CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-000

PHARMACOLOGY REVIEW(S)

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:	**22,000**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**12/21/05**
PRODUCT:	**Mesavance™ (mesalamine) Delayed Release Tablets**
INTENDED CLINICAL POPULATION:	**Patients with active, mild to moderate ulcerative colitis**
SPONSOR:	**Shire US Inc.**
DOCUMENTS REVIEWED:	**Not applicable (electronic submission)**
REVIEW DIVISION:	**Division of Gastroenterology Products (HFD-180)**
PHARM/TOX REVIEWER:	**David B. Joseph, Ph.D.**
PHARM/TOX SUPERVISOR:	**Jasti B. Choudary, B.V.Sc., Ph.D.**
DIVISION DIRECTOR:	**Brain E. Harvey, M.D., Ph.D.**
PROJECT MANAGER:	**Kristen Everett**

Date of review submission to Division File System (DFS): July 28, 2006

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

From a preclinical viewpoint, the application should be approved.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Revisions are needed in the "Renal", "Carcinogenesis, mutagenesis, impairment of fertility", and "Pregnancy" subsections. Wherever applicable, the final labeling should contain preclinical information that is the same as that in the approved labeling for Pentasa®. The Sponsor referred to NDA 20,049 (Pentasa® Controlled-Release Capsules) to support the approval of this application.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Mesalamine is a non-steroidal anti-inflammatory drug. Its mechanism of action in the treatment of ulcerative colitis is not completely understood, but appears to be topical rather than systemic. It is proposed that mesalamine reduces inflammation through inhibition of cyclooxygenase in the colon. The Sponsor submitted two published reports containing pharmacology studies, in support of a statement in the proposed labeling that provides new information about the mechanism of action. One of these studies demonstrated that treatment of ulcerative colitis patients with mesalamine (1.5-4.5 g/day) produced a decrease in NF-κB activation in the affected colon segments. The other study showed that mesalamine (20 mM) prevented TNF-α activation of NF-κB in mouse colon cell cultures. The toxicity of mesalamine was previously evaluated in repeat-dose studies in mice (13 weeks), rats (13 and 52 weeks), and monkeys (13 and 52 weeks). These studies were presented in the Pharmacology Review of NDA 20,049 dated June 3, 1991. In all species, kidney was the primary target organ of toxicity. Renal toxicity occurred at dose levels of 1200 mg/kg/day and higher in mice, 480 mg/kg/day and higher in rats, and 250 mg/kg/day and higher in monkeys. The severity of the renal lesions was sufficient to produce death in rats at 1200 mg/kg/day and in monkeys at 250 mg/kg/day. However, a NOAEL (no observed adverse effect level) or tolerated dose was established in each of the repeat-dose toxicity studies. Spleen and thymus were target organs of toxicity in rats, but only at doses associated with mortality.

B. Pharmacologic activity

See "Brief overview of nonclinical findings" above.

C. Nonclinical safety issues relevant to clinical use

Mesalamine has been shown to produce severe kidney toxicity in rats and monkeys. In addition, there are reports of renal toxicity (e.g. interstitial nephritis) in humans given mesalamine therapy. Given the results of the clinical studies with Mesavance™, and the extensive human experience with approved products containing mesalamine, the renal effects in animals are not considered to be a major safety concern. However, the final labeling should contain information about renal toxicity in animals, similar to that in the approved labeling for Pentasa®.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22,000

Review number: 1

Sequence number/date/type of submission: 000/December 21, 2005/Original

Information to sponsor: Yes (x) No ( )

Sponsor and/or agent: Shire US Inc.
Wayne, Pennsylvania

Manufacturers for drug substance:

Reviewer name: David B. Joseph, Ph.D.

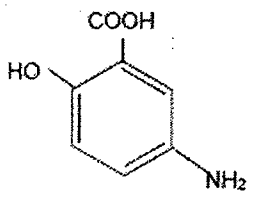
Division name: Gastroenterology Products

HFD #: 180

Review completion date: July 28, 2006

Drug:

Trade name: Mesavance™
Generic name: Mesalamine
Code name: SPD476
Chemical name: 5-Amino-2-hydroxybenzoic acid; 5-Aminosalicylic acid
CAS registry number: 89-57-6
Molecular formula/molecular weight: $C_7H_7NO_3$/153.14
Structure:



Relevant INDs/NDAs/DMFs: IND 66,193/NDA 19,651 (Asacol® Delayed-Release Tablets)/NDA 20,049 (Pentasa® Controlled-Release Capsules)/NDA 21,252 (Canasa® Rectal Suppositories)/NDA 19,618 (Rowasa® Rectal Suspension Enema)

Drug class: NSAID

Intended clinical population: adult patients with active, mild to moderate ulcerative colitis

Clinical formulation: Delayed ___ release tablets. The ingredients are shown in the table below. The drug substance is listed as "Mesalazine", which is an alternative name for mesalamine.

