CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

PHARMACOLOGY REVIEW(S)

PHARMACOLOGIST'S REVIEW OF NDA 21-830 (Amendment dated October 22, 2007)

Sponsor and Address: Procter and Gamble Pharmaceuticals, Inc.

Date of Submission: October 22, 2007

Date of Review: May 23, 2008

Drug: Asacol Delayed Release Tablets, 800 mg

Category: Nonsteroidal anti-inflammatory agent

Submission contents: The sponsor did not submit any nonclinical studies in support of the NDA application. A reference has been made to IND 26,093 and NDA 19-651 for Asacol 400 mg delayed-release tablets.

Background: Asacol (mesalamine) 400 mg delayed release tablets are currently approved for the treatment of mildly to moderately active ulcerative colitis and maintenance of remission of ulcerative colitis. The sponsor submitted NDA 21-830 on October 22, 2004 seeking marketing approval of Asacol 800 mg tablets for the treatment of moderately active ulcerative colitis. No Pharmacology/Toxicology data were submitted in the original submission, and the sponsor referred to IND 26,093 and NDA 19-651 for Asacol 400 mg delayed-release tablets in nonclinical support of the NDA application. The original NDA application was recommended for approval by the pharmacology reviewer based on previously reviewed nonclinical studies. However, due to clinical efficacy issues, the Agency issued a complete response letter. In response to the complete response letter, the sponsor submitted additional clinical study results under amendment 20 on October 22, 2007.

Summary and Evaluation:

NDA 21-830 was submitted on October 22, 2004 seeking marketing approval of Asacol 800 mg tablets for the treatment of moderately active ulcerative colitis. No Pharmacology/Toxicology data were submitted in the original submission, and the NDA application was recommended for approval by the pharmacology reviewer, based on previously reviewed nonclinical studies. However, due to clinical efficacy issues, the Agency issued a complete response letter. In response to the complete response letter, the sponsor submitted additional clinical study results on October 22, 2007 under amendment 20. Under the current submission, the sponsor did not submit any nonclinical studies.

Asacol 400 mg tablets are currently approved for the treatment of mildly to moderately active ulcerative colitis and maintenance of remission of ulcerative colitis. Nonclinical

toxicology studies in rats, mice and dogs showed that kidney is the primary target organ of toxicity in all species. Mesalamine had no effect on reproduction and fertility in male and female rats, and was not teratogenic in rats and rabbits. It was not mutagenic in a standard battery of genotoxicity assays, and had no carcinogenic potential in rats and mice.

LABELING:

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential

8 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-_____

b(4)

Sushanta Chakder, Ph. D. Date

Pharmacologist, HFD-180

cc.

NDA

HFD-180

HFD-180/RPM

HFD-180/SChakder

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/s/

Sushanta Chakder
5/23/2008 01:39:31 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-830**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**10/22/04**
PRODUCT:	**Asacol Delayed-Release Tablet, 800 mg**
INTENDED CLINICAL POPULATION:	**Treatment of Moderately Active Ulcerative Colitis**
SPONSOR:	**Procter & Gamble Pharmaceuticals, Inc.**
DOCUMENTS REVIEWED:	**Electronic Submission**
REVIEW DIVISION:	**Division of Gastrointestinal and Coagulation Drug Products (HFD-180)**
PHARM/TOX REVIEWER:	**Ronald Honchel, Ph.D.**
PHARM/TOX SUPERVISOR:	**Jasti B. Choudary, B.V.Sc., Ph.D.**
DIVISION DIRECTOR:	**Brian Harvey, M.D., Ph.D.**
PROJECT MANAGER:	**Monika Houstoun, Pharm.D.**

Date of review submission to Division File System (DFS): **7/22/05**

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EXECUTIVE SUMMARY

No preclinical studies were submitted. The sponsor cross-referenced IND 26,093 and NDA 19-651 (Asacol 400 mg delayed-release tablets) to support this 505(b)(1) submission.

I. Recommendations

A. Recommendation on approvability

The application is recommended for approval.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

The proposed labeling for Asacol 800 mg delayed-release tablets was based on the approved labeling for Asacol 400 mg delayed-release tablets. The proposed labeling was evaluated and recommended changes to the proposed labeled are discussed on pages 7-10 of this review.

II. Summary of nonclinical findings

Brief overview of nonclinical findings:

A. Pharmacologic activity:

The exact mechanism of action of mesalamine is unknown. The mechanism of action of mesalamine is likely due to its anti-inflammatory properties. Mesalamine is rapidly and completely absorbed from the upper intestine when administered orally. However, the therapeutic action of mesalamine appears to be topical rather than systemic. The delayed release formulation is coated in a manner designed to release the mesalamine in the terminal ileum and beyond, allowing mesalamine to reach the colon.

