CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA (Class II Resubmission; Complete Response to Approvable Letter)
Submission Number	21-830
Letter Date	October 22, 2007
Stamp Date	October 22, 2007
PDUFA Goal Date	April 22, 2008
Reviewer Name	Anil Rajpal, M.D.
Review Completion Date	May 29, 2008
Established Name	mesalamine
(Proposed) Trade Name	Asacol(R) 800
Therapeutic Class	Locally Acting Aminosalicylate
Applicant	Procter & Gamble
Priority Designation	S (Standard)
Formulation	Delayed-release tablets containing 800 mg mesalamine
Dosing Regimen	4.8 g/day PO (divided into three 1.6 g doses taken morning, midday, and evening)
Indication	Treatment of moderately active ulcerative colitis (UC)
Intended Population	Moderately active ulcerative colitis (UC) patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Asacol 800 delayed-release tablets at a dose of 4.8 g/day be approved for the treatment of adult patients with moderately active ulcerative colitis with revisions to the proposed labeling. The information in this submission provides substantial evidence to support the proposed indication, and there are data to provide adequate directions for use.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no applicable activity related to risk management for this New Drug Application (NDA).

1.2.2 Required Phase 4 Commitments

Safety and efficacy have not been established in pediatric patients. Partial waiver was granted for patients age 0 to 4 years old from enrollment in future UC pediatric studies with Asacol 800 during the first review cycle of this NDA. This reviewer recommends that pediatric studies in age 5 to 17 years old UC patients be deferred, that the Asacol 400 mg tablets be the age-appropriate formulation for Asacol 800, and that a required Phase 4 commitment for Asacol 800 be the completion of the following postmarketing study:

(1) A randomized, double-blind study of six weeks of at least two dose levels in pediatric patients ages 5 to 17 years to evaluate the safety and effectiveness of those doses and to compare with results seen in adults. The study should include at least 40 patients in each dosage arm; in each arm, five patients should be age 5 years to 8 years. A protocol should be submitted by August 15, 2008, study should start by October 15, 2008, study should be completed by November 13, 2009, and study report should be submitted by January 15, 2009.

1.2.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Asacol®(mesalamine) 400 mg delayed-release tablets were approved in 1992 for treatment of mildly to moderately active UC at a dose of 2.4 g/day for six weeks. Asacol 400 mg tablets were also approved in 1997 for the maintenance of remission of UC at a dose of 1.6 g/day for six months.

The applicant submitted a New Drug Application (NDA 21-830) on October 22, 2004, seeking approval for Asacol 800 mg delayed-release tablets at a dose of 4.8 g/day given in three divided daily doses for the treatment of moderately active UC for six weeks. Two studies (Study 82 and Study 83) were conducted in support of that application. An Approvable Letter was sent to the applicant on August 25, 2005, outlining the reason for the approvable action as follows (see also Clinical Review by Dr. Fathia Gibril dated August 26, 2005, and Statistics Review by Dr. Milton Fan dated August 4, 2005):

- Insufficient proof of the superiority of Asacol 800 mg dosed at 4.8 g/day over Asacol 400 mg dosed at 2.4 g/day to support your proposed indication of treatment of moderately active ulcerative colitis.

In order to resolve this deficiency, the applicant was given the recommendations below in that Approvable Letter:

- Provide at least one additional adequate and well-controlled study to demonstrate the added clinical benefit of Asacol 800 mg tablets at a dose of 4.8 g/day compared to Asacol 400 mg at 2.4 g/day in moderately active ulcerative colitis patients.
- Explain why Asacol 800 mg at 4.8 g/day was more efficacious than Asacol 400 mg at 2.4 g/day in male patients.

In this submission, the applicant has provided the results of an additional study (Protocol #2006444, ASCEND III) of Asacol 800 dosed 4.8 g/day versus Asacol dosed 2.4 g/day for the treatment of patients with moderately active UC. It should be noted that while the study was being conducted, the applicant amended the protocol to increase the sample size from 470 to 770 patients, and to change the primary objective from a test of superiority of Asacol 800 4.8 g/day to a test of non-inferiority between the two arms.

1.3.2 Efficacy

In the first cycle of review of NDA 21-830 that was completed in August 2005, it was determined that neither study 82 nor Study 83 showed statistically significant differences in treatment success in the overall mildly to moderately active UC population (PGA=1-2). In the mild UC subgroup (PGA=1), both studies showed lower rates of treatment success for 4.8 g/day (Study 83: 35.0% for Asacol 800 vs. 42.1% for Asacol; Study 82: 32.8% for Asacol 800 vs. 40.4% for Asacol).

In a post hoc analysis of the moderately active UC subgroup (PGA=2) in Study 83, the results appeared to show superiority of Asacol 800 (55.9% for Asacol 800 vs. 51.3% for Asacol; p=0.0384), but more patients were excluded from the Applicant's ITT analysis in the Asacol 800 4.8 g/day group than the Asacol 2.4 g/day group (8 for Asacol 800 vs. 3 for Asacol; see Dr. Milton Fan's review). Study 83 was completed first, and modifications to Study 82 were made based on results of Study 83.

The Study 82 protocol was amended (after 96% enrolled) to change the population from mildly to moderately active UC to those with moderately active UC at baseline and enroll up to 100

additional moderately active UC patients (82 additional enrolled); the results of the study were considered to be a post-hoc analysis because the focus changed to the moderately active UC subgroup and because the sample size changed (see Dr. Milton Fan's review). In the analysis of the moderately active UC subgroup of Study 82, superiority was shown (71.8% for Asacol 800 vs. 59.2% for Asacol; p=0.0357), but the benefit was driven by male patients (76% for Asacol 800 vs. 50% for Asacol in males; 69% for Asacol 800 vs. 67% for Asacol in females). The applicant was given the recommendation to provide at least one additional adequate and well-controlled study to demonstrate the added clinical benefit of Asacol 800 mg tablets at a dose of 4.8 g/day compared to Asacol 400 mg at 2.4 g/day in moderately active ulcerative colitis patients in the Approvable Letter of August 25, 2005.

When another mesalamine product, Lialda, was approved based on two three-arm (2.4 g/day, 4.8 g/day, and placebo) studies, the applicant contended that Asacol 800 (4.8 g/day) should be approved on the basis of demonstration of non-inferiority (NI) with Asacol (2.4 g/day) because Lialda (4.8 g/day) was not required to show a therapeutic benefit over Lialda (2.4 g/day). The Division agreed to consider the applicant's proposal if important details of the proposed NI study such as entry criteria and primary endpoint adhere to those of the placebo-controlled trials. The Division's final decision to accept the NI design included the following considerations: (1) There were no increased safety concerns identified in the completed studies of Asacol 800 (4.8 g/day) compared to Asacol (2.4 g/day); (2) There were no dose-related safety concerns over the range of 2.4 g/day to 4.8 g/day identified in studies of other mesalamine products; (3) The ratio of systemic exposure of Asacol 800 (4.8 g/day) to Asacol 400 mg tablets (2.4 g/day) is expected to be less than two-fold because the two products are not bioequivalent; the ratio is expected to be 1.5 times (based on AUC) and 1.3 times (based on Cmax) because one Asacol 800 tablet has a 25% lower AUC and a 36% lower Cmax than two Asacol 400 mg tablets.

In this submission dated October 22, 2007, the applicant submitted the results of study 2006444. Of the total of 772 patients with moderately active UC, 383 patients were assigned to the Asacol 2.4 g/day group, and 389 patients were assigned to the Asacol 800 (4.8 g/day) group.

The primary efficacy analysis (treatment success at Week 6) demonstrated statistical non-inferiority between Asacol 800 (4.8g/day) and Asacol (2.4g/day). Treatment success rates were 70.2% in the Asacol 800 group and 65.5% in the Asacol group. The difference (Asacol 800 – Asacol) was 5% (95% confidence interval: [-1.9%, 11.2%]).

The secondary efficacy analysis demonstrated the following: (1) Treatment success at Week 6 was similar for male and female subjects by treatment group. (2) The rates of improvement for individual clinical assessments (stool frequency, rectal bleeding, PFA, sigmoidoscopy) and composite scores (PGA and UCDAI) by Week 6 were similar by treatment group. (3) Success rates by treatment group at Week 6 in patients with left-sided disease were similar to those of the overall study population. (4) Stool frequency improvement by Week 3 was higher with Asacol 800 (4.8 g/day) than with Asacol 2.4g/day (76% vs. 66%; p=0.0019) but statistical measures to correct for multiple comparisons were not conducted and had not been pre-specified in the protocol.

