CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

ENVIRONMENTAL ASSESSMENT

FINDING OF NO SIGNIFICANT IMPACT

AND

ENVIRONMENTAL ASSESSMENT

FOR

Asacol (mesalamine)
Delayed-Release Tablet, 800 mg

NDA 21-830
Treatment of moderately active ulcerative colitis

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Gastrointestinal & Coagulation Drug Products
(HFD-180)

February 25, 2005

FINDING OF NO SIGNIFICANT IMPACT
NDA 21-830

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 Asacol (mesalamine) Delayed-Release Tablet 800 mg, Proctor & Gamble Pharmaceuticals, 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 of the product.

Mesalamine is a chemically synthesized drug that is indicated for the treatment of moderately active ulcerative colitis.

Mesalamine may enter the environment from patient use and disposal. It is expected to enter into the aquatic environment. Data demonstrating that mesalamine is "readily biodegradable" was provided. The toxicity of mesalamine 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.

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Attachment: Environmental Assessment
Appended Electronic Signature Page

Procter and Gamble Pharmaceuticals, Inc.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

October 6, 2004

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Environmental Assessment of Asacol Delayed Release Tablets

1. Date

October 6, 2004

2. Name of Applicant

Procter & Gamble Pharmaceuticals, Inc.

3. Address

Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

4. Description of Proposed Action

a. Requested Approval

Procter & Gamble Pharmaceuticals, Inc. has filed an NDA (application number 21-830) pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) delayed-release tablet, 800 mg, packaged in high density polyethylene bottles. An EA has been submitted pursuant to 21 CFR part 25.

b. Need for Action

Asacol delayed-release tablets, 800 mg, are effective in the treatment of moderately active ulcerative colitis.

c. Location of Use

The product will be used in hospitals, clinics, and in the home 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, incinerators, and recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

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

a. Nomenclature

i) Established name (USAN)

Mesalamine

ii) Brand/Proprietary Name/Tradename

Asacol delayed-release tablet

iii) Chemical Names (CAS index name)

5-Amino-2-hydroxybenzoic acid

b. CAS Number

89-57-6

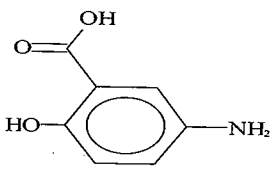
c. Molecular Formula

$C_7H_7NO_3$

d. Molecular Weight

153.14

e. Structure



5-Amino-2-hydroxybenzoic acid

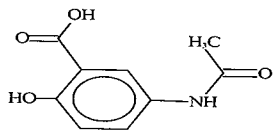
6. Environmental Issues

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

The active ingredient in Asacol delayed-release tablets is mesalamine (5-amino-2-hydroxybenzoic acid). Mesalamine is metabolized, primarily to N-

acetyl-5 amino-2-hydroxybenzoic acid, and both parent and the N-acetyl metabolite are excreted in urine and feces. In a review of the excretion of mesalamine, Sandborn and Hanauer (2003) reported that 10 to 35% of the administered dose is excreted in the urine and 40 to 64% is excreted in the feces within 96 hours of administration. In urine, approximately 80 to 100% of the mass of drug exists as the N-acetyl metabolite (Rasmussen et al. 1982; Hussain et al. 1998; Sandborn et al. 2004). In feces, approximately 65% is present as the N-acetyl metabolite (Rasmussen et al. 1982; Hussain et al. 1998). The N-acetyl metabolite of mesalamine is a structurally related substance (SRS). The structure of N-acetyl-5-amino-2-hydroxybenzoic acid is shown here (CAS number 51-59-2).



N-acetyl-5-amino-2-hydroxybenzoic acid

Environmental fate and effect studies were conducted on the parent rather than the N-acetyl metabolite since the later is less biologically active and there is high likelihood that it will be deacetylated back to the parent by microbes in wastewater and the environment. In addition, both materials have similar hydrophobicity. Thus, the fate and effects of the N-acetyl-5-amino-2-hydroxybenzoic acid is expected to be similar to the parent mesalamine.

ii. Physical and Chemical Characterization

The ionization of the mesalamine influences water solubility, volatility from water, and hydrophobicity properties. Mesalamine has three ionizable groups, a carboxylic acid, an amine, and a hydroxyl moiety. Measured pKa values from the literature are: 2.30 and 3.0 for the carboxyl group; 5.69 and 6.0 for the amine; and 13.9 for the hydroxyl (Allgayer et al. 1985; French and Mauger, 1993) (Table 1, Appendix 1). At environmental pHs (approximately 6 – 8.5), the carboxyl group will be deprotonated and have a negative charge, the amine group will either be protonated and have a positive charge or will be neutral, and the hydroxyl will be protonated.

