis, Ph.D.	March 30, 2003
Statistical Pharmacology:	N/A	
Chemist:	N/A	
Environmental Assessment (if needed):	Stuart Zimmerman, Ph.D.	Done (November 01, 2002)
Biopharmaceutical:	Elena Mishina, Ph.D.	March 30, 2003
Microbiology, sterility:	N/A	
Microbiology, clinical (for antimicrobial products only):	N/A	
DSI:	N/A	
Project Manager:	Edward Fromm	
Other Consults:	N/A	

Per reviewers, all parts in English, or English translation? YES__X__ NO___

CLINICAL – File ____X_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO___X____

MICROBIOLOGY CLINICAL – File____N/A__ Refuse to file_____

STATISTICAL – File ____X_____ Refuse to file _____

BIOPHARMACEUTICS – File ___X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____

PHARMACOLOGY – File ___X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__x__NO_____ File__X__ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X___The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

Other:

The application may be presented before the Cardio-Renal Advisory Committee in May 2003.

Dr. Throckmorton stated that DSI audits would not be requested for this application. He also noted that he would sign the action letter for this supplement.

Edward Fromm
Regulatory Project Manager, HFD-110

Rd: AProakis-11/10/02
EMishina-11/13/02
JChoi-11/14/02
MDesai-11/14/02
NStockbridge-11/14/02
DThrockmorton-11/15/02

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
11/22/02 10:21:12 AM

RUG PRODUCTS
TION

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

mber:	(484) 344-2516
ntion:	Dr. Jeff Tucker
Name:	Merck and Co.
Phone:	(484) 344-7788
bject:	**Hyzaar Meeting Minutes, August 21, 2002** **NDA 20-387**
Date:	September 6, 2002
sheet:	3
From:	**Edward Fromm**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Minutes of a Meeting between Merck and the FDA

Date: August 21, 2002

Sponsor: Merck & Co., Inc.

Subject: NDA 20-387 Hyzaar (Losartan Potassium/Hydrochlorothiazide) Tablets

Purpose: To Discuss Upcoming Study Results for Hyzaar as Initial Treatment for Severe Hypertension

FDA Participants:

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

Merck

Jeffrey Tucker, M.D., Director, Regulatory Affairs, Domestic
Michael Elia, Ph.D., Senior Director, Regulatory Affairs, Domestic
Laura Demopoulos, M.D., Executive Director, Clinical Research
Christina Salerno, Medical Program Coordinator, Cardio/Hypertension/Renal
Steven Snapinn, Ph.D., Senior Director, Scientific Staff, Clinical Biostatistics & Research Data Systems
Robin Mukherje, Ph.D., Senior Biometrician, Biostatistics, Clinical Biostatistics & Research Data Systems
Betsy Fallen, Manager, Worldwide Regulatory Regulatory Coordination
Ronald Carnal, Regulatory Coordinator, Worldwide Regulatory Coordination
Lauren Hetrick, Regulatory Agency Relations

Background

Hyzaar (losartan potassium/hydrochlorothiazide) is currently marketed for the treatment of hypertension. Merck requested a meeting with the Division to discuss study results that they believe will support the use of Hyzaar as initial therapy in patients with severe hypertension. The firm plans on submitting a supplemental NDA for this indication in late September 2002.

Meeting

Efficacy

Merck presented slides outlining the efficacy and safety results from studies that they believe show that Hyzaar is effective as an initial therapy for severe hypertension. The pivotal efficacy trial is protocol 232, entitled, "A Randomized, Double-Blind, Safety and Efficacy Study of Losartan Plus Hydrochlorothiazide Versus Losartan As First-Line Therapy after 6 Weeks In Patients With Severe Hypertension". They noted that Hyzaar, in patients with severe HTN (SiDBP $\geq$110 mmg Hg), was significantly more effective than Cozaar monotherapy in reducing SiDBP and SiSBP. 635 patients received Hyzaar 50/12.5 mg as first line therapy; protocol 204 was omitted from the database after difficulties verifying the data for this study.

Dr. Stockbridge asked if the firm knew what the effect of the drug was on different racial subgroups. Merck replied said that data at the 4 week timepoint showed that Hyzaar had a greater effect than Cozaar across all subgroups, although the difference was least among blacks (12.8% vs. 7.9%).