The applicant adequately responded to the recommendations in the Approvable Letter. First, the applicant conducted an additional adequate and well-controlled study; based on agreements in meetings that occurred after the approvable action, the study demonstrated non-inferiority rather than superiority. Second, the applicant addressed the question of why Asacol 800 (4.8 g/day) was more efficacious than Asacol 400 mg tablets (2.4 g/day) in male patients by including a comparison by gender of treatment success at Week 6 by treatment group in Study 2006444 as a secondary endpoint; similar treatment success at Week 6 was found in Study 2006444 for male and female subjects by treatment group.

1.3.3 Safety

In the safety review of the original NDA 21-830 application (based on Studies 82 and 83), nausea and vomiting was identified as occurring at a two to three times higher rate for the Asacol 800 (4.8 g/day) arm compared to the Asacol 400 mg tablets (2.4 g/day) arm. However, the overall safety profile was deemed comparable between the two arms. (See Clinical Review by Dr. Fathia Gibril dated August 26, 2005.)

One focus of the current safety review was to determine if the Asacol 800 (4.8 g/day) arm and the Asacol 400 mg tablets (2.4 g/day) arm have a comparable safety profile. Another focus was to determine if the risk of renal impairment is increased with Asacol 800 at 4.8 g/day over the currently approved Asacol 400 mg tablets (2.4 g/day). The current label for Asacol states in the Warnings and Precautions section that "Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported...."

Across the three studies (Studies 82, 83, & 2006444), 727 patients received Asacol 800 (4.8 g/day) and 732 patients received Asacol 2.4 g/day for a mean duration of approximately six weeks. Overall, a comparable safety profile between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day was found with some notable points.

SAEs were less common in the Asacol 800 group than in the Asacol group (0.8% vs. 1.8%); this is partly accounted for by a lower incidence of UC exacerbations in the Asacol 800 group than in the Asacol 2.4 g/day group (2.3% vs. 2.7%). Moderate AEs were more common in the Asacol 800 (4.8 g/day) group than the Asacol 2.4 g/day group (37% vs. 30%). Mild AEs were more common in the Asacol 2.4 g/day group than the Asacol 800 (4.8 g/day) group (55% vs. 63%).

The overall incidence of AEs seen with Asacol 800 therapy (27.7%) was similar to the overall incidence of adverse reactions seen with the Asacol 400 mg tablet (28.8%). The most common AEs reported (> 2% in either group) were nausea, abdominal pain, nasopharyngitis, headache, and exacerbation of ulcerative colitis.

Upper respiratory infections were more common in the Asacol 800 (4.8 g/day group than in the Asacol 2.4 g/day group (4.0% vs. 3.1%); this is largely accounted for by a higher incidence of nasopharyngitis in the Asacol 800 (4.8 g/day) group than in the Asacol 2.4 g/day group (2.5% vs. 1.4%).

The incidence of nausea and vomiting symptoms appears to be of similar magnitude in both treatment groups (3.3% in both groups). The finding of a higher incidence of nausea and vomiting in the 4.8 g/day Asacol 800 group than the Asacol 2.4 g/day group from the previous review (based on Studies 82 and 83) appears to not be present in the larger combined dataset that also includes the new study, Study 2006444.

The mean change in creatinine was +1% from Baseline to Week 6 in both treatment groups; the number of subjects with a normal to high shift was 4 in the 2.4 g/day arm and 1 in the 4.8 g/day arm. Although no evidence of change in renal function was identified based on the studies submitted, this may be because the duration of follow-up may not have been long enough and because there may not have been enough patients for a change in renal function to be identified. There was one case of nephritis in the 2.4 g/day group.

Since April 2005, Asacol 800 at a dose of 4.8 g/day has been marketed in Canada; the Applicant estimates that the exposure is approximately 11,000 patient-years. Ten spontaneous reports have been received, all of which were non-serious AEs.

1.3.4 Dosing Regimen and Administration

This reviewer recommends that the dose of Asacol 800 be two 800 mg tablets (1.6 g) to be taken three times a day for a total daily dose of 4.8 g for six weeks. Asacol 800 use beyond 6 weeks has not been evaluated. Asacol 800 should be swallowed whole without cutting, breaking, or chewing. One Asacol 800 tablet is not interchangeable with two Asacol 400 mg tablets, because the relative bioavailability study showed that the mean Cmax was 36% lower and the mean AUC was 25% lower with administration of the 800 mg tablet relative to two 400 mg tablets.

1.3.5 Drug-Drug Interactions

There are no known drug interactions with Asacol, and no drug-drug interaction studies were performed in this clinical development program.

1.3.6 Special Populations

Asacol 800 has not been studied in enough patients with renal insufficiency, hepatic insufficiency, age $\geq$ 65, age < 18, or in women who are pregnant or nursing to assess safety and efficacy in these populations. Asacol 800 should be used during pregnancy only if clearly needed.

It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol 800 and periodically while on therapy. Caution should be exercised when using Asacol 800 in patients with known renal dysfunction or history of renal disease.

Reports from uncontrolled clinical studies and postmarketing reporting systems for Asacol (mesalamine) suggested a higher incidence of blood dyscrasias, i.e., agranulocytosis, neutropenia, pancytopenia, in patients who were 65 years or older. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

During the first review cycle of this NDA, the Applicant was granted a partial waiver for patients age 0 to 4 years old from enrollment in future UC pediatric studies with Asacol 800. Based on the information submitted, this reviewer recommends that pediatric studies in age 5 to 17 years old UC patients be deferred, that the Asacol 400 mg tablets be the age-appropriate formulation for Asacol 800, and that a required Phase 4 commitment for Asacol 800 be the completion of the following postmarketing study:

(1) A randomized, double-blind study of six weeks of at least two dose levels in pediatric patients ages 5 to 17 years to evaluate the safety and effectiveness of those doses and to compare with results seen in adults. The study should include at least 40 patients in each dosage arm; in each arm, five patients should be age 5 years to 8 years. A protocol should be submitted by August 15, 2008, study should start by October 15, 2008, study should be completed by November 13, 2009, and study report should be submitted by January 15, 2009.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The chemical name, established name, proposed trade name, and pharmacological class are as follows:

- Chemical name: 5- amino-2-hydroxybenzoic acid
- Established name: mesalamine (5-aminosalicylic acid, also referred to as 5-ASA)
- Proposed trade name: Asacol 800
- Pharmacological class: locally acting aminosalicylate

Although the exact mechanism of action of mesalamine is unknown, available evidence suggests that mesalamine exerts topical anti-inflammatory effects on the colonic mucosa through inhibition of prostaglandin and leukotriene synthesis.

Each Asacol 800 mg delayed-release tablet is coated with an acrylic based resin Eudragit S (methacrylic acid copolymer B, NF) which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. A second enteric coating, which begins to dissolve earlier in the GI tract is added after the Eudragit S coating. This second coat consists of a combination of acrylic based resins, Eudragit S and Eudragit L (methacrylic acid copolymer A, NF).

2.2 Currently Available Treatment for Indications

Currently approved oral products for the treatment of moderately active UC include: (1) systemic steroids, (2) sulfasalazine (5-ASA-pyridine), (3) Asacol (mesalamine), (4) Pentasa (mesalamine), (5) Dipentum (two molecules of mesalamine conjugated by an azo-bond), (6) Colazal (mesalamine linked to an amino-acid), (7) Lialda (mesalamine).

Remicade (infliximab) is approved for treatment of moderately to severely active UC. Remicade is a monoclonal antibody administered by intravenous infusion.

A number of mesalamine-containing topical (rectal) formulations are available for the direct application of mesalamine to the rectum in distal UC. These include suppositories, enemas, and foams.

2.3 Availability of Proposed Active Ingredient in the United States

Various oral as well as rectal mesalamine-containing formulations are approved for marketing in the U.S.

2.4 Important Issues With Pharmacologically Related Products

There are no important issues with pharmacologically related products.

2.5 Presubmission Regulatory Activity

The table below summarizes the regulatory activity of Asacol 800 for moderately active UC; pertinent regulatory history for Asacol 400 mg tablets is also included.

