CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-387/S-013, 015 & 027

ENVIRONMENTAL ASSESSMENT/FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

for

HYZAAR Tablets

(50 mg Losartan Potassium – 12.5 mg Hydrochlorothiazide and 100 mg Losartán Potassium – 25 mg Hydrochlorothiazide)

NDA 20-387 / SE1-027

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
(HFD-110)

October 25, 2002

FINDING OF NO SIGNIFICANT IMPACT

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(50 mg Losartan Potassium – 12.5 mg Hydrochlorothiazide
and
100 mg Losartan Potassium – 25 mg Hydrochlorothiazide)

NDA 20-387 / SE1-027

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug application for Hyzaar Tablets (50 mg Losartan Potassium-12.5 mg Hydrochlorothiazide and 100 mg Losartan Potassium - 25 mg Hydrochlorothiazide), Merck & Co., Inc. prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal of the product. The product is currently approved for treating hypertension.

This supplement requests approval of Hyzaar Tablets (Losartan Potassium and Hydrochlorothiazide for:
(1) Initial treatment of severe hypertension (SiDBP ≥ 110 mm Hg) and
(2) Treatment of hypertension when initial treatment with losartan or hydrochlorothiazide alone does not result in adequate control of blood pressure.

Hydrochlorothiazide is categorically excluded from the requirement to prepare an Environmental Assessment because its EIC is less than 1 ppb.

Losartan potassium is a chemically synthesized drug, which is currently approved to treat hypertension. Losartan potassium may enter the environment from patient use and disposal. It is expected to enter predominately into the aquatic environment. As the drug is expected to persist in the environment for some time, the toxicity of losartan potassium to environmental organisms was characterized. The results indicate that the compound is not expected to be toxic to organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

PREPARED BY
Florian Zielinski
Chemist, Center for Drug Evaluation and Research

CONCURRED BY
Nancy B. Sager
Environmental Officer, Center for Drug Evaluation and Research

CONCURRED BY
Yuan-yuan Chiu, Ph.D.
Director, Office of New Drug Chemistry, Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

Losartan Potassium/HCTZ First-Line for Severe Hypertension
F. Environmental Assessment

1. **Date:** 12 September 2002

2. **Name of Applicant/Petitioner:** Merck & Co., Inc.

3. **Address:** Sumneytown Pike
West Point, PA 19486

4. **Description of Proposed Action:**

a. Requested Approval

The Merck Research Laboratories, a division of Merck & Co., Inc., is filing a Supplemental New Drug Application to NDA 20-387 HYZAAR® (Losartan Potassium-Hydrochlorothiazide) to request approval for a label change to add both a new indication and to modify a previous one.

- New Indication. HYZAAR® is indicated for the initial treatment of severe hypertension (SiDBP ≥ 110 mmHg).

- Revised Indication. HYZAAR® is indicated also for the treatment of hypertension when initial treatment with losartan or hydrochlorothiazide alone does not result in adequate control of blood pressure.

The request affects HYZAAR®-Tablets 50-12.5 (50 mg of losartan potassium and 12.5 mg hydrochlorothiazide) and HYZAAR® Tablets 100-25 (100 mg of losartan potassium and 25 mg hydrochlorothiazide). An Environmental Assessment has been submitted pursuant to §21 CFR 25.20 (l) for losartan, and to §21 CFR 25.31 (h) for hydrochlorothiazide. Hydrochlorothiazide meets the requirements of a categorical exclusion because the estimated concentration of the drug substance for all images at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb). Losartan requires a full environmental assessment (given below).

b. Need for Action

The new use for HYZAAR® Tablets 50-12.5 mg and 100-25 mg will allow for the initial treatment of severe hypertension (SiDBP ≥ 110 mmHg).

c. Locations of Use

The product will be used in hospitals, clinics, and/or in homes throughout the United States.

d. Disposal Sites

At U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and recycling, although minimal quantities of unused drug could be disposed of in the sewer system.