B. Pharmacokinetics (ADME):

Few preclinical ADME studies have been performed on mesalamine. Unlike most drugs, therapeutic action for orally administered mesalamine is related to the amount of drug that reaches the colon (the amount of drug not absorbed) and not to systemic exposure. Systemic exposure was much less in dogs orally administered approximately 40 mg/kg Asacol 400 (68 ± 57 μg/mL·hr) compared to dogs orally administered approximately 40 mg/kg immediate release mesalamine (167 ± 41 μg/mL·hr). Orally administered mesalamine is extensively

metabolized by intestinal epithelial cell and liver N-acetyl-transferase 1 to N-acetyl-5-aminosalicylic acid in rodents, non-human primates, and humans, whereas dogs are poor acetylators of mesalamine.

C. Toxicology:

No new preclinical toxicology studies were submitted in support of this NDA submission. In preclinical toxicology studies submitted for NDA 19-651 and IND 26,093, kidney was the primary target organ of toxicity for mesalamine. Mesalamine did not affect reproduction or fertility in male and females rats, and was not teratogenic in rats or rabbits, at doses up to 480 mg/kg/day. Mesalamine was not mutagenic in the Ames test, Chinese hamster ovary cell chromosomal aberration assay, or the mouse micronucleus test. Dietary mesalamine was not carcinogenic in rats at doses up to 840 mg/kg/day or in mice at doses up to 2000 mg/kg/day.

D. Nonclinical safety issues relevant to clinical use:

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

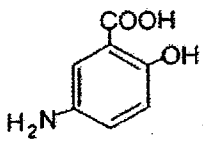
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-830
Review number: 01
Sequence number/date/type of submission: 000/October 22, 2004/Initial submission
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Procter & Gamble Pharmaceuticals, Inc., Mason, OH
Manufacturer for drug substance: b(4)

Reviewer name: Ronald Honchel, Ph.D.
Division name: Division of Gastrointestinal and Coagulation Drug Products
HFD #: 180
Review completion date:

Drug:

Trade name: Asacol® Delayed-Release Tablets, 800 mg
Generic name: Mesalamine
Code name: 5-aminosalicylic acid (5-ASA)
Chemical name: 5-amino-2-hydroxybenzoic acid
CAS registry number: 89-57-6
Molecular formula/molecular weight: 153.1
Structure:



Relevant INDs/NDAs/DMFs: NDA 19-651 (Asacol® Delayed-Release tablets, 400 mg; Procter & Gamble), IND 26,093 (Asacol® Delayed-Release tablets, 400 mg; Norwich Eaton Pharmaceuticals)

Drug class: Nonsteroidal anti-inflammatory

Intended clinical population: The treatment of patients with moderately active ulcerative colitis.

Route of administration: Oral

Clinical formulation: See sponsor's table below.

Composition Mesalamine Delayed-Release Tablets, 800 mg

Ingredient	Function	Unit Quantity (mg/tablet)	% w/w[a]
Tablet			
Mesalamine, USP	Active	800.00	
Lactose monohydrate, NF			
Sodium starch glycolate, NF			
Talc, USP			
Povidone, USP			
Magnesium stearate, NF			
Colloidal silicon dioxide, NF			
Methacrylic acid copolymer, NF, type B (Eudragit S			
Talc, USP			
Dibutyl phthalate, NF			
Ferric oxide, NF, red			
Methacrylic acid copolymer, NF, type A (Eudragit L			
Ferric oxide, NF, yellow			
Acetone, NF[b]			
Polyethylene glycol NF			
Printing			
Black Ink,			
Target Coated Tablet Weight			100%

b(4)

NA Not applicable
a % w/w in finished tablet
b Not present in final product
c Eudragit S methacrylic acid copolymer, NF, Type B
d Eudragit L methacrylic acid copolymer, NF, Type A
e In-house specification

b(4)

Disclaimer: Tabular and graphical information are constructed by the sponsor unless cited otherwise.

Studies reviewed within this submission: No preclinical studies were submitted.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

None submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No preclinical studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

None submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No preclinical studies were submitted.

2.6.6 TOXICOLOGY

None submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

No preclinical studies were submitted.

LABELING

The proposed labeling was based on the labeling currently approved for Asacol® 400mg Delayed-Release tablets. Significant changes were made to some of the preclinical portions of the proposed labeling. The preclinical portions of the proposed labeling compared to the original labeling are evaluated below.