Table 1: Composition of SPD476 1.2g Tablets

Ingredient	Amount (mg)	Function	Reference to Standards
Drug substance(s) Mesalazine	1200.0	Active ingredient	EP and USP/NF
Excipient(s)			
Sodium Carboxymethylcellulose			EP and USP/NF
Sodium Carboxymethylcellulose			EP and USP/NF
Carnauba Wax			EP and USP/NF
Stearic Acid			EP and USP/NF
Silica, Colloidal Hydrated			EP and USP/NF
Sodium Starch Glycolate (Type A)			EP and USP/NF
Talc			EP and USP/NF
Magnesium Stearate			EP and USP/NF
			EP and USP/NF
			EP and USP/NF
Methacrylic Acid Copolymer, Type A[2]			EP and USP/NF
Methacrylic Acid Copolymer, Type B[2]			EP and USP/NF
Triethylcitrate[2]			EP and USP/NF
Titanium Dioxide[2]			EP and USP/NF
Red Ferric Oxide (Ferric Oxide)[2]			USP/NF
Polyethylene glycol 6000[2]			EP and USP/NF
			EP and USP/NF
			EP and USP/NF
Total	1385.0		

EP. European Pharmacopoeia; NF United States National Formulary; USP United States Pharmacopoeia.

Route of administration: oral

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

Studies reviewed within this submission:

The Sponsor referred to NDA 20,049 (Pentasa® Controlled-Release Capsules) to provide the needed preclinical information. Two published reports of pharmacology studies were submitted in support of a statement in the proposed labeling that describes the mechanism of action.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

The Sponsor submitted two publications that demonstrate the ability of mesalamine to inhibit the activation of NF-κB. These studies are supportive of a statement in the "CLINICAL PHARMACOLOGY" section of the proposed labeling.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Mesalamine is a non-steroidal anti-inflammatory drug. Its mechanism of action in the treatment of ulcerative colitis is not completely understood, but appears to be topical rather than systemic. In the labeling of the approved mesalamine products, it is proposed that mesalamine reduces inflammation through inhibition of cyclooxygenase in the colon. Mucosal production of arachidonic acid metabolites through cyclooxygenase and lipoxygenase activity is increased in patients with inflammatory bowel disease. In the proposed labeling for Mesavance™, the Sponsor suggests that mesalamine can inhibit the activation of NF-κB, a nuclear transcription factor that regulates the transcription of many genes for pro-inflammatory proteins. Studies that support this proposal were included in this application, and are reviewed below.

Effects of Mesalamine Therapy on NF-κB Activation in the Colonic Mucosa of Patients with Ulcerative Colitis

Bantel et al, Am J Gastroenterol, 95, pg. 3452-3457, 2000.

Methods: Twenty patients with moderately active ulcerative colitis were treated orally with 1.5-4.5 g/day mesalamine for eight weeks. All immunosuppressive medication was withheld from the subjects starting at four weeks prior to initiation of mesalamine treatment. Biopsies of the affected colon segments were obtained before and after treatment period. Activation of NF-κB (nuclear factor-κB) was measured using an immunohistochemical staining method. Sections of colon were exposed to a mouse monoclonal antibody (IgG3) selective for the

activated p65 subunit of NF-κB, followed by exposure to biotinylated goat anti-mouse IgG, avidin conjugated with horseradish peroxidase, and substrate. Staining of tissue sections was also performed using a Cy3-conjugated goat anti-mouse antibody. Macrophages were identified using a FITC-conjugated anti-CD14 antibody. Subsequent to the initial staining procedure, all sections were stained with hematoxylin. Tissue sections were scored for activation of NF-κB, based on the proportion of cells that exhibited binding of antibodies for the activated p65 subunit of NF-κB.

Results: In the initial experiments, activated NF-κB was detected in the lamina propria of untreated ulcerative colitis patients, whereas little or no staining was observed in non-inflamed tissue from control individuals (not defined). The effect of mesalamine therapy on NF-κB activation in colon is shown in the table below.

NF-κB Activation Score Before and After Mesalamine Therapy

Score	Before	After
0	5	15
+	5	4
++	6	1
+++	4	0

Scoring Scale

\+ 2-5% of cells positive for NF-κB activation

\+ + 5-10% of cells positive for NF-κB activation

\+ + + 10-25% of cells positive for NF-κB activation

The results show that mesalamine treatment produced a reduction in the proportion of cells containing activated NF-κB. These cells were mostly macrophages in the lamina propria.