Safety

Merck said that a summary of overall adverse events, adverse events of special interest (e.g., dizziness, syncope), and first dose adverse events showed that Hyzaar was not worse than Cozaar for these events. Dr. Karkowsky noted that only 14% of the patients were over 65 years old in the study and said that this population should have been represented more heavily in the study for safety reasons.

Futility

Merck said that the supplemental NDA for this indication would show that only about 10% of patients are adequately controlled by monotherapy and asked if this would satisfy the Agency's definition of "futility". Dr. Temple said if the data show that only about 10% of hypertensive patients can be controlled by a single agent, then futility would be demonstrated.

Indication

Merck noted that the proposed indication for Hyzaar would include a statement that says, [ ] and asked if that was acceptable. Dr. Temple replied that single agents are already labeled for different grades of hypertension (mild, moderate, and severe) and therefore the above statement is not appropriate. Depending on the data and our analyses, a statement such as the following could be inserted into labeling: [ ]

Electronic Submission

Dr. Stockbridge noted that the sponsor's proposed format for electronic submission of the supplement was acceptable.

Conclusion

Merck presented data that they believe show that Hyzaar 50/12.5 mg safely provides a substantial antihypertensive benefit compared to monotherapy as a first-line therapy in patients with severe hypertension. The supplemental NDA for this indication is slated for submission in September 2002. Dr. Temple said that based on the sponsor's presentation of the data, and pending our review, it appears that the data support an indication for Hyzaar as first-line treatment for severe hypertension.

Minutes Preparation: /S/
Edward Fromm

Concurrence: /S/
Robert Temple, M.D.

dr/8-27-02/8-29-02

Rd: DThrockmorton-8/29/02
NStockbridge-8/28/02
AKarkowsky-8/28/02
JHung-8/27/02

APPEARS THIS WAY
ON ORIGINAL

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pages of trade

secret and/or

confidential

commercial

information

Fromm, Edward J

From: Kulick, Corrine
Sent: Wednesday, July 23, 2003 3:57 PM
To: Fromm, Edward J
Cc: Stockbridge, Norman L; Throckmorton, Douglas C
Subject: RE: Hyzaar for Severe Labeling

Thanks Ed. DDMAC has no comments on the Hyzaar label.
-Corrinne

Corrinne Kulick, Pharm.D., BCNSP
Regulatory Review Officer,
Division of Drug Marketing, Advertising, and Communications
Phone: 301-827-2831
Fax: 301-594-6771

Integrated Summary of Efficacy

The Integrated Summary of Efficacy is available on the EDR.

Integrated Summary of Safety

The Integrated Summary of Safety is available on the EDR.

APPEARS THIS WAY
ON ORIGINAL

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Per the sponsor, both of the submitted studies were "conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research."

E. Evaluation of Financial Disclosure

FDA forms 3454 and 3455 were completed and signed by the Sponsor.
As shown in the table below 15 of the 838 Investigators/Sub-investigators had "Significant payments of other sorts or Equity Interest" in the sponsor (Merck).
An analysis of the impact of financial conflict of interest on the primary endpoint is shown in Table1 in the Appendix.

Table 2: Details of financial disclosure of investigators/sub-investigators[a]

Investigator Category	Total Number
Grand Total Number of Investigators/Subinvestigators per Protocol and Site	838
Total Number of Investigators/ Subinvestigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site	786
Total Number of Investigators/Subinvestigators Not Providing Information and Not Certified per Protocol and Site	37
Total Number of Investigators/Subinvestigators Not Certified Due to "Significant Payments of Other Sorts" or Equity Interest per Protocol and Site	15
Total Number of Investigators/ Subinvestigators Receiving Payments based on Outcome of study per protocol and per site	0
Total Number of Investigators/ Subinvestigators with Proprietary Interest in the Test Product or Company per Protocol and Site	0

[a]Data from Table A-3, in the "Financial Information" section of the electronic submission of 9/2002

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The sponsor seeks approval of Hyzaar as a first line agent in the treatment of "severe" hypertension. Pivotal study P232 supports this claim by showing that Hyzaar 50/12.5 was superior to Losartan 50 mg titrated as needed to 100 mg. The patient population studied had a mean SiDBP of $\geq$ 110 mm Hg with a mean SiSBP $\leq$ 220 mm Hg at the time of randomization (after an adequate washout of existing anti-hypertensives). Hyzaar was superior in terms of the primary