Table 1. Regulatory History of Asacol 800*

Date	Action
January 1992	Asacol (400 mg tablets) approved for mildly to moderately active UC (NDA 19-651)
August 1997	Asacol (400 mg tablets) approved for maintenance of remission of UC (NDA 19-651)
October 2004	NDA 21-830 submitted for Asacol 800
August 2005	Approvable Letter for Asacol 800 (NDA 21-830)
February 2006	Meeting with Division - design of ASCEND III (Study 2006444)
January 2007	Meeting request - prompted by Lialda approval
March 2007	ASCEND III primary objective change from superiority of Asacol 800 to non-inferiority
March 2007	Meeting with Division – Acceptability and design of non-inferiority study (ASCEND III)
October 2007	Class II Resubmission – Complete Response to Approvable Letter

*Pertinent regulatory history for Asacol 400 mg tablets also included.

Asacol®(mesalamine) 400 mg delayed-release tablets were approved in 1992 for treatment of mildly to moderately active UC at a dose of 2.4 g/day (divided dosing) for six weeks. Asacol 400 mg tablets were also approved in 1997 for the maintenance of remission of UC at a dose of 1.6 g/day (divided dosing) for six months.

The applicant submitted a New Drug Application (NDA 21-830) on October 22, 2004, seeking approval for Asacol 800 mg delayed-release tablets at a dose of 4.8 g/day given in three divided daily doses for the treatment of moderately active UC for six weeks. Two studies (Study 82 and Study 83) were conducted in support of that application. An Approvable Letter was sent to the applicant on August 25, 2005, outlining the reason for the approvable action as follows (see also Clinical Review by Dr. Fathia Gibril and Statistics Review by Dr. Milton Fan):

- "Insufficient proof of the superiority of Asacol 800 mg dosed at 4.8 g/day over Asacol 400 mg dosed at 2.4 g/day to support your proposed indication of treatment of moderately active ulcerative colitis. "

In order to resolve this deficiency, the applicant was given the recommendations below in that Approvable Letter:

- "Provide at least one additional adequate and well-controlled study to demonstrate the added clinical benefit of Asacol 800 mg tablets at a dose of 4.8 g/day compared to Asacol 400 mg at 2.4 g/day in moderately active ulcerative colitis patients."
- "Explain why Asacol 800 mg at 4.8 g/day was more efficacious than Asacol 400 mg at 2.4 g/day in male patients. "

On February 3, 2006, the applicant met with the Division to discuss the study design of ASCEND III (Protocol 2006444). The following key agreements were reached:

- The primary objective would be demonstration of superiority of Asacol 800 4.8 g/day over Asacol (400 mg tablets) 2.4 g/day.
- The primary endpoint of treatment success would be based on the Physician's Global Assessment (PGA) which has individual components of stool frequency, rectal bleeding, and sigmoidoscopy. [It should be noted that unlike Studies 82 and 83, the Physician's Functional Assessment (PFA) is not included as an individual component of the PGA for Study 2006444.]
- The number of patients planned was 470.
- Score criteria and cutoffs (stool frequency, rectal bleeding, and sigmoidoscopy) to standardize enrollment of moderate UC patients were agreed upon.

Another mesalamine product, Lialda, was approved on January 16, 2007, based on two three-arm (2.4 g/day, 4.8 g/day, Placebo) studies in which both doses demonstrated superiority to placebo in each study, and in which there were no greater safety concerns with the 4.8 g/day dose. On January 26, 2007, the applicant requested a meeting with the Division shortly after the applicant became aware of the approval of Lialda (mesalamine) at doses of both 2.4 g/day and 4.8 g/day, based on studies that did not show superiority of the 4.8 g/day dose over the 2.4 g/day dose. On March 2, 2007, the applicant amended the protocol to increase the sample size from 470 to 770 patients, and to change the primary objective from a test for superiority of Asacol 800 4.8 g/day to a test of non-inferiority between the two arms.

On March 16, 2007, a meeting occurred with the Division to discuss the acceptability and design of the proposed non-inferiority (NI) study. The Division recommended demonstration of superiority, but said demonstration of NI might be sufficient, providing important details (e.g., entry criteria, primary endpoint) adhere to those of the placebo-controlled trials. The Division did not agree on the 10% NI Margin at this time but was willing to review additional justification.

In this submission, dated October 22, 2007, the applicant has provided the results of Study 2006444 (ASCEND III), Asacol 800 dosed 4.8 g/day versus Asacol dosed 2.4 g/day for the treatment of patients with moderately active UC.

2.6 Other Relevant Background Information

Globally, mesalamine (5-ASA) has been available worldwide for the treatment of UC for more than 20 years, and as the active component in sulfasalazine for more than 50 years.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

In the first review cycle, the CMC reviewer indicated that the approved NDA 19-651 for Asacol 400 mg tablets contains the drug substance chemistry, manufacturing, and control information. The mesalamine drug substance (5-amino-2-hydroxybenzoic acid) used in the manufacture of the 800 mg tablet is the same as that approved for use on the manufacture of the currently marketed Asacol 400 mg tablets.

In this review cycle, the CMC reviewer indicated that the manufacturing sites were re-inspected and received an Acceptable recommendation. No other issues were raised from a CMC perspective.

3.2 Animal Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this NDA. Animal pharmacology/toxicology data were reviewed previously under NDA 19-651 for Asacol 400 mg tablets and are described in the current Asacol label.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This review is primarily based on data from clinical trials conducted by the applicant. Postmarketing reports for other mesalamine products including Asacol 400 mg tablets also contributed to this review.

4.2 Tables of Clinical Studies

The table below summarizes the clinical trials conducted as part of the development for the UC indication. The results of Studies 82 and 83 were reviewed in the original NDA review. The results of Study 2006444 form the primary basis for this review.

Table 2. Clinical Studies of Asacol 800

Study	Objectives	Design	Test product Dosage regimen	Population	Number Enrolled/ completed	Treatment Duration
2000082	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double- blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Mildly to moderately active UC	Total: 386/330 2.4 g/day 195/162 4.8 g/day 191/168	6 weeks
2000083	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double- blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Mildly to moderately active UC*	Total: 301/256 2.4 g/day 154/133 4.8 g/day 147/123	6 weeks
2006444	To assess safety and efficacy of Asacol 4.8 g/day (800 mg tablet) vs. Asacol 2.4 g/day (400 mg tablet)	Double- blind, randomized, 6-week, parallel group, active control	Two 800 mg tablets and two placebo tablets 3 times daily oral	Moderately active UC	Total: 772/700 2.4 g/day 383/347 4.8 g/day 389/353	6 weeks

* The primary population for efficacy assessment in Study 82 was amended to change from subjects with mild to moderate disease to subjects with only moderate disease (See Clinical Review by Dr. Fathia Gibril and Statistics Review by Dr. Milton Fan.)
(Table above is summarized from the Applicant's Tabular Listing of All Clinical Studies.)

4.3 Review Strategy

Clinical review of the efficacy data, the safety data, and the proposed labeling of this Class II Resubmission was done by this reviewer, Dr. Anil Rajpal. Dr. Milton Fan reviewed the statistical aspects of the Class II Resubmission. Clinical pharmacology results were reviewed by Dr. Insook Kim from the Office of Clinical Pharmacology. In addition, this review relied on conclusions from the reviewers of the first review cycle of this application.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) performed three clinical site audits for this application. The two domestic sites with the largest number of subjects were selected. Because the two largest domestic sites had only 6 subjects and 5 subjects, it was decided to also select an international site in order to have a larger overall sample for inspection; the most readily available large international site was selected. Sites selected for inspection are shown in the table below.

Table 3. Sites Selected for Inspection

Investigator	Site No.	Location	Study (n at site)
Dr. Jeffrey Axler	103188	Toronto, ON, Canada	13
Dr. David Stanton	103208	Orange, CA	6
Dr. Arthur Poch	103194	Shreveport, LA	5

DSI recommended that data from each of the sites can be used in support of the NDA. (See DSI Clinical Inspection Summary dated April 16, 2008.)

4.5 Compliance with Good Clinical Practices

The Applicant stated that Studies 2000082, 2000083, and 2006444 were each carried out in accordance with International Conference on Harmonization (ICH) / Good Clinical Practice (GCP) guidelines.

4.6 Financial Disclosures

The Applicant certified that it did not enter into any financial agreement with the clinical investigators whereby the value of their compensation could be affected by outcome of the studies.

5 CLINICAL PHARMACOLOGY

The clinical pharmacology data were submitted in the previous review cycle and were reviewed by Dr. Suliman Al-Fayoumi and labeling recommendations were provided (see review dated July 28, 2005). No additional clinical pharmacology data was provided for this review cycle. The clinical pharmacology reviewer for the current review cycle, Dr. Insook Kim, provided additional labeling recommendations (see review dated April 8, 2008). A summary of the clinical pharmacology findings is presented below.