Mesalamine is highly soluble in waste and surface waters with a reported solubility of approximately 18 mg/ml at pH 6.7 and 37°C (French and Mauger, 1993). Due to its ionization at environmental pHs and the fact that ionized compounds do not volatilize from water, the Henry's Law Constant was not measured for mesalamine. Mesalamine's low volatility

from water is supported by the estimated Henry's Law constant of 5.02×10^{-12} atm m^3/mol (25°C) (HENRYWIN v1.90, ©2000 US Environmental Protection Agency) (Table 1, Appendix 1). This value was estimated using the bond estimation method. The octanol water partition coefficient of mesalamine is 1.30 (logKow = 0.11) at pH 6.9 (Jung et al. 1998) (Table 1, Appendix 1). Given the low log Kow, mesalamine is not expected to partition significantly to sludge during wastewater treatment and, hence, concentrations in soils will be negligible. This is further supported by the rapid and complete biodegradation of mesalamine to CO_2 in a screening test supportive of rapid biodegradation during wastewater treatment and in soil.

iii. Environmental Depletion Mechanisms

An environmental biodegradation study was conducted with mesalamine according to OECD method 301B. After an initial lag period of four to six days during which microbial populations were likely acclimating to the test material, biodegradation of mesalamine progressed rapidly. Mesalamine degraded rapidly ($t_{½}$ = 1.2 - 1.3 days) and completely (Table 1, Appendix 1). The CO_2 generated from this study accounted for 94% of the total amount of mesalamine (as percent theoretical CO_2) dosed into the system, and the material is considered ready biodegradable. Due to the speed and extent of this depletion mechanism and the fact that microbial communities are ubiquitous in the environment, other depletion mechanisms were not studied.

iv. Environmental Concentrations

Estimates of environmental concentrations for mesalamine are in appendix 2 (confidential). The expected introduction concentration (EIC) was estimated using FDA Guidance for Industry (1998). The expected environmental concentration (EEC) was estimated by applying wastewater treatment removal and dilution to the EIC. The biodegradation of mesalamine during wastewater treatment can be accounted for in the calculation of the expected environmental concentration (EEC) by assuming a first-order biodegradation rate constant during wastewater treatment. For compounds which meet the ready degradability criteria, a first-order biodegradation rate of 1.0 $hour^{-1}$ in activated sludge can be assumed (European Commission, 2003). Wastewater treatment plant removal was predicted to be 87% by the method of Struijs et al. (1991) (Appendix II of European Commission, 2003). Using a dilution factor of 10 (FDA, 1998) and the removal during wastewater treatment, the EEC is approximately a factor of 75 less than the EIC.

Based on the ready biodegradability, solubility, and log Kow (1.3 at pH 6.8) of mesalamine, sludge and soil concentrations of mesalamine are expected to be low and will not pose an issue in the soil compartment.

v. Summary of Environmental Fate of Released Substances

Mesalamine is water soluble and has a low volatility and Kow, thus, the majority of mesalamine released to the environment will partition into the aquatic compartment. Hence, the fate assessment focused on this compartment. Mesalamine will be excreted by patients primarily as the parent molecule or as a conjugate which will likely be converted to the parent during wastewater treatment. The EIC for mesalamine was estimated to be in the low parts per billion range (see appendix 2 / confidential). After inclusion of the rapid and complete biodegradation of mesalamine during waste treatment and dilution into surface waters, the EEC is predicted to be far less than 1.0 ppb (see appendix 2 / confidential).

b. Environmental Effects

A microbial respiration inhibition test was conducted with mesalamine according to OECD 209 at nominal concentrations ranging from 3.2 to 800 mg/L (Table 1, Appendix 1). There was no significant reduction in respiration at any mesalamine concentration tested. Based on the EIC and the more realistic EEC (see appendix 2 / confidential) no effects on microbes are expected in wastewater treatment plants or the environment, respectively.