FROM DR. Desai's Medical Review

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-Hydrochlorothiazide Versus Losartan Potassium in Severe Hypertension	

(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
[signature]	Aug. 8, 2002

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 1 hour 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 the address to the right:

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-Hydrochlorothiazide Versus Losartan Potassium in Severe Hypertension (*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
David Arkowitz	Aug. 8, 2002

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

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. Corporate Finance 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. "Significant payments of other sorts" are calculated cumulatively when an investigator is involved in more than one protocol in the submission.

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:

A Double-Blind, Randomized, Parallel, Placebo-Controlled, Efficacy Study of Losartan Potassium 100 mg - Hydrochlorothiazide 25 mg Versus Losartan Potassium 50 mg - Hydrochlorothiazide 12.5 mg in Patients with Essential Hypertension (Protocol 228)

For this clinical protocol, the First Patient In (FPI) was 20-May-2000 and the Last Patient Out (LPO) was 18-Jul-2001. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of 20-May-2000 through 31-Oct-2001 and included, as appropriate. The cut-off date for financial information provided by the investigators was 31-May-2002.

A Randomized, Double-Blind Safety and Efficacy Study of Losartan + Hydrochlorothiazide Versus Losartan as First-Line Therapy After Six Weeks in Patients with Severe Hypertension (Protocol 232)

For this clinical protocol, the First Patient In (FPI) was 21-Sep-2000 and the Last Patient Out (LPO) was 25-Jul-2001. In compliance with the Financial Disclosure requirements, "significant payments of other sorts" information has been reviewed for the time period of 21-Sep-2000 through 31-Oct-2001 and included, as appropriate. The cut-off date for financial information provided by the investigators was 31-May-2002.