5.1 Pharmacokinetics

Relative Bioavailalability Study: In a single dose, cross-over pharmacokinetic study in 20 healthy volunteers, the mean mesalamine C_{max} was 36% lower, and the mean mesalamine AUC was 25% lower with administration of the Asacol 800 tablet relative to two Asacol 400 mg tablets. The reviewers concluded that bioequivalence between one Asacol 800 tablet and two Asacol 400 mg tablets was not demonstrated, and that the two products are not interchangeable.

Multiple-dose PK Study: In an open label study in 16 healthy subjects where two Asacol 800 mg tablets were administered TID for seven days, significant accumulation of 5-ASA and N-Ac-5-ASA was found to take place with the TID regimen.

Food-effect Study: A significant food-effect was observed on the PK of the Asacol 800 tablet. Mean Cmax of 5-ASA decreased by 47% under fed conditions, and a marked delay in tmax was observed under fed conditions with mean tmax increasing by 14 hours relative to fasting conditions. Because Asacol 800 was administered without regard to food in the clinical studies, the clinical pharmacology reviewer recommended that the Asacol 800 table can be labeled for administration without regard to food.

5.2 Pharmacodynamics

Asacol (mesalamine) is thought to exert its pharmacologic effects topically on the GI tract. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase

pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

5.3 Exposure-Response Relationships

Studies to assess exposure-response relationships were not conducted as part of the clinical pharmacology program.

Efficacy: Labeling recommendations in the current review cycle include a statement in the Pharmacokinetics section that informs the reader that the relationship between measures of systemic exposure (e.g., Cmax and AUC) and clinical efficacy are not known because the action of mesalamine is believed to be topical, and not systemic. This statement was added in order to communicate that the 25% lower AUC and 36% lower Cmax of one Asacol 800 tablet compared to two Asacol (400 mg tablets) may not be associated with a change in efficacy. (See Section 9.4 also.)

Safety: The Division of Gastroenterology Products requested Ann Corken Mackey, RPh, MPH, from the Division of Adverse Event Analysis 1, to conduct a search of the Adverse Event Reporting System (AERS) for evidence that hypersensitivity and renal impairment associated with mesalamine use are dose- related. The safety evaluator also conducted a literature search. The safety evaluator concluded that the AERS database cannot identify dose-related adverse events due to lack of confirmation that the AE is due to increased or decreased dose, due to incomplete data submission on dosage for each case, and due to a lack of denominator for each dose and AE. The safety evaluator concluded based on reports in the medical literature, that the risk of mesalamine-induced renal impairment does not appear to be dose-related. (See Safety Evaluator Review dated March 19, 2008 included in Section 10.4 of this review; filed under NDA — in DFS.) b(4)

6 INTEGRATED REVIEW OF EFFICACY

In this review, efficacy data generated from Study 2006444 are discussed. (Efficacy data from Studies 82 and 83 are described in the Clinical Review by Dr. Fathia Gibril for the original NDA 21-830.)

6.1 Indication

In the "Indications and Usage" section, the Applicant proposed the underlined wording below for the ulcerative colitis indication:

b(4)

6.1.1 Methods

The clinical data from one randomized, double-blind, active-controlled study (Study 2006444) was analyzed to determine whether non-inferiority was demonstrated between test product of Asacol 800 (4.8 g/day dose) and Asacol 400 (2.4 g/day dose).

It should be noted that the applicant amended the protocol on March 2, 2007. The applicant increased the sample size from 470 to 770 patients, and changed the primary objective from a test for superiority of Asacol 800 4.8 g/day over Asacol 400 mg tablets 2.4 g/day to a test of non-inferiority between the two treatment arms.

6.1.2 General Discussion of Endpoints

6.1.2.1 Primary Endpoint

The primary endpoint was based on the Physician's Global Assessment (PGA), a four-point scale (0-3) that encompasses three clinical assessments (rectal bleeding, stool frequency, and sigmoidoscopy assessment score). Stool frequency and rectal bleeding scores were based on patient's recall of the previous three days. (See also Section 10.1.1).

The primary endpoint was treatment success at Week 6 (improvement from baseline to Week 6) defined as either of the following:

(1) Complete response (remission): a PGA score of 0 and complete resolution of the clinical assessments (stool frequency, rectal bleeding, and sigmoidoscopy assessment score).
(2) Partial response (improvement): improvement from baseline in the PGA score, and no worsening in any of the clinical assessments (stool frequency, rectal bleeding, and sigmoidoscopy assessment score).

The PGA is a reasonable scoring index for UC because assessments that are widely used in clinical practice, rectal bleeding and stool frequency, are integrated with an endoscopic assessment, thus providing an overall assessment of a subject's disease status. However, the PGA has some weaknesses. First, sigmoidoscopy assessments have been described in the literature as being subjective and having high inter-observer variability (Cooney RM et al., Trials 2007); the applicant has attempted to standardize the sigmoidoscopy assessments by adding the contact friability test (CFT; see Section 10.1.3) and the provision that a central sigmoidoscopy reader will view the initial and all subsequent sigmoidoscopy tapes specified in the protocol as quality control for assessments of disease severity in the patients recruited (see Section 6.1.3.4). Second, because stool frequency and rectal bleeding scores are based on the patient's recall of the previous three days, these assessments may also be subjective. Unlike in Crohn's disease where standard definitions for clinical improvement and clinical remission on standard indices have come into common use, there is no single disease activity index that is universally accepted in UC. (Higgins PD et al., Gut 2005)

Although the first part of the primary endpoint definition, complete remission (normal stool frequency, absent rectal bleeding, and intact vascular pattern with no friability or granularity on

endoscopy) alone would be a highly sensitive measure of response to treatment, addition of the second part of the definition, partial remission (which only requires patients to improve in the overall score with no worsening of individual components) decreases the sensitivity of the primary endpoint.

It should be noted that the PGA used in Studies 82 and 83 differed from that used in Study 2006444 in that it had the additional clinical assessment of Patient's Functional Assessment (PFA), a four-point scale (0-3) that is based on the patient's recall of the previous three days (see Section 10.1.3). It should also be noted that the definition of partial response (improvement) in Studies 82 and 83 differed from that of Study 2006444 in that it had the additional requirement that at least one clinical assessment (stool frequency, rectal bleeding, sigmoidoscopy, or PFA) improves. The primary endpoint used in the clinical trials leading to the approval of Asacol 400 mg tablets (2.4 g/day) in mildly to moderately active UC was the same primary endpoint as that of Studies 82 and 83.

See Sections 10.1.1 to 10.1.3 for information on scoring systems used in Study 2006444.

6.1.2.2 Secondary Endpoints

There were multiple secondary endpoints analyzed in Study 2006444. These included:

(1) Treatment success in male patients at Week 6
(2) Change in each of the individual assessments (stool frequency, rectal bleeding, PFA, and sigmoidoscopy) and composite scores (PGA and Ulcerative Colitis Disease Activity Index [UCDAI]) from baseline to Week 6
(3) Change in individual assessments (stool frequency, rectal bleeding, and PFA) from baseline to Week 3
(4) Treatment success in the left-sided disease subgroup at Week 6

It should be noted that statistical measures to correct for multiple comparisons were not prespecified in the protocol. (See Statistics Review by Dr. Milton Fan.)

6.1.3 Study Design

Study 2006444 (ASCEND III) was a double-blind, randomized, multi-center, multi-national, active-control study in patients who were experiencing a moderately active flare of UC. Patients were randomly assigned to receive either Asacol 400 mg tablet (2.4 g/day) or Asacol 800 (4.8 g/day) for six weeks. Patients were randomized to one of the two treatment groups in a 1:1 ratio and were stratified by sex. Approximately 470 patients were to be enrolled in the study at approximately 150 study sites.

On March 2, 2007, the applicant amended the protocol to increase the sample size from 470 to 770 patients, and to change the primary objective from a test for superiority of Asacol 800 4.8 g/day to a test of non-inferiority between the two arms.