Effects of Mesalamine on TNF-α-Stimulated NF-κB Translocation in Young Adult Mouse Colon Cells

Kaiser et al, Gastroenterology, 116, pg. 602-609, 1999.

YAMC (young adult mouse colon) cell cultures were incubated in the presence or absence of mesalamine (20 mM) for 30 min. The incubation was continued for an additional 30 min in the presence of 100 ng/ml TNF-α. The cells were then fixed and incubated with antibodies specific for the p65 subunit of NF-κB. Cells were then exposed to anti-rabbit IgG antibody conjugated to Cy3 for detection by confocal laser immunofluorescent microscopy. Cell images showed that prior to TNF-α exposure, NF-κB was primarily located in the cytoplasm (inactivated state). Treatment with TNF-α produced an almost complete translocation of NF-κB to the nucleus (activated state), which was prevented by pretreatment with mesalamine. In a follow-up experiment, the authors demonstrated that mesalamine also inhibited the degradation of Iκ-Bα, a principal regulator of NF-κB activation.

4 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Mesalamine (5-aminosalicylic acid or 5-ASA) is a non-steroidal anti-inflammatory drug that is approved for treatment of ulcerative colitis and ulcerative proctitis. Mesalamine is an active metabolite of sulfasalazine, which is also approved for treatment of ulcerative colitis. Approved products containing mesalamine include Asacol® Delayed-Release Tablets (NDA 19,651), Pentasa® Controlled-Release Capsules (NDA 20,049), Canasa® Rectal Suppositories (NDA 21,252), and Rowasa® Rectal Suspension Enema (NDA 19,618). The present application is for Mesavance™ Delayed — Release Tablets. This novel formulation contains mesalamine — coated with a polymer that is resistant to acidic pH and degrades at pH 7. When the enteric coating degrades, ' the drug diffuses out of the — The Sponsor claims that —

The Agency did not request preclinical studies to support the approval of this application, given the availability of preclinical information from other approved drug products containing mesalamine. The Sponsor cited its own NDA for Pentasa® (NDA 20,049) to support approval of the present application. In addition, the Sponsor submitted two published reports of pharmacology studies in support of a new statement in the "CLINICAL PHARMACOLOGY" section of the proposed labeling. One of these studies demonstrated that treatment of ulcerative colitis patients with mesalamine produced a decrease in NF-κB (nuclear factor-κB) activation in the affected colon segments. The other study showed that mesalamine prevented TNF-α activation of NF-κB in mouse colon cell cultures.

The proposed indication for Mesavance™ is the induction of remission of active, mild to moderate ulcerative colitis. The proposed dose level for Mesavance™ is 2.4 to 4.8 g/day (48 to 96 mg/kg/day based on a 50-kg bodyweight) for eight weeks, whereas the highest approved oral dose level of mesalamine is 4 g/day (Pentasa® Controlled-Release Capsules). Thus, the proposed maximum dose level is slightly higher than the highest approved dose level. Toxicology studies with information relevant to the proposed dose and duration of treatment for Mesavance™ are available in NDA 20,049 (Pentasa® Controlled-Release Capsules). These studies were reviewed in the Pharmacology Review of NDA 20,049 dated June 3, 1991, and are summarized below.

A 13-week dietary toxicity study in mice was performed using dose levels of 0, 300, 1200, 2400, and 4800/4000 mg/kg/day mesalamine. The high dose was reduced from 4800 to 4000 mg/kg/day after five days due to mortality. Kidney was a target organ of toxicity at 1200, 2400, and 4800/4000 mg/kg/day. Since renal lesions (i.e. hydronephrosis) in the 1200 mg/kg/day group occurred in only 2/30 mice, the maximum tolerated dose is considered to be 1200 mg/kg/day. Granular and hyaline casts were observed at 2400 and 4800/ 4000 mg/kg/day. The NOAEL (no observed adverse effect level) in females was 300 mg/kg/day. A NOAEL was not established in males due to impaired weight gain in the 300, 1200, and 4800/4000 mg/kg/day groups.