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
228	A Double-Blind, Randomized, Parallel, Placebo-Controlled, Efficacy Study of Losartan Potassium 100 mg - Hydrochlorothiazide 25 mg Versus Losartan Potassium 50 mg - Hydrochlorothiazide 12.5 mg in Patients with Essential Hypertension	20-May-2000	18-Jul-2001	20-May-2000 Through 31-Oct-2001
232	A Randomized, Double-Blind Safety and Efficacy Study of Losartan + Hydrochlorothiazide Versus Losartan as First-Line Therapy After 6 Weeks in Patients with Severe Hypertension	21-Sep-2000	25-Jul-2001	21-Sep-2000 Through 31-Oct-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	838	Table B-1
Total Number of Investigators/ Subinvestigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site	786	Table C-1
Total Number of Investigators/ Subinvestigators Not Providing Information and Not Certified per Protocol and Site	37	Table C-2 Investigators no longer at site, unable to obtain information (n=36). Investigators not returning requested information (n=1).
Total Number of Investigators/ Subinvestigators Not Certified Due to "Significant Payments of Other Sorts" or Equity Interest per Protocol and Site	15	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
228-002	Bernstein, David A.	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
		NO
228-004	Bittar, Neville	NO
		NO
		NO
228-006	Chrysant, Catherine	NO
		NO
		NO
		NO
		NO
		NO
228-007	Colton, Julian A.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-008	Ali, Iman	NO
		NO
		NO
		NO
		NO
		NO
		NO
228-010	Bozzo, Patricia	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-011	Burke, Joy Ann	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
		NO
		NO
		NO
		NO
228-012	Bakris, George L.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-015	Acevedo, Celso	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-016	Herman, Theodore S.	NO
		NO
		NO
		NO
228-017	Connors, Jason D.	NO
		NO
		NO
		NO
		NO
228-018	Casals, Leon C.	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
		NO
		NO
		NO
228-019	Clancy, Elizabeth A.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-020	Connolly, Joseph	NO
		NO
		NO
		NO
		NO
228-021	Doens, Elissa	NO
		NO
		NO
		NO
		NO
228-022	Hafer, Lyndsey R.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-023	Blum, Jeffrey	NO
		NO
		NO
		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
		NO
228-025	Bashor, Kendrick B.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-026	Abeysinghe, Champa D.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-028	Del Rio, Magalys	NO
		NO
		NO
		NO
		NO
		NO
		NO
228-029	Johnson, Earlene	NO
		NO
		NO
		NO
		NO
228-030	Bishop, Troy W.	NO
		NO
		NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-031	Monzon, Patricia	NO
		NO
		NO
		NO
228-032	Allott, Leonard	NO
		NO
		NO
		NO
		NO
		NO
		NO
228-033	Hill, Connie	NO
		NO
		NO
		NO
		NO
		NO
228-034	Arnold, Stanley	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		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
		NO
228-036	Grayson, Clellia	NO
		NO
		NO
		NO
		NO
	Truitt, Timothy S.	NO
		NO
		NO
228-037	Barnes, Annette	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-038	Bridges, Jane E.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
	Swiger, Penny A.	NO
		NO
		NO
228-039	Benedict, Cheryl S.	NO
		NO
		NO
		NO
		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
		NO
		NO
228-040	Baiardo, Jacqui	NO
		NO
		NO
		NO
228-041	Dodson, Mary S.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-042	Drozda, Joseph P., Jr	NO
		NO
		NO
		NO
228-043	Carter, Vicki L.	NO
		NO
		NO
		NO
228-044	Baker, William J.	NO
		NO
		NO
		NO
		NO
		NO
228-045	Byrd, Kathy L.	NO
		NO
		NO
228-046	Anderson, Angela	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-047		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
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-048	Chipman, Howard, III	NO
		NO
		NO
		NO
		NO
		NO
		NO
228-051	Bloch, T. Dawn	NO
		NO
		NO
		NO
228-052	Denton, Lin	NO
		NO
		NO
		NO
		NO
228-053	Chappel, Christopher M.	NO
		NO
		NO
228-054	Ashpole, David	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-055	Gillie, Edward	NO
		NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
228-056	Carlino, Margaret A.	NO
		NO
		NO
		NO
		NO
		NO
228-057	Anderson, Alicia	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-058	Chumley, Sheridan W.	NO
		NO
		NO
228-060	de la Garza, Carlos A.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-064	Franks, Elliott	NO
228-065	Biddinger, Michelle Lee	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
228-066	Rios, Yvonne F.	NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
		NO
228-068	Canavan, Frank P., Jr	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-002	Bays, Harold E.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-003	Brazg, Ronald Leonard	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-004	Ardon, Luis F.	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
		NO
232-005	Calhoun, David A.	NO
		NO
		NO
		NO
232-006	Best, Peggy A.	NO
		NO
		NO
		NO
		NO
		NO
232-007	Beauchamp, DLivro L.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-009	Billerbeck-Root, Kindra	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-010	Biddinger, Michelle Lee	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		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
	/	NO
232-011	Easley, Christa B.	NO
	/	NO
	/	NO
232-012	Acevedo, Celso	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-014	Bloch, Dawn	NO
	/	NO
		NO
232-015	Herman, Theodore S.	NO
	/	NO
232-018	Krasner, Jay B.	NO
	/	NO
232-020	Dilzer, Stacy C.	NO
	/	NO
	/	NO
	/	NO
	/	NO
232-021	Bonilla, Rosa A.	NO
	/	NO
	/	NO
	/	NO
	/	NO
	/	NO
	/	NO
232-022	Lester, F. Martin	NO
	/	NO
232-023	Chao, Helen Huaguo	NO
	/	NO
	/	NO
	/	NO
232-024	Abeysinghe, Champa D.	NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-025	Abt, Frank	NO
		NO
		NO
		NO
232-026	Magee, P. F. Adrian	NO
		NO
		NO
		NO
		NO
232-027	LaMott, Dorothy L.	NO
		NO
		NO
		NO
		NO
		NO
		NO
232-028	Barnes, Annette	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-030	Metcalfe, Madeline	NO
		NO
		NO
		NO
232-032	Diamond, Joseph	NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
		NO
		NO
		NO
232-033	Byrd, Kathy L.	NO
		NO
		NO
232-034	Moser, Karen	NO
		NO
232-037	Barstow, Karol	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-040	Barnett-Avery, Leslie	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-043	Jackson, Jennifer C.	NO
		NO
		NO
		NO
		NO
232-045	Davis, Matthew G.	NO
		NO
		NO
		NO
		NO
		NO
		NO
232-046	Wei, Fong	NO
		NO
232-048	Wagner, Urban L.	NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
232-050	Kingcade, Alvin, Jr	NO
		NO
		NO
232-052	Crane, Deborah L.	NO
		NO
232-053	Bajaj, Ravi K	NO
		NO
		NO
		NO
		NO
		NO
		NO
232-054	Angles, Luis	NO
		NO
		NO
		NO
		NO
		NO
		NO
232-058	Bloom, Bernice	NO
		NO
		NO
232-059	Adams, Amy R.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-060	Baxter, Sharon	NO
		NO
		NO
		NO
		NO
		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
		NO
232-063	Barbaria, Suzanne T.	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-064	Bridges, Jane E.	NO
		NO
		NO
		NO
		NO
		NO
		NO
232-065	Adkins, Lee Ann	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-066	Anderson, Angela	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-067	Chiang, Anna	NO
		NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
		NO
		NO
		NO
232-068	Brewer, Julie Kay	NO
		NO
		NO
		NO
		NO
232-070	Dugan, Tim	NO
		NO
		NO
232-071	Coffey, Anne	NO
		NO
		NO
		NO
232-072	Bezeau, Marc	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-073	Fan, Wei Hu	NO
		NO
		NO
232-074	Jiang, Wen	NO
		NO
232-075	Chazova, Irina	NO
		NO
232-076	Chita, Gajendra	NO
		NO
		NO
232-077	Mokhobo, Kubedi	NO
		NO
232-078	Armas, Maria Cristina	NO
		NO
		NO
232-079	Burdmann, Emmanuel Almeida	NO
		NO
		NO