6.1.3.1 Eligibility Criteria

Main Inclusion Criteria:

(1) Age ≥ 18 years
(2) Endoscopically-confirmed moderately active UC extending proximally beyond 15 cm from the anal verge; only patients with positive mucosal friability based on the contact friability test were to be enrolled (see Section 10.1.3)
(3) PGA score of 2
(4) Stool frequency score of 1 or more, Rectal bleeding score of 1 or more, and Sigmoidoscopy score (with positive contact friability test) of 2 or more (see Section 10.1.3)

Main Exclusion Criteria:

(1) Received the following medications
    (a) mesalamine or prodrug (mesalamine dose or equivalent of 1.6 g/day or more) within 7 days
    (b) any topical rectal therapy within 7 days
    (c) systemic steroids within 30 days
    (d) biologic treatment within 90 days
(2) Current renal disease (Cr more than 1.5 X ULN)
(3) History of hepatic disease (AST or ALT more than 2 X ULN)

It should be noted that in Studies 82 and 83, stool frequency score or rectal bleeding score was required to be 1 or more, and Sigmoidoscopy score was required to be 1 or more.

6.1.3.2 Treatments

Treatment 1

Asacol 2.4g/day (400 mg formulation): Two 400 mg tablets and two placebo tablets (matching the 800 mg formulation) orally three times daily (morning, midday, evening) for six weeks.

Treatment 2

Asacol 800 (4.8g/day): Two 800 mg tablets and two placebo tablets (matching the 400 mg formulation) orally three times daily (morning, midday, evening).

Concomitant Therapy

The following concomitant therapy was prohibited:

- mesalamine or prodrug
- topical rectal therapy
- systemic steroids
- immunomodulatory agents (including but not limited to azathioprine, 6-MP, methotrexate, or cyclosporine)
- antibiotics for more than 10 days during the study

6.1.3.3 Efficacy Assessment Schedule

Key study assessments are summarized below:

Procedures	Screening / Baseline[a]	Week 3	Week 6/Exit
Physical examination	X		X
Serum creatinine[b]	X		X
Sigmoidoscopy including friability assessment	X[c]		X
Clinical assessments[d]	X	X	X
Composite clinical assessment score (PGA)	X		X

a. Baseline visit to occur within 7 days of the screening visit.
b. Screening specimen will be split, one sample analyzed by the local laboratory and the other by the central laboratory. Week 6 / Exit sample analyzed by central laboratory only.
c. Sigmoidoscopy or colonoscopy including assessment of friability performed as close as possible to the Baseline Visit and study drug dispensing.
d. Includes stool frequency, rectal bleeding, and PFA.

6.1.3.4 Analysis Plan

For the primary efficacy analysis, the ITT study population was used. The primary efficacy parameter was the proportion of patients in each treatment group that achieved treatment success, defined as improvement from baseline at Week 6. For patients whose treatment outcome was missing at Week 6, their treatment outcome at Week 6 was set to treatment failure.

For both the primary and secondary analyses, the Investigators' assessment of UC disease activity was used. However, the sigmoidoscopy with CFT procedure using a central sigmoidoscopy reader was used for training; a central sigmoidoscopy reader viewed the initial and all subsequent sigmoidoscopy tapes specified in the protocol as quality control for assessments of disease severity in the patients recruited.

6.1.3.5 Protocol Amendments

The applicant amended the original protocol on March 2, 2007, to adopt a primary non-inferiority analysis approach to demonstrate efficacy of Asacol 800. The amendment included the following 2 changes:

(1) The primary efficacy analysis was changed from a test of treatment differences to a test for non-inferiority of Asacol 800 (4.8g/day) to Asacol 400mg tablet (2.4g/day) with a noninferiority margin of 10%. If non-inferiority of Asacol 800 (4.8g/day) was established, a test of the superiority of Asacol 800 (4.8g/day) was to be performed.
(2) The planned number of patients enrolled was increased from n=470 to approximately n=770.

6.1.4 Efficacy Findings

6.1.4.1 Demographics and Baseline Characteristics

All the demographic characteristics of the ITT Population were comparable between the two treatment groups. More than 90% of the patients were < 65 years old and more than 90% were Caucasian. There were slightly more males (approximately 56%) than females in each treatment group. UC history and baseline disease state characteristics were also well-balanced between the two treatment groups. (See tables below.)

Table 4. Demographic Characteristics - Intent-to-Treat Population (Study 2006444)

Variable Statistic or Category	Asacol 2.4 g/day (N=383)	Asacol 800 4.8 g/day (N=389)	p-value
Age (yr)			0.067
Mean (SD)	42.4 (13.6)	44.1 (13.4)	
Median (Min, Max)	41.0 (18, 75)	44.0 (19, 75)	
Age Group [N (%)]			0.509
≤ 65 yrs	355 (93%)	355 (91%)	
> 65 yrs	28 (7%)	34 (9%)	
Gender N (%)			0.885
Male	216 (56%)	217 (56%)	
Female	167 (44%)	172 (44%)	
Race N (%)			0.673
Caucasian	368 (96%)	378 (97%)	
Black	6 (2%)	3 (1%)	
Indian (Asian)	5 (1%)	4 (1.0%)	
Asian (Oriental)	1 (0.3%)	0 (0.0%)	
Multi-Racial	3 (0.8%)	4 (1.0%)	
Weight (kg)			0.886
Mean (SD)	73.93 (15.6)	74.09 (15.4)	
Median (Min, Max)	73 (42.0, 131)	74 (37.0, 134)	
Height (cm)			0.586
Mean (SD)	171.4 (9.2)	171.1 (9.3)	
Median (Min, Max)	171 (145, 202)	171 (152, 200)	
Smoking History			0.733
Currently	41 (10.7%)	37 (9.5%)	
Never	239 (62.4%)	239 (61.4%)	
Previously	103 (26.9%)	113 (29.0%)	

Categorical p-values are chi-square test and continuous p-values are one-way ANOVA.
(Table above is taken from Pages 30 of the Clinical Study Report for Study 2006444)

Table 5. Ulcerative Colitis History - ITT Population (Study 2006444)

Parameter Category	Asacol 2.4g/day Asacol (N = 383) n (%)	Asacol 800 4.8g/day Asacol (N = 389) n (%)	p-value
Disease Extent at Baseline			0.999
Proctosigmoiditis	183 (48%)	185 (48%)	
Left-Sided Colitis	136 (36%)	138 (36%)	
Pancolitis (Pancolitis + Extensive)	60 (16%)	61 (16%)	
Length of Disease History			0.401
<1 year	111 (29%)	98 (25%)	
1 to 5 yrs	131 (34%)	148 (38%)	
>5 to 10 yrs	72 (19%)	82 (21%)	
>10 yrs	69 (18%)	61 (16%)	
Steroids (oral or IV)			0.884
No	226 (59%)	232 (60%)	
Yes	157 (41%)	157 (40%)	
Immunomodulators			0.860
No	366 (96%)	373 (96%)	
Yes	17 (4.4%)	16 (4.1%)	
Biologics			1.00
No	380 (99%)	385 (99%)	
Yes	3 (0.8%)	4 (1%)	
Sulfasalazine			0.517
No	187 (49%)	180 (46%)	
Yes	196 (51%)	209 (54%)	
Sulfa-free oral 5-ASAs			0.601
No	143 (37%)	138 (36%)	
Yes	240 (63%)	251 (64%)	
Any oral 5-ASAs			0.356
No	60 (16%)	51 (13%)	
Yes	323 (84%)	338 (87%)	
Rectal Therapies			0.943
No	195 (51%)	197 (51%)	
Yes	188 (49%)	192 (49%)	
Relapse Frequency			0.297
Newly diagnosed	76 (20%)	69 (18%)	
Less than once a year	56 (15%)	69 (18%)	
Once every 6-12 months	122 (32%)	118 (30%)	
Once every 6 months	108 (28%)	121 (31%)	
More than once a month	21 (5.5%)	12 (3.1%)	

P-value corresponds to the test of no treatment difference using chi-square test.
(Table above is taken from Pages 32-33 of the Clinical Study Report for Study 2006444)

Table 6. Baseline Disease State Characteristics – ITT Population (Study 2006444)

