CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-386/S-019 and 029

ENVIRONMENTAL ASSESSMENT/FONSI

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 — 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 September 20, 2001
   Project Manager: Ed Fromm
   Chemist: Ram Mittal

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

   ADEQUATE

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

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

   a. **Requested Approval (NDA 20-386 / S-029):**

   A pediatric formulation of 50 mg Cozaar Tablets (losartan potassium) will be marketed. Merck filed NDA 20-386 / S-029 pursuant to section 505(b) of the Federal, Food, Drug and Cosmetic Act for the use of this pediatric formulation for treating hypertension in pediatric patients.

   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.

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   b. **Need for Action:**

   Cozaar Tablets (losartan potassium) are indicated for treatment of hypertension. This supplement provides for a pediatric formulation for use by pediatric hypertensive patients.

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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: $C_{22}H_{22}ClN_6OK$
d. Molecular Weight: 461.01
e. Chemical Structure is in the EA

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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.

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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 (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.

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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) 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 10 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 (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
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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 LC_{50} 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 in non-confidential appendix A

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10. References

References are provided.

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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

/S/

Florian Zielinski
May 20, 2002

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
5/20/02 03:14:22 PM
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