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

Protocol/Site	Investigator/Subinvestigator	Merck & Co., Inc. Employee
232-080	Carrasco, Marcela	NO
	/	NO
	/	NO
232-081	Amuchastegui, Luis Maria	NO
	/	NO
	/	NO
232-082	Bartolacci, Ines	NO
	/	NO
	/	NO
	/	NO
	/	NO
	/	NO
	/	NO
232-083	Medina, Felix	NO
	/	NO
	/	NO
232-084	Castillo, Reynaldo	NO
	/	NO
	/	NO
	/	NO
	/	NO
232-085	Aheimastos, Apostolos	NO
	/	NO
	/	NO
232-087	Huang, Shu-Jung	NO
	/	NO
	/	NO
232-088	Hung Yu-Tak	NO
	/	NO
	/	NO
232-089	Chong, Ada Wai-Ying	NO
	/	NO
	/	NO
	/	NO
232-090	Basem, Abdel-Haq	NO
	/	NO
	/	NO
232-091	Douglas-Walsh, Marlene	NO
	/	NO
	/	NO
232-092	Mallett, Emma Charlotte	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
		NO
		NO
		NO
232-094	Gough, Nigel Anthony	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-095	Franco, Carlos Augusto	NO
		NO
		NO
232-096	Cervantes, Melissa	NO
		NO
		NO
		NO
232-097	Brice, Linda	NO
		NO
		NO
		NO
		NO
		NO
		NO
		NO
232-098	Ambrosioni, Ettore	NO
		NO
		NO
232-099	Lembo, Giuseppe	NO
		NO
232-100	Bryant, Gareth	NO
		NO
		NO
		NO
		NO
		NO
		NO
		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
228-002	Bernstein, David A.
228-004	Bittar, Neville
228-006	Chrysant, Catherine
228-007	Colton, Julian A.
228-008	Craven, Pamela
228-010	Bozzo, Patricia

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
228-011	Burke, Joy Ann
228-012	Basta, Emad
228-015	Acevedo, Celso
228-016	Herman, Theodore S.
228-017	Connors, Jason D.

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
228-018	Casals, Leon C.
228-019	Clancy, Elizabeth A.
228-020	Kelly, Michael P.
228-021	Doens, Elissa
228-022	Hafer, Lyndsey R.
228-023	Contorakes, Cheri Dague

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
228-025	Bashor, Kendrick B.
228-026	Abeysinghe, Champa D.
228-028	Del Rio, Magalys
228-029	Johnson, Earlene

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
228-030	Bishop, Troy W.
228-031	Monzon, Patricia
228-032	Allott, Leonard
228-033	Hill, Connie
228-034	Arnold, Stanley

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	
228-036	Grayson, Clellia
228-037	Barnes, Annette
228-038	Bridges, Jane E.
228-039	Benedict, Cheryl S.

