

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-032

ENVIRONMENTAL ASSESSMENT/FONSI

**REVIEW OF
ENVIRONMENTAL ASSESSMENT**

For

Cozaar Tablets

(50 and 100 mg Losartan Potassium)

NDA 20-386 / SE1-032

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

Date Completed: Oct 23, 2002

EXECUTIVE SUMMARY – ENVIRONMENTAL ASSESSMENT

This supplement pertains to 50 and 100 mg Cozaar Tablets only. 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 — 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; NOEC = 80 mg/L |
| Pimephales promelas | 48 hour LC ₅₀ > 1000 mg/L; NOEC = 100 mg/L |
| Oncorhynchus mykiss | 96 hour LC ₅₀ > 929 mg/L; NOEC > 929 mg/L |
| 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 June 21, 2002 was received by CDR/CDER on July 26, 2002.
Project Manager: Ed Fromm
Chemist: Ram Mittal

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

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

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

a. **Requested Approval (NDA 20-386 / SE1-032):**

The request pertains to Cozaar Tablets (50 and 100 mg losartan potassium). Merck filed NDA 20-386 / SE1-032 pursuant to section 505(b) of the Federal, Food, Drug and Cosmetic Act for the use of Cozaar Tablets to protect against major cardiovascular morbidity and mortality in hypertensive patients with electrocardiographic (ECG) evidence of left ventricular hypertrophy.

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b. **Need for Action:**

Cozaar Tablets (losartan potassium) are indicated to protect against major cardiovascular morbidity and mortality in hypertensive patients with electrocardiographic (ECG) evidence of left ventricular hypertrophy.

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

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

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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.

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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: C₂₂H₂₂ClN₆OK
- d. Molecular Weight: 461.01
- e. Chemical Structure is in the EA, page F-5

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6. Environmental Issue:

This EA references data and testing procedures submitted in 1995 in the original NDA 20386. A FONSI for the original NDA 20386 was approved on Mar 31, 1995.

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 — % of the administered dose of losartan potassium. If metabolism is considered to be a depletion mechanism, EIC is reduced from — to — ppb. (Appendix B, page F-11)

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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 at approx. 25°C. (The resultant pH reported in an earlier EA is 9.7)

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.

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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.

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iv. Environmental Concentration, aquatic

The total amount of losartan potassium required in the peak market is — kg/year. (Merck provided this information in the CONFIDENTIAL part of the EA, Appendix B, page F-11) The Expected Introduction Concentration ($EIC_{aquatic}$) of losartan potassium entering into the external aquatic environment is — ppb (— 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 — fold dilution when losartan potassium is introduced into the aquatic compartment gives the Expected Environmental Concentration, $EEC =$ — ppb. To be conservative, $EICs$ and EEC were not adjusted for removal by photolysis.

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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.

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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 |
| 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 |
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* NOECs for daphnia and fathead minnows were reported in 1995 in the EA in NDA 20-387

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 929 mg/L. This NOEC is much greater than the EIC, namely — mg/L. The LC₅₀ to EIC ratio is much greater than 1000 in tests with daphnia, fathead minnows and rainbow trout indicating that no effects would be expected.

Based on the data, a FONSI is recommended.

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7. Mitigation Measures

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

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8. Alternatives to the proposed action

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

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9. Preparer

The name and professional experience of the EA preparer are provided

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10. References

Two references are provided.

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11. Appendices

The EA contains a data summary table in non-confidential Appendix A.

The confidential Appendix B includes calculations of EIC with and without adjustment for metabolism. EICs are based on the maximum annual production estimate in the next 5 years.

The production estimate is lower than the estimate submitted on May 6, 2002

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Florian Zielinski
Oct 23, 2002

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

/s/

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