PRECAUTIONS

Sponsor's Proposed Version:

b(4)

Evaluation: The dose levels stated as equivalents to human doses should be derived from doses based on body surface area. The original labeling for Asacol 400 mg Delayed-Release tablets stated "In animal studies (rats and dogs), the kidney is the

principal organ for toxicity. At doses of approximately 750 mg/kg to 1000 mg/kg [15 to 20 times the administered recommended human dose (based on a 50 kg person) on a mg/kg basis and 3-4 times on a mg/m^2 basis] mesalamine causes renal papillary necrosis." Only a few acute and subchronic animal toxicity studies had been performed in the original IND and NDA submissions. Several chronic studies have been submitted since including the data that showed renal toxicity at 170 mg/kg/day in a 6-month rat study and 80 mg/kg/day in a 12-month dog study. Additionally, the human dose of Asacol will be doubled compared to the dose originally approved (96 mg/kg/day compared to 48 mg/kg/day approved dose in NDA 19-651). The net result is there is no longer a safety factor for the daily dose of Asacol that induced kidney toxicity in animals compared to the proposed daily human dose for Asacol in NDA 21-830 **based on body surface area**. Since the therapeutic effect of mesalamine is local (not systemic) and major differences in metabolism are observed between species, comparisons between the animal and human AUC and C_{max} values are not valid.

Recommended Version:

Renal: Renal impairment, including minimal change nephropathy and acute and chronic interstitial nephritis, has been reported in patients taking **Asacol** tablets as well as other products that contain or are converted to mesalamine.

Caution should be exercised when using Asacol in patients with known renal dysfunction or history of renal disease. It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy.

In animal studies, the kidney was the principal organ for toxicity. Renal changes have occurred in dogs given chronic administration of mesalamine at doses of 80 mg/kg/day (0.5 times the recommended human dose based on body surface area). Similarly, in chronic rat studies, renal toxicity occurred at 170 mg/kg/day (0.3 times the recommended human dose based on body surface area).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Sponsor's Proposed Version:

b(4)

Evaluation: The original labeling stated that "Dietary mesalamine was not carcinogenic in rats at a 480 mg/kg/day...". The mg/kg/day value stated in the proposed version accurately reflects results from a more recent rat carcinogenicity study. However, dose comparisons should be made based on body surface area and to the **Asacol** 800 tablet daily dose of 4.8 g/day, not the **Asacol** 400 tablet maintenance dose.

Recommended Version:

Dietary mesalamine was not carcinogenic in rats at doses up to 840 mg/kg/day (approximately 1.4 times the recommended human dose based on body surface area), or in mice at doses up to 2000 mg/kg/day (approximately 1.7 times the recommended human dose based on body surface area). Mesalamine was not genotoxic in the Ames test, the Chinese hamster ovary cell chromosomal aberration assay, and the mouse micronucleus test. Mesalamine, at doses up to 480 mg/kg/day (approximately 0.8 times the recommended human dose based on body surface area), had no adverse effect on fertility or reproductive performance of male and female rats.

Pregnancy: Teratogenic Effects:

Sponsor's Proposed Version:

b(4)

Evaluation: The sponsor's proposed version is the same as the original version. Dose comparisons should be based on body surface area. Labeling should also reflect current labeling guidelines (CFR 21 Part 201.57).

Recommended Version:

Pregnancy: Teratogenic Effects:

Pregnancy Category B: Reproduction studies have been performed in rats at oral doses up to 480 mg/kg (approximately 0.8 times the recommended human dose based on body surface area) and in rabbits at oral doses up to 480 mg/kg (approximately 1.6 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

OVERDOSAGE

Sponsor's Proposed Version:

b(4)

Evaluation: Dog results should be deleted. Dose levels stated as equivalents of human doses should be based on body surface area. The maximum non-lethal dose could not be

determined based on the information provided by the sponsor or from previous IND/NDA Pharmacology and Toxicology Reviews. The 5000 and 4595 mg/kg values stated as causing significant lethality for mice and rats were listed as LD_{50} values in a table provided by the sponsor.

Recommended Version:

There are no documented reports of serious human toxicity following overdose with mesalamine. There is no specific antidote for mesalamine overdose, and treatment is symptomatic and supportive.

Single oral doses of 5000 mg/kg in mice (approximately 4.2 times the recommended human dose based on body surface area), 4595 mg/kg in rats (approximately 7.8 times the recommended human dose based on body surface area), and 3000 mg/kg in cynomolgus monkeys (approximately 10 times the recommended human dose based on body surface area) were lethal.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

No preclinical studies were submitted in this application. The sponsor cross-referenced IND 26,093 and NDA 19-651 (Asacol 400 mg delayed-release tablets) to support this 505(b)(1) submission.