Parameter Category	Asacol 2.4g/day Asacol (N = 383) n (%)	Asacol 800 4.8g/day Asacol (N = 389) n (%)	p-value
Stool Frequency Score			0.447
1 (1 to 2 greater than normal)	53 (14%)	50 (12.9%)	
2 (3 to 4 greater than normal)	271 (71%)	290 (74.6%)	
3 (≥ 5 greater than normal)	59 (15%)	49 (12.6%)	
Rectal Bleeding Score			0.694
1 (Streak, less than 1/2 time)	112 (29%)	120 (30.8%)	
2 (Obvious, most of time)	266 (70%)	266 (68.4%)	
3 (Blood alone)	5 (1.3%)	3 (0.8%)	
Patient's Functional Assessment Score			0.325
0 (Generally well)	16 (4.2%)	24 (6.2%)	
1 (Fair)	172 (45%)	177 (45.5%)	
2 (Poor)	191 (50%)	187 (48.1%)	
3 (Terrible)	4 (1.0%)	1 (0.3%)	
Sigmoidoscopy with CFT score			0.302
1 (Mild)	2 (0.5%)	0 (0.0%)	
2 (Moderate)	364 (95%)	368 (94.6%)	
3 (Severe)	17 (4.4%)	21 (5.4%)	
Baseline UCDAI			0.613
Mean (SD)	7.8 (0.68)	7.8 (0.68)	
Median (Min, Max)	8 (7, 9)	8 (6, 9)	
Number of days in Flare			0.755
0 to 14	51 (13%)	49 (13%)	
15 to 28	84 (22%)	94 (24%)	
> 28	246 (65%)	244 (63%)	

UCDAI = Ulcerative Colitis Disease Activity Index
Categorical p-values are chi-square test and continuous p-values are one-way ANOVA.
(Table above is taken from Page 34 of the Clinical Study Report for Study 2006444)

6.1.4.2 Subject Disposition

More than 90% of the patients completed the study in both treatment groups. Patients who discontinued were evenly distributed between the two treatment groups. (See table below.)

Table 7. Subject Disposition: Intent-to-Treat Population (Study 2006444)

	Asacol 2.4 g/day (N=383) N (%)	Asacol 800 4.8 g/day (N=389) N (%)	p-value
Randomized To Treatment			
Completed	347 (91%)	353 (91%)	1.000
Discontinued	36 (9.4%)	36 (9.3%)	
Reason For Discontinuation			
Adverse Events	15 (3.9%)	15 (3.9%)	1.000
Investigator Discretion	0 (0.0%)	1 (0.3%)	1.000
Lost to Follow-up	1 (0.3%)	2 (0.5%)	1.000
Lack of Treatment Effect	6 (1.6%)	6 (1.5%)	1.000
Unable to Meet Protocol Criteria	7 (1.8%)	5 (1.3%)	0.575
Protocol Violation	1 (0.3%)	0 (0.0%)	0.496
Voluntary Withdrawal	6 (1.6%)	7 (1.8%)	1.000

p-value corresponds to the test of no treatment difference using Fisher's Exact Test.
(Table above is taken from Page 27of the Clinical Study Report for Study 2006444.)

6.1.4.2.1 Protocol Deviations

The number of patients with protocol deviations was balanced between the two treatment groups. (See table below.)

Table 8. Protocol Deviations

Violation	Asacol 2.4 g/day (N=383) n (%)	Asacol 800 4.8 g/day (N=389) n (%)
Overall	82 (21%)	96 (25%)
Excluded Medication	9 (2.3%)	3 (0.8%)
Inclusion/Exclusion Criteria	16 (4.2%)	14 (3.6%)
Other	64 (17%)	84 (22%)
Wrong Treatment or Incorrect Dose	0 (0.0%)	1 (0.3%)

(Table above is taken from Page 27of the Clinical Study Report for Study 2006444.)

Sixteen (4.2%) patients in the 2.4g/day treatment group and 14 (3.6%) patients in the Asacol 800 (4.8g/day) treatment group had deviations of Inclusion/Exclusion criteria. The most common deviation of Inclusion/Exclusion criteria in patients from both treatment groups (seven patients in the 2.4g/day treatment group and seven patients in the Asacol 800 [4.8g/day] treatment group) was the Exclusion Criterion "Does the patient have a positive stool examination for *C. difficile*, bacterial pathogens, or ova and parasites?"

Sixty-four (16.7%) patients in the Asacol 2.4g/day treatment group and 84 (21.6%) patients in the Asacol 800 (4.8g/day) treatment group had violations that were noted in the "Other" category. The most common violations in the "Other" category were deviations from scheduled visits and blood collections.

In the category "Wrong treatment or incorrect dose", one patient that was randomized to Asacol 800 (4.8g/day) forgot to take 11 doses during the first three-week treatment period and forgot to

take two doses during the second 3-week treatment period. This patient was randomized to Asacol 800 (4.8g/day).

In general, the violations appeared minor and would not be expected to directionally affect the results of the trial.

6.1.4.2.2 Data Sets Analyzed

The table below includes data sets analyzed for all randomized, intent-to-treat, and per-protocol patients. The intent-to-treat (ITT) study population included all patients who were randomized and took at least one dose of study medication. For the primary efficacy analysis, the ITT study population was used. For patients whose treatment outcome was missing at Week 6, treatment outcome at Week 6 was set to failure.

Table 9. Study Populations

Category	Asacol 2.4 g/day	Asacol 800 4.8 g/day
All Randomized Patients	383	392
Patients Not Dosed	0	3
Intent-to-treat Patients	383	389
Patients without Week 6 Outcome	17	20
Patients with Week 6 Outcome	366	369
Per Protocol Patients	348	359
Per Protocol Exclusions[a]	35	33
Compliance	13	14
Exclusion Criteria	13	10
Excluded Medication	2	1
Inclusion Criteria	2	0
No Week 6 Outcome	17	23

a. Patients may be counted in more than 1 exclusion category.
(Table above is taken from Page 29 of the Clinical Study Report for Study 2006444.)

6.1.4.3 Efficacy Results

6.1.4.3.1 Intent-to-Treat Population

6.1.4.3.1.1 Primary Efficacy Analysis

The primary endpoint was treatment success at Week 6 (improvement from baseline to Week 6). This was defined as either complete response (remission; a PGA score of 0 and complete resolution of the clinical assessments [stool frequency, rectal bleeding, and sigmoidoscopy] or partial response (improvement; improvement from baseline in the PGA score, and no worsening in any of the clinical assessments [stool frequency, rectal bleeding, and sigmoidoscopy]). (See also Section 6.1.2.1.)

The primary efficacy analysis (treatment success at Week 6) demonstrated statistical non-inferiority between Asacol 800 (4.8g/day) and Asacol (2.4g/day). Treatment success rates were 70.2% in the Asacol 800 group and 65.5% in the Asacol group. The difference (Asacol 800 – Asacol) was 4.6% (95% confidence interval: [-1.9%, 11.2%]). (See table below.)

Table 10. Primary Efficacy Analysis - Non-Inferiority of Treatment Outcome at Week 6* (ITT Population)

Treatment Outcome	Asacol 2.4g/day (N = 383) n (%)	Asacol 800 4.8g/day (N = 389) n (%)	Total (N = 772) n (%)	4.8-2.4 Difference in Success Rates[a]	95% Confidence Interval for 4.8 - 2.4[b]
Success	**251 (65.5%)**	**273 (70.2%)**	**524 (67.9%)**		
Failure	132 (34.5%)	116 (29.8%)	248 (32.1%)		
Total	383	389	772	**4.6**	**(-1.9, 11.2)**

* Missing Observations Set to Treatment Failure
a. Difference between Asacol 2.4g/day and Asacol 800 (4.8g/day)
b. Confidence interval for the difference in success rates between 2.4g/day compared to 4.8g/day with no stratification.
(Table above is taken from Page 35 of the Applicant's Clinical Study Report for Study 2006444.)

6.1.4.3.1.2 Secondary Efficacy Analysis

It should be noted that statistical measures to correct for multiple comparisons were not prespecified in the protocol. (See Statistics Review by Dr. Milton Fan.)

Treatment Success in Male Patients at Week 6

The treatment success proportions were similar for male and female subjects. See table below.

Table 11. Treatment Success by Gender (ITT Population)

Gender Treatment Outcome	2.4g/day Asacol (400 mg Tablet) (N = 383) n (%)	4.8g/day Asacol (800 mg Tablet) (N = 389) n (%)	Total (N = 772) n (%)	Difference in Success Rate (95% CI) for 4.8 - 2.4a
Male				
Success	141 (65.3%)	150 (69.1%)	291 (67.2%)	3.8 (-5.0, 12.7)
Female				
Success	110 (65.9%)	123 (71.5%)	233 (68.7%)	5.6 (-4.2, 15.5)

(Table above is taken from Page 64 of the Applicant's Clinical Study Report for Study 2006444.)

Change in Each of the Individual Assessments (Stool frequency, Rectal bleeding, PFA, and Sigmoidoscopy) and Composite Scores (PGA and UCDAI) from Baseline to Week 6

The rates of improvement for individual clinical assessments (stool frequency, rectal bleeding, PFA, sigmoidoscopy) and PGA were similar at Week 6 in both treatment groups. There appeared to be a trend of higher treatment success in the Asacol 800 4.8 g/day group for all the assessments except sigmoidoscopy. (See table below.)