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
228-040	Baiardo, Jacqui
228-041	Dodson, Mary S.
228-042	Drozda, Joseph P., Jr
228-043	Carter, Vicki L.
228-044	Baker, William J.
228-045	Byrd, Kathy L.
228-046	Anderson, Angela
228-047	Aldridge, Johnnie P.

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
228-048	Chipman, Howard, III
228-051	Bloch, T. Dawn
228-052	Denton, Lin
228-053	Chappel, Christopher M.
228-054	Ashpole, David
228-055	Gillie, Edward

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
228-056	Carlino, Margaret A.
228-057	Anderson, Alicia
228-058	Shanes, Jeffrey G.
228-060	de la Garza, Carlos A.
228-064	Franks, Elliott
228-065	Biddinger, Michelle Lee
228-066	Rios, Yvonne F.

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
228-068	Canavan, Frank P., Jr
232-002	Bays, Harold E.
232-003	Brazg, Ronald Leonard
232-004	Ardon, Luis F.
232-005	Calhoun, David A.

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
232-006	Best, Peggy A.
232-007	Beauchamp, DLivro L.
232-009	Billerbeck-Root, Kindra
232-010	Biddinger, Michelle Lee
232-011	Easley, Christa B.
232-012	Acevedo, Celso

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
232-014	Bloch, Dawn
232-015	Herman, Theodore S.
232-018	Krasner, Jay B.
232-020	Dilzer, Stacy C.
232-021	Bonilla, Rosa A.
232-022	Lester, F. Martin
232-023	Chao, Helen Huaguo
232-024	Abeysinghe, Champa D.

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
232-025	Abt, Frank
232-026	Magee, P. F. Adrian
232-027	LaMott, Dorothy L.
232-028	Barnes, Annette
232-030	Metcalfe, Madeline
232-032	Diamond, Joseph
232-033	Byrd, Kathy L.
232-034	Moser, Karen
232-037	Barstow, Karol

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
232-040	Barnett-Avery, Leslie
232-043	Jackson, Jennifer C.
232-045	Davis, Matthew G.
232-046	Wei, Fong
232-048	Wagner, Urban L.
232-050	Williamson, Clarke E.
232-052	Crane, Deborah L.
232-053	Bajaj, Ravi K
232-054	Angles, Luis

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
232-058	Bloom, Bernice
232-059	Adams, Amy R.
232-060	Calhoun, Sally
232-063	Barbaria, Suzanne T.
232-064	Bridges, Jane E.

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
232-065	Adkins, Lee Ann
232-066	Anderson, Angela
232-067	Chiang, Anna
232-068	Brewer, Julie Kay
232-070	Dugan, Tim
232-071	Coffey, Anne
232-072	Bezeau, Marc

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
232-073	Fan, Wei Hu
232-074	Jiang, Wen
232-075	Chazova, Irina
232-076	Chita, Gajendra
232-077	Mokhobo, Kubedi
232-078	Armas, Maria Cristina
232-079	Burdmann, Emmanuel Almeida
232-080	Carrasco, Marcela
232-081	Amuchastegui, Luis Maria
232-082	Bartolacci, Ines
232-083	Medina, Felix
232-084	Castillo, Reynaldo

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
232-085	Aheimastos, Apostolos
232-087	Huang, Shu-Jung
232-088	Hung Yu-Tak
232-089	Chong, Ada Wai-Ying
232-090	Basem, Abdel-Haq
232-091	Douglas-Walsh, Marlene
232-092	Mallett, Emma Charlotte
232-094	Gough, Nigel Anthony
232-095	Franco, Carlos Augusto
232-096	Cervantes, Melissa

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
232-097	Brice, Linda
232-098	Ambrosioni, Ettore
232-099	Lembo, Giuseppe
232-100	Bryant, Gareth

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
228-007	Lantz, Jean	Investigator no longer at site / Cannot certify. Forms sent on 03-05-2001.
	Weems, Sandra	Investigator no longer at site / Cannot certify. Forms sent on 03-05-2001.
228-008	Ali, Iman	Investigator no longer at site / Cannot certify.
228-010	Perkins, Judy	Did not return form with requested information. Forms sent on 11-19-2001; 02-25-2002.
228-012	O'Sullivan, Kathleen M.	Investigator no longer at site / Cannot certify. Forms sent on 05-07-2001.