5. Identification of Substances that are Subject of the Proposed Action:

a. Nomenclature

i. **Established Name (U.S. Adopted Name – USAN):** Losartan potassium

ii. **Brand/Proprietary Name/Trade Name:** HYZAAR®

iii. Chemical Names:

- **Chemical Abstracts (CA) Index Name (inverted form):** 1*H*-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium salt

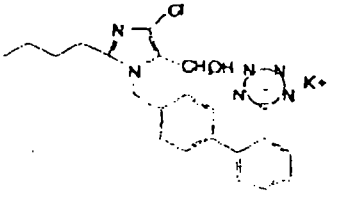
- **Systematic Chemical Name (uninverted form):** 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-Imidazole-5-methanol monopotassium salt

b. Chemical Abstracts Service (CAS) Registration Number: 124750-99-8

c. Molecular Formula: $C_{22}H_{22}ClN_6OK$

d. Molecular Weight: 461.01

e. Structural (graphic) Formula:



6. Environmental Issues:

Summary. The pharmacologic agent Losartan Potassium is the active material in HYZAAR® (NDA 20-387), and is also an active in a related drug COZAAR® (NDA

20-386, *Losartan Potassium*). The *Expected Introduction Concentration (EIC)* for Losartan for both products, based on the greatest of fifth year production estimates (Confidential/Appendix B) is 2.81 ppb, or 1.88 ppb applying metabolism as a depletion factor. Since the EIC is greater than 1 ppb, an Environmental Assessment (EA) was conducted as described by the Guidance for Industry (July, 1998). Data and testing procedures used for the assessment were originally reported in the 1995 revised Environmental Assessment (Bacher, 1995) submitted with original NDA 20-386. Based on the very slight environmental toxicity of Losartan, no environmental impact is expected from the use of this drug.

Physical/Chemical Characteristics. A Summary of Physical/Chemical data is given in Appendix A. Losartan is freely soluble in water (500 mg/mL). The Log K_{ow} is 1.19 (pH 7.0). The solubility and low octanol/water partitioning suggest little potential for binding to sludge or other organic material. As a result Losartan is not expected to bind to sludge that is applied to soil; and, therefore, soil biodegradation data were not obtained. The vapor pressure of Losartan ($<10^{-7}$ torr) also indicates that the compound will not volatilize to the air compartment. The aquatic environment was further evaluated since patient use of Losartan will introduce it to the water compartment via POTW (Publicly Owned Treatment Works) effluents.

Depletion Mechanisms. Depletion mechanisms are summarized in Appendix A. While Losartan is stable to hydrolysis and biodegradation, it photolyzes rapidly in the presence of light. This characteristic was not included in the Assessment due to the unpredictable potential for exposure to light, but does play a role in reducing Losartan in the aquatic environment. The absorbance of an oral dose of Losartan is 33%. (Supporting data and test methodology were provided in original NDA 20-386, Part F (Bacher, 1995). This depletion mechanism is factored into the reported EIC. Absorbed Losartan is extensively metabolized with 10% or less being excreted as a mix of metabolites and some residual Losartan.

EIC Calculation. The EIC was calculated in accordance with the formula given in Guidance for Industry (July, 1998), and was determined to be 2.81 ppb without consideration of metabolism, or 1.88 ppb (µg/L) if dose absorbance is factored in. The calculations are provided in Appendix B/Confidential. Since the EIC exceeded 1ppb, a Tiered Assessment was performed in accordance with the Guidance.

Tier 1 Assessment. Losartan does not partition to the soil compartment. The high solubility and low K_{ow} preclude partitioning to sludge that may be applied to soil. Losartan also does not volatilize to air (vapor pressure $<10^{-7}$ torr). However Losartan may potentially enter the water compartment so that route was evaluated further. Losartan does not rapidly hydrolyze or biodegrade in water. Microbial Inhibition Tests were performed, and Appendix A provides these data. The MIC's for all organisms tested are > 1000 mg/L. The inhibition of activated sludge organisms is ≥ 1000 mg/L. Consequently the EIC for Losartan will not impact aquatic or sewage plant microorganisms. Since the Log K_{ow} for Losartan is less than 3.5, the

Assessment proceeded to Tier 1. Acute toxicity values for Losartan are given in Appendix A (All test methods and results were reported in the Environmental Assessment submitted in 1995.) The most sensitive organism in acute toxicity testing was *Daphnia magna* with a 48 hr. LC_{50} = 331 mg/L. The EIC (1.88 µg/L) was selected as the MEEC (Maximum Expected Environmental Concentration).

[331 x (1000, conversion factor mg to µg)] ÷ 1.88 = 176064

Since the ratio is greater than 1000, and there are No Observed Effects for Losartan at the MEEC, the assessment was considered complete with a conclusion of no environmental impact due to the use of Losartan in both HYZAAR® and COZAAR®.

7. Mitigation Measures:

No adverse environmental effects have been identified. Therefore, no mitigation measures are needed.