Environmental effects testing was also conducted with the fathead minnow (*Pimephales promelas*) according to OECD method 203 to better understand the potential for adverse effects of mesalamine in the environment. Range-finding and definitive tests were conducted with analysis of test material concentrations during the definitive test. Test material concentrations declined from approximately 100% of the nominal dose at test initiation to approximately 80% of the nominal dose at 96 hours. No mortality was associated with mesalamine exposure and the 96 hour LC_{50} value for the fathead minnow was greater than the highest test concentration, 91.1 mg/L (Table 1, Appendix 1).

c. Summary of Mesalamine Environmental Fate and Effects

Mesalamine is water soluble and has a low volatility and Kow, thus, the majority of mesalamine released to the environment will partition into the aquatic compartment. The lowest available $L(E)C_{50}$ value is from an acute toxicity tests on fish and is >91.1 mg/L. The ratio of the lowest toxicity value to the MEEC (see appendix 2 / confidential) is far greater than 10,000. Since this ratio is greater than the assessment factor of 1000 (FDA, 1998), the conclusion is reached that the mass of mesalamine which may be distributed over the next five years in the U.S. will not pose a risk to the aquatic compartment of the environment. Mesalamine biodegradation and dilution into surface water will further reduce the concentration of mesalamine in the aquatic environment. The EEC is approximately a factor of 75 less than the EIC.

7. Mitigation Measures

No adverse environmental effects of the drug active have been identified at the expected introduction concentration. Therefore, no mitigation measures are needed.

8. Alternatives to the Proposed Action

No adverse environmental effects of the drug active have been identified at the expected environmental concentration. Therefore, no alternatives to the proposed action are needed.

9. List of Preparers

This environmental assessment was prepared by:

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Senior Principle Research Scientist
The Procter & Gamble Company

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Ph.D. 1985, Environmental Toxicology, Michigan State University, E. Lansing, MI

List of Consultants:
Contract testing laboratory:
ABC Laboratories, Inc, 7200E. ABC Lane, Columbia, MO 65202

10. References

Allgayer, H, J Sonnenbichler, W Kruis, G Paumgartner. Determination of the pH values of 5-amino salicylic acid and N-acetylaminosalicylic acid and comparison of the pH dependent lipid-water partition coefficients of sulphasalazine and its metabolites. Arzneimittel-Forschung/Drug Research 35(9): 1457-1459.

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Jung YJ, JS Lee, HH Kim, YM Kim SK Han. 1998. Synthesis and evaluation of 5-aminosalicyl-glycine as a potential colon-specific prodrug of 5-aminosalicylic acid. Archives of Pharmaceutical Research 21(2): 174-178.

Rasmussen, SN, S Bondesen, EF Hvidberg, SH Hansen, V Binder, S Halskov, H Flachs. 1982. 5-aminosalicylic acid in a slow-release preparation: Bioavailability, plasma level, and excretion in humans. Gastroenterology 83: 1062-1070.

Sandborn, WJ, SB Hanauer. 2003. Systematic review: the pharmacokinetic profile of oral mesalazine formulation and mesalazine prodrugs used in the management of ulcerative colitis. Alimentary Pharmacology and Therapeutics 17: 29-42.

Sandborn, WJ, SB Hanauer, A Buch. 2004. Comparative pharmacokinetics of equimolar doses of 5-aminosalicylate administered as oral mesalamine (Asacol) and balsalazide: a randomized, single-dose, crossover study in healthy volunteers. Alimentary Pharmacology and Therapeutics 19: 1089-1098.

Struijs, J, J Stoltenkamp, D van de Meent. 1991. A spreadsheet-based box model to predict the fate of xenobiotics in a municipal wastewater treatment plant. Water Research 25: 891-900.

11. Appendices

Appendix 1 / NonConfidential

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Table 1. A summary of the environmental fate and effects of mesalamine. Nonconfidential.

