CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-028

ENVIRONMENTAL ASSESSMENT/FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

for

Cozaar Tablets

(losartan potassium)

25, 50, and 100 mg

NDA 20-386 / SE1-028

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

May 7, 2002

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-386 / SE1-028

Cozaar Tablets

(losartan potassium)

25, 50, and 100 mg

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 their supplemental new drug application for Cozaar Tablets, Merck & Co., Inc. has prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 which evaluates the potential environmental impacts of the use and disposal from use of the product.

Losartan potassium is a chemically synthesized drug, which is currently approved to treat hypertension. This supplemental application provides for a new indication for the treatment of nephropathy in Type 2 diabetic patients with proteinuria.

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
Appendex Electronic Signature Page

1. **Date:** 06 (FAX) May 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 20-386 COZAAR® (Losartan Potassium) to request approval for a new indication for COZAAR® for use in Type 2 diabetic patients with proteinuria to delay the progression of renal disease. The usual starting dose will be 50 mg COZAAR® Tablets. NDA 20-386 also includes Tablets 25 mg and Tablets 100 mg that may also be used in these patients. An EA has been submitted pursuant to 21 CFR part 25. COZAAR® 25 mg Tablets, 50 mg Tablets and 100 mg Tablets are packaged in High Density Polyethylene Bottles (HDPE).

   b. **Need for Action**

   COZAAR® has been shown to be effective in delaying the progression of renal disease *in Type 2 diabetic patients with proteinuria.*

   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:** COZAAR®

   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

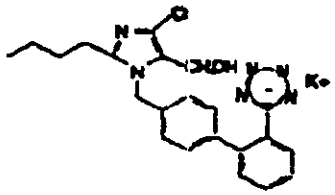
- **Systematic Chemical Name (uninverted form):** 2-butyl-4-chloro-1-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1*H*-Imidazole-5-methanol monopotassium salt

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 COZAAR® (NDA 20-386), is also an active in a related drug HYZAAR® (NDA 20-387, losartan potassium/hydrochlorothiazide). The Expected Introduction Concentration (EIC) for Losartan for both products, based on the greatest of fifth year production estimates (Confidential/Appendix B) is —— ppb, or —— 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 materia . 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 extentively 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 ___ ppb without consideration of metabolism, or ___ ppb (µg/L) if dose absorbance (bioavailability) 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 ___, 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 (___ µg/L) was selected as the MEEC (Maximum Expected Environmental Concentration).

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 COZAAR® and HYZAAR®.

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. 1998. 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

08 May 2002

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 *Pimephales promelas* 48 hr. LC_{50} = >1000 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

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/s/

Florian Zielinski
5/7/02 01:06:40 PM

Nancy Sager
5/7/02 01:13:30 PM

Yuan-Yuan Chiu
5/7/02 04:17:24 PM
concurred

REVIEW OF

ENVIRONMENTAL ASSESSMENT

For

Cozaar Tablets

(25, 50 and 100 mg Losartan Potassium)

NDA 20-386 / S-028

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

Date Completed: May 7, 2002

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

FONSI recommended.

Losartan potassium is not volatile and will not enter the air compartment. Losartan potassium is not expected to bind to sludge because its log octanol water partition coefficient is 1.19 at pH 7.

Losartan potassium is very soluble in water (more than 500 mg/L) and therefore, it is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration ($EIC_{aquatic}$) is — ppb assuming no metabolism. The Expected Environmental Concentration (EEC) in the aquatic environment is — ppb. The EEC was calculated using a dilution factor of 10 for wastewater effluents discharged into the receiving waters. Rapid hydrolysis does not occur at pH 5, 7 and 9. The photolysis half-life is 10, 12 and 18 hours at pH 5, 7 and 9 respectively.

Environmental effect data were generated for aquatic species. It is unlikely that losartan potassium represents a risk to the aquatic environment based on the available data.