Table C-2	Table of All Investigators/Subinvestigators Not Providing Information and Not Certified	
228-016	Hotaling, Susan A.	Investigator no longer at site / Cannot certify. Forms sent on 08-29-2000.
228-020	Connolly, Joseph	Investigator no longer at site / Cannot certify.
228-023	Blum, Jeffrey	Investigator no longer at site / Cannot certify. Forms sent on 06-27-2000; 01-23-2001.
228-025	Carpenter, Carol L.	Investigator no longer at site / Cannot certify.
	—	Investigator no longer at site / Cannot certify.
	—	Investigator no longer at site / Cannot certify.
228-028	Perrotta, Lidia	Investigator no longer at site / Cannot certify. Forms sent on 06-27-2000; 01-23-2001.
228-037	Burch, Robert R.	Investigator no longer at site / Cannot certify. Forms sent on 06-27-2000; 01-23-2001.
	—	Investigator no longer at site / Cannot certify. Forms sent on 06-27-2000; 01-23-2001.
228-047	Hodge, Teresa Burt	Investigator no longer at site / Cannot certify. Forms sent on 11-13-2000.
228-048	Grimes, Michael	Investigator no longer at site / Cannot certify. Forms sent on 11-13-2000.
228-054	Gunderson, Lisa	Investigator no longer at site / Cannot certify. Forms sent on 11-19-2001.
228-055	Wickham, Patricia	Investigator no longer at site / Cannot certify. Forms sent on 10-29-2001.
228-058	Chumley, Sheridan W.	Investigator no longer at site / Cannot certify. Forms sent on 07-02-2001.
232-002	Mayer, Kimberly	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001; 02-16-2001.
232-003	Umayam, Mary Grace	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
232-004	Dunn, Joseph Scott	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001; 02-21-2001; 04-24-2001; 06-25-2001.
	—	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001; 02-21-2001; 04-24-2001; 06-25-2001.
232-007	Gray, Jennifer A.	Investigator no longer at site / Cannot certify. Forms sent on 04-09-2001; 06-25-2001; 09-10-2001.
232-027	Roffi, Brenda	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
232-028	Burch, Robert R.	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
	—	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
232-032	McGreal, John J.	Investigator no longer at site / Cannot certify. Forms sent on 11-12-2001; 02-25-2002.
232-037	Clemons, Linda Ann	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001; 02-21-2001.
232-040	Bush, Roxanne	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
	—	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
	—	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
232-043	Yogi, Linda	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.

Table C-2	Table of All Investigators/Subinvestigators Not Providing Information and Not Certified	
232-050	Kingcade, Alvin, Jr	Investigator no longer at site / Cannot certify. Forms sent on 04-09-2001; 06-25-2001; 09-10-2001; 11-12-2001.
	[redacted]	Investigator no longer at site / Cannot certify. Forms sent on 04-09-2001; 06-25-2001; 09-10-2001; 11-12-2001.
232-054	Holmes, John A., III	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.
232-060	Baxter, Sharon	Investigator no longer at site / Cannot certify. Forms sent on 02-05-2001.

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)).
Bias has been minimized, when appropriate, through study design, e.g., double- or triple-blind, placebo-controlled, multicenter study sites, etc.

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
228-008		
228-011		
228-012		
228-015		
228-016		
228-030		
228-037		
228-043		
232-004		
232-010		
232-011		
232-012		
232-028		
232-043		
232-068		

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

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

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

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

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-20
P.O. Box 4
West Point, PA 19486

2. TELEPHONE NUMBER *(Include Area Code)*

(484) 344-7597

3. PRODUCT NAME

HYZAAR™

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

20-387

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

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

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4421

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

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

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

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

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

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See Item 8, reverse side if answered YES)

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

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

and

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

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Dennis M. Erb	Dennis M. Erb, Ph.D. Executive Director, Regulatory Affairs	9/24/02

FORM FDA 3397 (4/01)

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