PHYSICAL / CHEMICAL CHARACTERIZATION	
Water Solubility	0.84 mg/ml, 25°C, pH 4.01[1] 1.41 mg/ml, 37°C, pH 3.61 ~18 mg/L, 37°C, pH 6.71
Dissociation Constants, pKa	2.30 (carboxyl), 5.69 (amino)[1] 3.0 (carboxyl), 6.0 (amino), 13.9 (hydroxyl)[2]
Octanol/Water Partition Coefficient	1.30 (logKow=0.11) (pH 6.8, 37°C)[3]
Henry's Law Constant HENRYWIN v 1.9 (©2000 U.S. EPA)	5.02 x 10^{-12} atm m^3/mol (25°C)
DEPLETION MECHANISMS	
Aerobic Biodegradability OCED 301B	$t_{½}$ = 1.2 – 1.3 days, readily degradable 94% CO_2 by day 29
ENVIRONMENTAL EFFECTS	
Microbial Respiration Inhibition Test OECD 209	EC_{50} = >800 mg/L NOEC =800 mg/L
Acute Toxicity to Fish (*Pimephales promelas*) OECD 203	96 hr LC_{50} = >91.1 mg/L 96 hr NOEC = 91.1 mg/L

1. French and Mauger, 1993.
2. Allgayer et al. 1985
3. Jung et al. 1998.

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/s/

Jon E. Clark
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Moheb Nasr
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REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

Asacol (mesalamine)
Delayed-Release Tablet, 800 mg

NDA 21-830
Treatment of moderately active ulcerative colitis

Food and Drug Administration
Center for Drug Evaluation and Research

Division of Gastrointestinal & Coagulation Drug Products
(HFD-180)

February 10, 2005

Environmental Assessment Review #1, NDA 21-830

Asacol (mesalamine) Delayed-Release Tablet, 800 mg

SUMMARY

A FONSI is recommended

Proctor and Gamble has an approved application (NDA 19-651) for Asacol (mesalamine) Delayed-Release Tablet, 400 mg.

This NDA pertains to a higher strength, Asacol (mesalamine) Delayed-Release Tablet, 800 mg. The Environmental Assessment (EA) is dated October 6, 2004.

The highest quantity of the active pharmaceutical ingredient (API) produced for all strengths and indications in any of the first five years after NDA approval is expected to be [redacted] This corresponds to Expected Introduction Concentration [$EIC_{(aq)}$] = [redacted]. After biodegradation of mesalamine to CO_2 during wastewater treatment [redacted] and [redacted] dilution into surface waters, the Expected Environmental Concentration (EEC_{aq}) is [redacted]. b(4)

The Ready Biodegradability of Mesalamine Using the CO_2 Evolution Test (OECD # 301B) revealed 94% degradation through day 29. Therefore, mesalamine is classified "readily biodegradable."

The 96-hour acute toxicity determined by OECD Method # 203 for *Pimephales promelas* (fathead minnow) revealed LC_{50} = > 91.1 mg/L and NOEC = 91.1 mg/L. The LC_{50} is more than 1000 times greater than EIC_{aq} and the NOEC is greater than the EIC_{aq}. b(4)

The Activated Sludge, Respiration Inhibition Test (OECD # 209) revealed EC_{50} > 800 mg/liter.

Based on eco-tox data provided, a FONSI is recommended for NDA 21-830.

REVIEW OF EA FOR NDA 21-830

I. DATE: October 6, 2004

II/ III APPLICANT: Procter & Gamble Pharmaceuticals, Inc.
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462
Dr Mark Leusch, US Regulatory Affairs, (513) 622-2620

IV PROPOSED ACTION:

a. Requested Approvals

Proctor & Gamble, Inc. filed NDA 21-830 pursuant to section 505(b) of the Federal Food, Drug & Cosmetic Act for Asacol (mesalamine) Delayed-Release Tablet, 800 mg, packaged in high-density polyethylene bottles.

ADEQUATE

b. Need for Action

Asacol (mesalamine) Delayed-Release Tablet, 800 mg, may be used to treat moderately active ulcerative colitis

ADEQUATE

c. Expected Locations of Use (Drug Product)

Asacol (mesalamine) Delayed-Release Tablet, 800 mg, will be used in hospitals, clinics and in homes throughout the United States.