	Losartan Potassium Effects Testing Data
Activated Sludge Inhibition	Maximum Non-Inhibitory Effect Concentration is ≥ 1000 mg/mL
Microbial Inhibition	Azotobacter paspali MIC > 1000 mg/mL Scenedesmus quadricauda MIC > 1000 mg/mL Fusarium acuminatum MIC > 1000 mg/mL Aspergillus niger MIC > 1000 mg/mL Pseudomonas putida MIC > 1000 mg/mL Anabaena flos-aquae MIC > 1000 mg/mL Paramecium caudatum MIC > 1000 mg/mL
Daphnia, acute	48 hour LC_{50} = 331 mg/L for water fleas
Pimephales promelas	48 hour LC_{50} more than 1000 mg/L for fathead minnows
Oncorhynchus mykiss	96 hour LC_{50} more than 929 mg/L for rainbow trout
Oncorhynchus mykiss	NOEC more than 929 mg/L for rainbow trout
Alga Microbial Inhibition (10 day)	Selenastrum capricornutum (green alga) Cell growth: NOEC = 143 mg/L; MIC = 245 mg/L Growth rate: NOEC = 245 mg/L; MIC = 381 mg/L
Alga Microbial Inhibition (10 day)	Microcystis aeruginosa (blue green alga) Cell growth: NOEC = 556 mg/L; MIC = 949 mg/L Growth rate: NOEC > 949 mg/L; MIC > 949 mg/L

No significant environmental impact is anticipated based on the data submitted.

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated May 6, 2002 (received by FAX on May 6, 2002)
   Project Manager: Ed Fromm
   Chemist: Ram Mittal

2. **Name of applicant/petitioner:** Merck & Co., Inc.

   ADEQUATE

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

   ADEQUATE

4. **Description of the proposed action:**

   a. **Requested Approval (NDA 20-386 / S-028):**

   Cozaar Tablets (losartan potassium) will be marketed as 25, 50 and 100 mg tablets. Merck filed NDA 20-386 / S-028 pursuant to section 505(b) of the Federal, Food, Drug and Cosmetic Act for the use of Cozaar Tablets for treating nephropathy in Type 2 diabetic patients with proteinuria.

   This EA references data and testing procedures submitted in 1995 in the original NDA. A FONSI for the original ND 20-386 was approved on March 31, 1995.

   ADEQUATE

   b. **Need for Action:**

   Cozaar Tablets (losartan potassium) are indicated for treatment of nephropathy in Type 2 diabetic patients with proteinuria.

   ADEQUATE

   c. **Expected Locations of Use (Drug Product):**

   Cozaar Tablets (losartan potassium) will be used in hospitals, clinics and patients' homes throughout the U.S.

   ADEQUATE

d. Disposal Sites

Empty or partially empty packages containing losartan potassium will be disposed by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed in the sewer system.

ADEQUATE

5. **Identification of chemicals that are the subject of the proposed action:**

a. Nomenclature
   i. Established Name (USAN): Losartan potassium
   ii. Proposed Trade Name: Cozaar
   iii. Chemical 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
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. Chemical Structure is in the EA

ADEQUATE

6. **Environmental Issue:**

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

Losartan potassium is the active ingredient in Cozaar Tablets (NDA 20-386) and Hyzaar Tablets (NDA 20-387). Summing all production estimates for all indications, the maximum annual production estimate is ____ kg. This is equivalent to EIC = ____ ppb in the aquatic environment.

The firm states that humans metabolize approximately 30% of the administered dose of losartan potassium. If metabolism is considered to be a depletion mechanism, EIC is reduced from ____ ppb.

ADEQUATE

ii. Physical and Chemical Characterization

Losartan potassium exists as a cation in the environmental pH range. Its solubility in water is more than 500 mg/L (The pH & temperature are not specified. These are insignificant qualifiers in this case.)

The log of the n-octanol / water partition coefficient (log P_{ow}) is 1.19 at pH 7. Because log P_{ow} is not more than 3, the probability for bioaccumulation, adsorption to particulate matter, humic acids and sediments is low.

Vapor pressure of losartan potassium is $< 10^{-7}$ torr. Therefore, vaporization into the atmosphere is not expected.

ADEQUATE

iii. Environmental Depletion Mechanisms

Losartan potassium is stable to hydrolysis and biodegradation. Photolysis is rapid and provides an effective means for eliminating losartan potassium from the environment.