8. Alternatives to the Proposed Action:

No potential adverse environmental effects have been identified for the proposed action so no alternatives are necessary.

9. List of Preparers:

Judith A. Bland. Ph.D.
Principal Scientist
Occupational & Environmental Health Sciences
Safety & the Environment
Merck Manufacturing Division
B. A., Biology, Thomas More College, Crestview Hills, KY, 1968
M. S., Microbiology, Indiana University, Bloomington, IN, 1970
Ph.D., Microbiology, Indiana University, Bloomington, IN, 1972

10. References:

a. Bacher, S. 1995. COZAAR and HYZAAR Environmental Assessments: Revision submitted to FDA (Chemical and Pharmaceutical Manufacturing and Control Documentation, Section F. Environmental Assessment).

b. U.S. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. CMC 6, Revision 1.

11. Appendices:

(Attached)

APPENDIX A/Non-Confidential

APPENDIX A: DATA SUMMARY TABLE/NON-CONFIDENTIAL

PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	>500 mg/mL
Dissociation Constant (pK_a)	4.1 (1% methanol) 4.9 (1:1 methanol:water)
Log Octanol/Water Partition Coefficient (Log K_{ow})	Log K_{ow} = 1.19 @ pH 7.0
Vapor Pressure	$<10^{-7}$ torr @ 59°C
DEPLETION MECHANISMS	
Hydrolysis	Stable at pHs 5, 7, and 9
Aerobic Biodegradation	28 day recovery = 93.1%
Soil Biodegradation	Not relevant
Photolysis	Half-life @ pH 5 = 10.9 hrs Half-life @ pH 7 = 11.8 hrs Half-life @ pH 9 = 17.6 hrs
Bioavailability	ca 33% orally (67% into waste stream)
Metabolism	90 % of absorbed dose is metabolized 10% excreted – 4% losartan 6% active carboxylic acid metabolite
ENVIRONMENTAL EFFECTS	
Microbial Inhibition	*Azotobacter paspali* MIC > 1000 mg/L *Scenedesmus quadricauda* MIC > 1000 mg/L *Fusarium acuminatum* MIC > 1000 mg/L *Aspergillus niger* MIC > 1000 mg/L *Pseudomonas putida* MIC > 1000 mg/L *Anabaena flos-aquae* MIC > 1000 mg/L *Paramecium caudatum* MIC > 1000 mg/L
Activated Sludge Inhibition	Maximum Non-Inhibitory Effect Concentration ≥ 1000 mg/L
Acute Toxicity	*Daphnia magna* 48 hr. LC_{50} = 331 mg/L; NOEC = 80 mg/L *Pimephales promelas* 48 hr. LC_{50} = >1000 mg/L; NOEC = 100 mg/L *Oncorhynchus mykiss* 96 hr. LC_{50} = >929 mg/L *O. mykiss* NOEC = >929 mg/L
Chronic Toxicity	*Selenastrum capricornutum* 10 days (Alga) Cell growth NOEC 143 mg/L, MIC = 245 mg/L Growth rate NOEC 245 mg/L, MIC = 381 mg/L *Microcystis aeruginosa* 10 days (Alga) Cell growth NOEC 556 mg/L, MIC = 949 mg/L Growth rate NOEC ≥949 mg/L, MIC ≥ 949 mg/L

from original EA

JWZ/FDA 10/28/02

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

/s/

Florian Zielinski
10/31/02 09:49:19 AM

Nancy Sager
10/31/02 10:55:11 AM

Yuan-Yuan Chiu
11/1/02 03:36:46 PM
Concurred

Fromm, Edward J

From: Desai, Mehul
Sent: Tuesday, August 26, 2003 9:43 AM
To: Throckmorton, Douglas C
Cc: Choi, Jasmine; Fromm, Edward J
Subject: Hyzaar

Doug, Jeff Tucker from Merck had some discussions with Jasmine re: the 6 week results. Jasmine noted there was one subject in the Hyzaar arm that concomitantly was receiving a beta blocker. Jasmine and I agree that this subject should be excluded in the efficacy analysis. Merck also agrees with this. The numbers they sent to us: 30% vs 12.5% (Hyzaar vs Losartan) do not reflect the exclusion of this one subject. Jeff Tucker called me this morning to acknowledge this and assures me that this subject will be excluded in the next revision that they send to us (as a result the numbers in the Hyzaar arm will change slightly). They want to make this doesn't hold up their application. I told him I didn't think it would and that I would make sure I talked to you about it.

Mehul