Table 12. Treatment Outcomes for Individual Symptoms and PGA at Week 6* (Intent-to-treat)

Treatment Outcome	Out-come	Asacol 2.4g/day n (%)	Asacol 800 4.8g/day n (%)	Total n (%)	p-value[a]	4.8 - 2.4 Difference in Success Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
Stool Frequency	Improved	258 (74.4%)	280 (79.3%)	538 (76.9%)			
	Total	347	353	700	0.1186	5.0	(-1.3, 11.2)
Rectal Bleeding	Improved	276 (79.5%)	298 (84.4%)	574 (82.0%)			
	Total	347	353	700	0.0934	4.9	(-0.8, 10.6)
PFA	Improved	243 (72.3%)	254 (76.0%)	497 (74.2%)			
	Total	336	334	670	0.2667	3.7	(-2.9, 10.3)
Sigmoid-oscopy[#]	Improved	106 (30.7%)	105 (30.2%)	211 (30.4%)			
	Total	345	348	693	0.8823	-0.6	(-7.4, 6.3)
PGA	Improved	252 (73.0%)	276 (79.3%)	528 (76.2%)			
	Total	345	348	693	0.0528	6.3	(-0.1, 12.6)

* Excluding Patients With Both Baseline and Visit Scores of Zero
[#] Sigmoidoscopy with CFT
a 4.8g/day compared to 2.4g/day, stratified by sex using the Cochran-Mantel-Haenszel test.
b Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
c Confidence interval for the difference in success rates between 4.8g/day and 2.4g/day with no stratification
(Table above is modified from Pages 39-40 of the Applicant's Clinical Study Report for Study 2006444.)

The mean change from baseline in UCDAI was statistically significant for both the 4.8 g/day group and the 2.4 g/day group; however, the difference between the 2 treatment groups was not statistically significant. See table below.

Table 13. Mean Change from Baseline in Ulcerative Colitis Disease Activity Index (Intent-to-treat)

2.4g/day Asacol (400 mg Tablet)				4.8g/day Asacol (800 mg Tablet)				Between Treatment p-value[b]	Difference Between Means	95% CI for Between Means
n	Mean	(SE)	p-value[a]	n	Mean	(SE)	p-value[a]			
383	-3.1	-0.12	< 0.0001	389	-3.3	-0.11	< 0.0001	0.1951	-0.2	(-0.54, 0.11)

a Compared to baseline using the paired t-test
b Between-treatment comparison using ANOVA
(Table above is taken from Page 41 of the Applicant's Clinical Study Report for Study 2006444.)

Change in Individual Assessments (Stool frequency, Rectal bleeding, and PFA) from Baseline to Week 3

At Week 3, significantly more patients receiving Asacol 800 (4.8 g/day) experienced improvement in stool frequency versus Asacol 2.4g/day (400 mg) (p=0.0019, see table below); however, this was not adjusted for multiplicity. The rectal bleeding and PFA scores were similar in each of the treatment groups. However, the 4.8 g/day treatment group showed a trend of higher improvement rate than the 2.4 g/day treatment group at Week 3 for PFA, although this difference was not statistically significant.

Table 14. Treatment Outcomes for Individual Symptoms at Week 3* (Intent-to-treat)

Treatment Outcome	Out-come	Asacol 2.4g/day n (%)	Asacol 800 4.8g/day n (%)	Total n (%)	p-value[a]	4.8 - 2.4 Difference in Success Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
Stool Frequency	Improved	237 (66.0%)	279 (76.4%)	516 (71.3%)			
	Total	359	365	724	0.0019	10.4	(3.9, 17.0)
Rectal Bleeding	Improved	278 (77.4%)	283 (77.5%)	561 (77.5%)			
	Total	359	365	724	0.9736	0.1	(-6.0, 6.2)
PFA	Improved	223 (63.9%)	244 (70.7%)	467 (67.3%)			
	Total	349	345	694	0.0562	6.8	(-0.1, 13.8)

* Excluding Patients With Both Baseline and Visit Scores of Zero
a 4.8g/day compared to 2.4g/day, stratified by sex using the Cochran-Mantel-Haenszel test.
b Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
c Confidence interval for the difference in success rates between 4.8g/day and 2.4g/day with no stratification
(Table above is modified from Pages 39-40 of the Applicant's Clinical Study Report for Study 2006444.)

Treatment Success in the Left-sided Disease Subgroup at Week 6

After 6 weeks of treatment, both 4.8g/day and 2.4g/day were associated with success rates in patients with left-sided disease that were similar to the success rates in the 4.8g/day and 2.4g/day groups of the overall study population (see table below). The difference between treatment groups was not statistically significant.

Table 15. Summary of Treatment Outcomes at Week 6 for Patients with Left-sided Disease History (Intent-to-treat)

Treatment Outcome	Asacol 2.4g/day (N = 319) n (%)	Asacol 800 4.8g/day (N = 323) n (%)	Total (N = 642) n (%)	p-value[a]	4.8 - 2.4 Difference in Success Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
Success	215 (67.4%)	233 (72.1%)	448 (69.8%)			
Total	319	323	642	0.1918	4.7	(-2.4, 11.8)

a 4.8g/day compared to 2.4g/day, stratified by sex using the Cochran-Mantel-Haenszel test
b Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
c Confidence interval for the difference in success rates between 4.8g/day and 2.4g/day with no stratification
(Table above is modified from Page 41 of the Applicant's Clinical Study Report for Study 2006444.)

6.1.4.3.1.3 Post-hoc Analyses

Clinical Remission at Week 3 and Week 6

At Week 3 and Week 6, statistically significantly more patients (p=0.0154 – Week 3; p=0.0447 – Week 6) who received Asacol 800 (4.8g/day) compared to Asacol (2.4g/day) had clinical remission of UC (defined as a rectal bleeding and stool frequency score of 0). However, this was not a pre-specified endpoint. See table below.

Table 16. Summary of Clinical Remission (Intent-to-treat)

Week Clinical Remission	Asacol 2.4g/day n (%)	Asacol 800 4.8g/day n (%)	Total n (%)	CMH General Association p-value[a]	4.8 - 2.4 Difference in Improvement Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
Week 3						
Yes	64 (17.8%)	92 (25.2%)	156 (21.5%)			
Total	359	365	724	0.0154	7.4	(1.4, 13.3)
Week 6						
Yes	123 (35.4%)	151 (42.8%)	274 (39.1%)			
Total	347	353	700	0.0447	7.3	(0.1, 14.5)

a 4.8g/day compared to 2.4g/day, stratified by sex using the Cochran-Mantel-Haenszel test
b Difference between Asacol 800 (4.8g/day) and Asacol 2.4g/day
c Confidence interval for the difference in success rates between 4.8g/day and 2.4g/day with no stratification
(Table above is taken from Page 38 of the Applicant's Clinical Study Report for Study 2006444)

6.1.4.3.2 Per-Protocol Population

The Per Protocol efficacy analysis demonstrated statistical non-inferiority between Asacol 800 (4.8g/day) and Asacol 2.4g/day with a lower limit confidence interval of -2.3%. This result is consistent with that of the ITT population. See table below.

Table 17. Per Protocol Analysis - Treatment Outcome at Week 6

Treatment Outcome	Asacol 2.4g/day (N = 348) n (%)	Asacol 800 4.8g/day (N = 359) n (%)	Total (N = 707) n (%)	p-value[a]	4.8 - 2.4 Difference in Success Rates[b]	95% Confidence Interval for 4.8 - 2.4[c]
Success	247 (71.0%)	270 (75.2%)	517 (73.1%)			
Total	348	359	707	0.2069	4.2	(-2.3, 10.8)

a 4.8g/day compared to 2.4g/day stratified by sex using the Cochran-Mantel-Haenszel test
b Difference between 4.8g/day and 2.4g/day
c Confidence interval for the difference in success rates between 4.8g/day compared to 2.4g/day with no stratification.
(Table above is taken from Page 62 of the Applicant's Clinical Study Report for Study 2006444)

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Previous Review Cycle

In the previous review cycle, the Clinical Reviewer concluded that the application, which was based on the results of Studies 82 and 83, did not provide sufficient evidence of efficacy to support approval of Asacol 800 for the proposed indication of treatment of moderately active UC.