Asacol® (mesalamine) 400 mg delayed-release tablets are currently approved for the treatment of mildly to moderately active ulcerative colitis and maintenance of remission of ulcerative colitis. The exact mechanism of action of mesalamine is unknown. The mechanism of action of mesalamine is likely due to its anti-inflammatory properties. Mesalamine is rapidly and completely absorbed from the upper intestine when administered orally. However, the therapeutic action of mesalamine appears to be topical rather than systemic. The delayed release formulation is coated in a manner designed to release the mesalamine in the terminal ileum and beyond, allowing mesalamine to reach the colon.

Few preclinical ADME studies have been performed. Unlike most drugs, therapeutic action for orally administered mesalamine is related to the amount of drug that reaches the colon (the amount of drug not absorbed) and not to systemic exposure. Systemic exposure was much less in dogs orally administered approximately 40 mg/kg Asacol 400 (68 ± 57 μg/mL·hr) compared to dogs orally administered approximately 40 mg/kg immediate release mesalamine (167 ± 41 μg/mL·hr). Orally administered mesalamine is extensively metabolized by intestinal epithelial cell and liver N-acetyl-transferase 1 to N-acetyl-5-aminosalicylic acid in rodents, non-human primates, and humans, whereas dogs are poor acetylators of mesalamine.

The primary target organ of toxicity for mesalamine is the kidney. In a 3-month mouse toxicity study, lethality was observed a doses of 4000 mg/kg and greater. Histopathology was performed for only the 2000 and 4000 mg/kg groups with bladder inflammation

observed in the 2000 and 4000 mg/kg female groups, and renal tubular nephrosis, tubulo-interstitial inflammation, and renal papillary necrosis observed in the 4000 mg/kg male group. In a 6-month rat toxicity study, papillary edema and tubular degeneration of the kidney were observed in the 170 and 360 mg/kg dose groups. Necrosis of the renal papilla, tubular mineralization, urothelial hyperplasia, inflammation of the urinary bladder, and mucosal/submucosal fibrosis of the stomach were also observed in the 360 mg/kg dose groups. In a one-year dog toxicity study, chronic nephritis was observed in 80 and 160 mg/kg dose groups.

Mesalamine had no adverse effect on fertility or reproductive performance in male and female rats at oral doses up to 480 mg/kg/day (approximately 0.8 times the recommended human dose based on body surface area), and was not teratogenic in rats or rabbits at oral doses up to 480 mg/kg/day (approximately 0.8 and 1.6 times, respectively, the recommended human dose based on body surface area).

Mesalamine was not genotoxic in the Ames test, the Chinese hamster ovary cell chromosomal aberration assay, and the mouse micronucleus test.

Dietary mesalamine was not carcinogenic in a 2-year rat study at oral doses up to 840 mg/kg/day, or in a 2-year mouse study at doses up to 2000 mg/kg/day.

The Sponsor's drug product is an 800 mg modified delayed-release formulation similar to the already approve Asacol 400 mg delay-release formulation. Asacol 400 mg has been approved at a dose of 2.4 g/day for a duration of 6 weeks in the treatment of mild to moderately active ulcerative colitis and 1.6 g/day for the maintenance of remission of ulcerative colitis. The proposed indication for Asacol 800 mg is moderately active ulcerative colitis and the proposed dose is 4.8 g/day for 6 weeks. All the inactive ingredients in Asacol 800 mg tablets are listed on FDA's inactive ingredient list and will be administered at quantities that have been previously approved by the FDA. From a preclinical standpoint, adequate pharmacology, ADME, and toxicology studies were available to evaluate this submission. Therefore, from a preclinical viewpoint, this application is recommended for approval.

Unresolved toxicology issues:

None.

Recommendations:

From a preclinical viewpoint, the application is recommended for approval with a provision that the labeling be changed as described in the "Labeling" section.

Ronald Honchel, Ph.D. Date
Pharmacologist, HFD-180

Comment:

Jasti B. Choudary, B.V.Sc., Ph.D. Date
Supervisory Pharmacologist, HFD-180

cc:
IND
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Honchel
HFD-048/Dr. Viswanathan
R/D Init. J. Choudary 6/22/05

APPENDIX/ATTACHMENTS

None.

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

/s/

Ronald Honchel
7/22/05 06:22:30 AM
PHARMACOLOGIST

Jasti Choudary
7/22/05 10:47:10 AM
PHARMACOLOGIST