ADEQUATE

iv. Environmental Concentration, aquatic

The total amount of losartan potassium required in the peak market is [redacted] kg/year. (Merck provided this information in the CONFIDENTIAL part of the EA) The Expected Introduction Concentration ($EIC_{aquatic}$) of losartan potassium entering into the external aquatic environment is [redacted] ppb, [redacted] mg/L). This assumes no metabolism. This is the concentration used in the risk assessment for effects on microorganisms and acute toxicity studies.

Adjusting $EIC_{aquatic}$ by 10 fold dilution when losartan potassium is introduced into the aquatic compartment gives the Expected Environmental Concentration, EEC = [redacted] ppb. To be conservative, EICs and EEC were not adjusted for removal by photolysis.

ADEQUATE

v. Summary

Losartan potassium will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Losartan potassium is not volatile and therefore will not enter the air compartment. Losartan potassium is not expected to be persistent in the environment due to its potential for photolysis.

ADEQUATE

b. Environmental Effects

The environmental effect data for aquatic species are in the original NDA submitted in 1995. It is unlikely that losartan potassium represents a risk to the aquatic environment based on the available data.

	Losartan Potassium Effects Testing Data
Activated Sludge Inhibition	Maximum Non-Inhibitory Effect Concentration is ≥ 1000 mg/mL (No effect observed at 1 gram / Liter)
Microbial Inhibition	Azotobacter paspali MIC > 1000 mg/mL Scenedesmus quadricauda MIC > 1000 mg/mL Fusarium acuminatum MIC > 1000 mg/mL Aspergillus niger MIC > 1000 mg/mL Pseudomonas putida MIC > 1000 mg/mL Anabaena flos-aquae MIC > 1000 mg/mL Paramecium caudatum MIC > 1000 mg/mL
Daphnia, acute	48 hour LC_{50} = 331 mg/L for water fleas
Pimephales promelas	48 hour LC_{50} more than 1000 mg/L for fathead minnows
Oncorhynchus mykiss	96 hour LC_{50} more than 929 mg/L for rainbow trout
Oncorhynchus mykiss	NOEC more than 929 mg/L for rainbow trout
Alga Microbial Inhibition (10 day)	Selenastrum capricornutum (green alga) Cell growth: NOEC = 143 mg/L; MIC = 245 mg/L Growth rate: NOEC = 245 mg/L; MIC = 381 mg/L
Alga Microbial Inhibition (10 day)	Microcystis aeruginosa (blue green alga) Cell growth: NOEC = 556 mg/L; MIC = 949 mg/L Growth rate: NOEC > 949 mg/L; MIC > 949 mg/L

c. **Summary**

The introduction of the losartan potassium into sewage treatment plants and into the environment through use and disposal of the product is not expected to pose an environmental risk.

Based on the Activated Sludge Inhibition test, losartan potassium does not inhibit sewage microorganisms at concentrations expected in wastewater treatment plants and therefore it is not expected to disrupt the wastewater treatment process. Furthermore, based on the 10-day Alga Microbial Inhibition test, it does not inhibit green and blue-green alga.

The applicant performed acute toxicity testing with daphnia magna, fathead minnows and rainbow trout. The NOEC measured in rainbow trout is more than — mg/L. This NOEC is much greater than the EIC, namely — mg/L. The LC_{50} to EIC ratio is much greater than — in tests with daphnia, fathead minnows and rainbow trout indicating that no effects would be expected.

Based on the data, a FONSI is recommended.

ADEQUATE

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

ADEQUATE

8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

ADEQUATE

9. Preparer

The name and professional experience of the EA preparer are in non-confidential appendix A

ADEQUATE

10. References

References are provided.

ADEQUATE

11. Appendices

The EA contains a data table in the non-confidential appendix. A confidential appendix includes information dated September 7, 2001 about the maximum annual production estimate in the next 5 years.

ADEQUATE

Florian Zielinski
May 7, 2002

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/s/

Florian Zielinski
5/7/02 01:00:25 PM
ENV ASSESSMENT

Nancy Sager
5/7/02 01:10:14 PM
ENV ASSESSMENT

Yuan-Yuan Chiu
5/7/02 04:13:56 PM
CHEMIST
concurred without comment