ADEQUATE

d. Disposal Sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages in accordance with their waste handling procedures. When used in the home, empty or partially empty packages will be disposed of by a community's solid waste management system, which may include landfills, incineration and recycling. Minimal quantities of unused drug may be disposed on in the sewer or septic systems.

ADEQUATE

V IDENTIFICATION OF CHEMICALS

a. Nomenclature
   i. Established Name (USAN): Mesalamine
   ii. Trade Name: Asacol Delayed-Release Tablet
   iii. Chemical Name: 5-Amino-2-hydroxybenzoic acid
b. CAS Registration Number: 89-57-6
c. Molecular Formula: $C_7H_7NO_3$
d. Molecular Weight, salt: 153.14
e. Chemical Structure is in Section 5e of the EA, page 4

ADEQUATE

VI ENVIRONMENTAL ISSUES

The highest quantity of mesalamine, the active pharmaceutical ingredient (API), produced by Procter and Gamble for all strengths and indications in any of the first five years after approval of this NDA is expected to be [redacted]. (Quantity confirmed by E-mail from DJ Versteeg, 2/11/2005) This corresponds to an Expected Introduction Concentration [$EIC_{(aq)}$] of [redacted]. After biodegradation of mesalamine during wastewater treatment [redacted] dilution in surface waters, the Expected Environmental Concentration (EEC_{aq}) is [redacted]

b(4)

When mesalamine, 5-Amino-2-hydroxybenzoic acid, is administered to patients, it is metabolized to N-acetyl-5-amino-2-hydroxybenzoic acid that is less active pharmacologically. The API and metabolite are excreted. Microbes in the aqueous environment are expected to deacetylate the metabolite back to the API. Therefore, the environmental fate and effects are determined for mesalamine, the API, only.

OECD testing procedures conducted in accordance with GLPs were used to obtain fate and effects data for mesalamine. The test reports established that scientifically sound methods were used to develop the data reported in the Environmental Assessment.

Environmental Fate of released Substances

i. Identification of Substances of Interest

Mesalamine (5-amino-2-hydroxybenzoic acid) is the active pharmaceutical ingredient. Mesalamine is metabolized, primarily to N-acetyl-5-amino-2-hydroxybenzoic acid. The N-metabolite is a structurally related substance (SRS). The CAS number is 51-58-2, and the structure is provided in section 6.a.i. of the EA, page 5. Within 96 hours of administration, 10 to 35% of the administered dose is excreted in the urine and 40 to 64% is excreted in the feces. In urine, approximately 80-100% of the mass of the drug exists as the N-acetyl metabolite, and in feces, approximately 65% is present as the N-acetyl metabolite.

ADEQUATE

ii. Physical and Chemical Characterization

The aqueous solubility is 18 mg/ml at pH 6.7 at 37°C and 0.84 mg/ml at pH 4.1 at 25°C.

Reported pKa values are 2.30 and 3.0 for the carbonyl group, 5.69 and 6.0 for the amine, and 13.9 for the hydroxyl. At environmental pH (6-8.5), the carboxyl group will be deprotonated and have a negative charge, the amine group will either be protonated and have a positive charge or will be neutral, and the hydroxyl group will be protonated.

The n-octanol/water partition coefficient (K_{OW}) at pH 6.8 and 37°C is 1.30; log K_{OW} is 0.11. Given the low log K_{OW}, mesalamine is not expected to partition significantly to sludge during wastewater treatment and, hence, concentrations in soils will be negligible.

The Ready Biodegradability of Mesalamine Using the CO_2 Evolution Test (OECD # 301B) revealed 94% degradation through day 29. Therefore, mesalamine is classified readily biodegradable which predicts rapid and complete biodegradation of mesalamine to CO_2 during wastewater treatment and in soil.

Vaporization into the atmosphere is not expected because mesalamine is ionized at environmental pH and the fact that ionized compounds do not volatilize from water.

Mesalamine's low volatility from water is supported by the estimated Henry's Law constant of 5.02×10^{-12} atm m^3/mol.