A 13-week dietary toxicity study in rats was performed using dose levels of 0, 200, 480, 1150, and 2770 mg/kg/day mesalamine. The NOAEL was 200 mg/kg/day, and the maximum tolerated dose was 480 mg/kg/day. Approximately one half of the 2770 mg/kg/day group died by week 10. Severe renal toxicity was observed in this group, in which most animals exhibited papillary necrosis, dilated tubules, tubular degeneration, and tubular regeneration. A smaller proportion of the 2770 mg/kg/day group also had renal inflammation, mineralization in pelvis, tubular necrosis, granular cast formation, and renal fibrosis. Renal toxicity also occurred in the 1150 mg/kg/day males. The 480 mg/kg/day group exhibited increased BUN, decreased urine pH, and increased urine specific gravity in the absence of microscopic lesions, indicative of mild renal toxicity. The effects on urine pH and specific gravity were dose-dependent. Other target organs of toxicity in the 2770 mg/kg/day group included spleen, thymus, and stomach.

A 52-week dietary toxicity study in rats was performed using dose levels of 0, 200, 400, 800, and 1200/1600/1200 mg/kg/day mesalamine. The maximum tolerated dose was 800 mg/kg/day, and the NOAEL was 400 mg/kg/day. Death occurred in several males in the 1200/1600/ 1200 mg/kg/day group. Kidney was a target organ of toxicity in groups treated with 800 or 1200/1600/1200 mg/kg/day. However, renal lesions in the 800 mg/kg/day group were limited to hemorrhage in 3/20 rats, whereas each animal in the 1200/1600/1200 mg/kg/day group exhibited papillary necrosis and interstitial nephritis. Atrophy of spleen and thymus occurred in the 1200/1600/1200 mg/kg/day group.

A 13-week oral toxicity study in monkeys was performed using dose levels of 0 (vehicle), 125, 250, and 500 mg/kg/day mesalamine. The NOAEL was 125 mg/kg/day. Mortality occurred at 250 and 500 mg/kg/day (females only). Renal interstitial fibrosis was observed in the dead animals. This lesion also occurred in the surviving 500 mg/kg/day females. Fatty and pale liver was observed in the 250 mg/kg/day female that was sacrificed prematurely.

A 1-year oral toxicity study in monkeys was performed using dose levels of 0, 125, 250, and 500 mg/kg/day mesalamine. Deaths occurred in the 500 mg/kg/day group due to marked kidney toxicity (i.e. nephrosis). Renal toxicity also occurred in the 250 mg/kg/day males. Small and large intestine were target organs of toxicity in the 500 mg/kg/day males. The NOAEL was 125 mg/kg/day.

In all species, kidney was the primary target organ of toxicity. Renal toxicity occurred at dose levels of 1200 mg/kg/day and higher in mice, 480 mg/kg/day and higher in rats, and 250 mg/kg/day and higher in monkeys. The proposed maximum human dose is 4.8 g/day, which is equal to 96 mg/kg/day in a 50-kg individual. Therefore, dose levels that produced renal toxicity in animals exceeded the proposed maximum clinical dose for Mesavance™, albeit by small margins. In addition, a NOAEL or tolerated dose was established in each of the repeat-dose toxicity studies. Spleen and thymus were target organs of toxicity in rats, but only at doses associated with mortality.

The most relevant information about the safety of Mesavance™ is contained within the submitted clinical studies. The Sponsor submitted two double-blind, placebo-controlled studies of Mesavance™ to support the efficacy and safety of this product. In both studies, ulcerative colitis patients were treated for eight weeks with 2.4 or 4.8 g/day, which are the proposed dose

levels. The drug was well tolerated at both dose levels. Given the results of the clinical studies with Mesavance™, and the extensive human experience with approved products containing mesalamine, the renal effects in animals are not considered to be a major safety concern.

For each of the excipients in Mesavance™, the daily intake associated with the proposed maximum dose of mesalamine is less than or approximately equal to the daily intake that occurs with other approved drug products for oral administration. Therefore, there are no safety concerns with respect to excipient-related toxicity.

Unresolved toxicology issues:

None.

Recommendations:

From a preclinical viewpoint, the application should be approved, with the provision that the "Renal", "Carcinogenesis, mutagenesis, impairment of fertility", and "Pregnancy" subsections of the proposed labeling will be changed as described in the "LABELING" section of this review.

Suggested labeling: The labeling should be changed as described in the "LABELING" section of this review.

Reviewer Signature _____
David B. Joseph, Ph.D.
Pharmacologist, HFD-180

Supervisor Signature_____Concurrence Yes ___ No ___
Jasti B. Choudary, B.V.Sc., Ph.D.
Supervisory Pharmacologist, HFD-180

cc:
Orig NDA 22,000
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Joseph

R/D Init.: J. Choudary 7/5/06

DJ/dbj: 7/28/06
C:\DATA\N22000608.0DJ

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/

David Joseph
7/28/2006 10:58:08 AM
PHARMACOLOGIST

Jasti Choudary
8/3/2006 01:49:31 PM
PHARMACOLOGIST