ADEQUATE

iii. Environmental Depletion Mechanisms

Mesalamine is considered readily biodegradable according to the CO_2 evolution test (OECD 301B). This biodegradation study demonstrates that mesalamine degrades rapidly ($t_{1/2}$ = 1.2-1.3 days) after an initial lag period (4 to 6 days) during which time the microbes adapt to the test substance. The CO_2 generated through day 29 accounts for 94% of the total amount of mesalamine added.

ADEQUATE

iv. Environmental Concentrations, aquatic

The highest quantity of the active pharmaceutical ingredient (API) produced by Procter and Gamble for all indications and strengths in any of the first five years after NDA approval is expected to (Appendix 2 / Confidential, p 13). This corresponds to an Expected Introduction Concentration [$EIC_{(aq)}$] of b(4)

Due to the potential for environmental microbes to convert the N-acetyl metabolite to the parent compound, removal by human metabolism is not considered in the determination of the EEC_{aq}.

The biodegradation of mesalamine during wastewater treatment — is calculated by assuming a first-order biodegradation rate constant of 1.0 $hour^{-1}$ (Reference: European Commission 2003). Then — dilution occurs after the effluent from the wastewater treatment plant is released to surface waters. The calculated Expected Environmental Concentration (EEC_{aq}) is —. b(4)

EEC_{aq} is not adjusted for removal by photolysis and hydrolysis because these depletion mechanisms do not apply to mesalamine.

ADEQUATE

v. Summary

Mesalamine is expected to partition into the aquatic environment. The EIC_{aq} is —. Following rapid biodegradation of mesalamine during wastewater treatment and dilution into surface waters, the EEC_{aq} is predicted to be —. b(4)

ADEQUATE

Environmental Effects of Mesalamine

Data on the environmental effects of mesalamine on aquatic species is provided on page 11 of the EA dated October 6, 2004.

Mesalamine Effects, Testing Data	
Microbial Respiration Inhibition Test OECD 209	EC_{50} = >800 mg/L NOEC = 800 mg/L
Acute Toxicity to Fish (*Pimephales promelas, aka fathead minnow*) OECD 203	96 hr LC_{50} = >91.1 mg/L 96 hr NOEC = 91.1 mg/L

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

The lowest $L(E)C_{50}$ value is from acute toxicity tests of fish and is >91.1 mg/L. The ratio of the lowest toxicity value to the EIC_{aq} is greater than 10,000, which is greater than the assessment factor of 1000, allowing the conclusion that the mesalamine released into the environment during any of the next 5 years will not pose a risk to the aquatic environment.

Furthermore, the EIC_{aq} for mesalamine is reduced by biodegradation — and — dilution into surface water. The EEC_{aq} is approximately a factor of 75 less than the EIC_{aq}. b(4)

ADEQUATE

Summary Evaluation: Based on the above data, a FONSI is recommended for NDA 21-830.

VII MITIGATION MEASURES

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

ADEQUATE

VIII ALTERNATIVES

No alternatives to the proposed action are required because there are no potential effects.

ADEQUATE

IX PREPARERS

Name, job title and qualifications are provided.
ABC Laboratories Inc is listed as a contract testing laboratory and consultant.

ADEQUATE

X REFERENCES

Ten references are provided.

ADEQUATE

XI APPENDICES

Non-confidential Appendix I contains a summary of the environmental fate and effects of mesalamine. Confidential Appendix 2 contains the calculation of the EIC_{aq} and EEC_{aq}.

The firm also provided the studies titled (1) Determination of the Ready Biodegradability of Mesalamine Using the CO_2 Evolution Method, (2) Activated Sludge, Respiration Inhibition Test of Mesalamine and (3) Mesalamine: Acute Toxicity Test to the Fathead Minnow, *Pimephales promelas*, Determined Under Static Conditions.

ADEQUATE

XII CERTIFICATION

Provided by Mark S Leusch, PhD, a P&G executive, on Form FDA 356h (9/02) dated 10/22/04.

ADEQUATE

Review by: Ruth Ganunis, Jan 27, 2005 and Florian Zielinski, Feb 11, 2005

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/s/

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2/25/05 03:59:16 PM
ENV ASSESSMENT

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2/28/05 09:02:58 AM
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