That reviewer concluded that in the mild UC subgroup (PGA=1), both studies showed lower rates of treatment success for Asacol 800 (4.8 g/day). In Study 83, Asacol 800 had a treatment success rate of 35.0% compared to 42.1% for Asacol. In Study 82, Asacol 800 had a treatment success rate of 32.8% compared to 40.4% for Asacol.

That reviewer noted that in a post hoc analysis of the moderately active UC subgroup (PGA=2) in Study 83, the results appeared to show superiority of Asacol 800 (55.9% for Asacol 800 vs. 51.3% for Asacol; p=0.0384), but more patients were excluded from the Applicant's ITT analysis in the Asacol 800 4.8 g/day group than the Asacol 2.4 g/day group thus biasing the results.

That reviewer noted that in the analysis of the moderately active UC subgroup of Study 82, superiority was shown (71.8% for Asacol 800 vs. 59.2% for Asacol; p=0.0357), but the benefit was driven by male patients (76% for Asacol 800 vs. 50% for Asacol in males; 69% for Asacol 800 vs. 67% for Asacol in females).

That reviewer concluded that a single clinical study finding of efficacy, unsupported by another independent study is not adequate for a conclusion of a substantial evidence of effectiveness. She recommended that to support the proposed indication, an additional adequate and well-controlled clinical study would be necessary to confirm the findings from Study 82. She also recommended that the applicant should adequately address the inconsistency in the efficacy benefit in important subgroups of patients with moderate disease, namely, males versus females.

Integrated Efficacy Conclusions

In Study 2006444, the primary efficacy analysis (treatment success at Week 6) demonstrated non-inferiority between Asacol 800 (4.8g/day) and Asacol (2.4g/day). Treatment success rates were 70.2% in the Asacol 800 group and 65.5% in the Asacol group. The difference (Asacol 800 – Asacol) was 5% (95% confidence interval: [-1.9%, 11.2%]). Treatment success in the Asacol 800 group in Study 82 with moderately active UC was 71.8%; this treatment success rate was similar to that observed in the Asacol 800 group in Study 2006444. Thus, this reviewer concludes that based on the results of the two studies, Study 2006444 and Study 82, non-inferiority of Asacol 800 (4.8 g/day) and Asacol (2.4 g/day) has been demonstrated. This reviewer recommends that Asacol 800 be approved for the treatment of adult patients with moderately active ulcerative colitis with revisions to the proposed labeling.

This reviewer concludes that in Study 2006444, treatment success at Week 6 was similar for male and female subjects by treatment group; a gender difference in treatment effect was not seen in Study 2006444 as it had been seen in Study 82. The gender difference observed in Study 82 remains unexplained; however, this reviewer does not believe that additional studies to investigate the gender difference are warranted. The applicant has adequately addressed the gender difference by obtaining and analyzing results by gender in Study 2006444.

This reviewer notes that in Study 2006444, a *post hoc* analysis of Week 6 remission rates (defined as stool frequency and rectal bleedings scores of 0) were nominally statistically significantly greater in the Asacol 800 group (43% vs. 35%, nominal p=0.045). This reviewer further notes that the rates of improvement for individual clinical assessments (stool frequency, rectal bleeding, PFA, sigmoidoscopy) and composite scores (PGA and UCDAI) by Week 6 were similar by treatment group.

7 INTEGRATED REVIEW OF SAFETY

In the safety review of the original NDA 21-830 application (based on Studies 82 and 83), nausea and vomiting was identified as occurring at a two to three times higher rate for the Asacol 800 4.8 g/day arm compared to the Asacol (400 mg tablets) 2.4 g/day arm. However, the overall safety profile was deemed comparable between the two arms. (See Clinical Review by Dr. Fathia Gibril.)

One focus of the current safety review was to determine if the Asacol 800 (4.8 g/day) arm and the Asacol 400 mg tablets (2.4 g/day) arm have a comparable safety profile. In particular, distribution by treatment arm of serious adverse events (SAEs), adverse events (AEs) classified by severity, common AEs, and AEs leading to withdrawal was assessed.

Another focus of the current safety review was to determine if the risk of renal impairment is increased with Asacol 800 at 4.8 g/day over the currently approved Asacol 2.4 g/day (400 mg tablets). The current label for Asacol (400 mg tablets) states in the Warnings and Precautions section that "Renal impairment, including minimal change nephropathy, acute and chronic interstitial nephritis, and, rarely, renal failure, has been reported...."

Since April 2005, Asacol 800 at a dose of 4.8 g/day has been marketed in Canada; the Applicant estimates that the exposure is approximately 11,000 patient-years. This also contributes some additional safety data that was reviewed.

7.1 Methods and Findings

The safety data for each of the mentioned studies are reviewed in this safety section by reviewing all pertinent safety events that occurred in each study. Analysis of safety was conducted by conventional parameters. In tabulating common adverse events, Medical Dictionary of Regulatory Activities (MedDRA), Version 6.0 preferred terms were used.

Extent of Exposure

Across the three studies (Studies 82, 83, & 2006444), 727 patients received Asacol 800 at a dose of 4.8 g/day (in three divided doses) for a mean duration of exposure of approximately six weeks. In addition, another study (Study 2004112) was conducted in the United States (under IND 26,093) and Europe comparing Asacol 4.8 g/day (800) [redacted] 169 more patients received Asacol 4.8 g/day (800) for a mean duration of exposure of approximately seven weeks. (See tables below.) b(4)

Table 18. Extent of Exposure to Study Drug (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Parameter	2.4g/day Asacol (400mg Tablet) (N=732)	4.8g/day Asacol (800mg Tablet) (N=727)
Mean number of patient-days of exposure		
n	724	721
Mean(SD)	40.13 (8.79)	40.05 (9.13)
Min	2	1
25%-tile	41	41
Median	42	42
75%-tile	44	44
Max	61	62
Duration of Treatment		
>0 Weeks	732 (100%)	727 (100%)
>3 Weeks	674 (92%)	670 (92%)

(Table above is taken from Page 3 of the Applicant's Summary of Clinical Safety.)

Table 19. Extent of Exposure to Study Drug Among Patients Taking 4.8 g/day (Study 2004112)

Exposure	Asacol 4.8 g/day (N=169)
n	169
Total patient-days of exposure	8615
Mean patient-days of exposure	51.0
Total Patient-years of exposure	23.6

(Table above is taken from Page 3 of the Applicant's Summary of Clinical Safety.)

Overall Adverse Event Profile

A summary of the overall treatment-emergent AE profile among intent-to-treat patients in the Phase III studies is presented in the table below. There appeared to be a lower incidence of serious adverse events (SAEs) in the Asacol 800 4.8 g/day group than in the Asacol 2.4 g/day group (see table below).

Table 20. Summary of Adverse Events (Studies 2000082, 2000083, and 2006444 Combined; ITT)

Category	2.4g/day (400) (N=732)	4.8g/day (800) (N=727)
Adverse Events	28.8%	27.7%
Serious Adverse Events	1.8%*	0.8%#
Withdrawn due to Adverse Events	4.2%	3.9%
Deaths	0	0

* Includes 5 UC exacerbations and 4 abdominal pain – in 2.4 g/day (400) dose group
# Includes 1 UC exacerbation and 1 abdominal pain – in 4.8 g/day (800) dose group
(Table above is modified from Page 5 of the Applicant's Summary of Clinical Safety.)

Adverse Event Profile by Severity

A summary of the adverse event profile by severity for the intent-to-treat population for the Phase III studies is presented in the table below. There appears to be a higher incidence of moderate AEs in the Asacol 800 4.8 g/day group than in the Asacol 2.4 g/day group. There appears to be a higher incidence of mild AEs in the Asacol 2.4 g/day group than in the Asacol 800 4.8 g/day group (see table below).

Table 21. Summary of Adverse Events by Severity (Studies 2000082, 2000083, and 2006444 Combined; ITT)

Adverse Event Severity	2.4g/day (400) (N=732)	4.8g/day (800) (N=727)
Mild	63%	55%
Moderate	30%	37%
Severe	8%	8%

(Table above is modified from Page 6 of the Applicant's Summary of Clinical Safety.)

Common AEs

Based on the combined population from the three studies, the incidence of nausea and vomiting symptoms appears to be of similar magnitude in both treatment groups (3.3% in both groups). The finding of a higher incidence of nausea and vomiting in the 4.8 g/day Asacol 800 group than the Asacol 2.4 g/day group from the previous review (based on Studies 82 and 83) appears to not be present in the larger combined dataset that also includes Study 2006444.

Infections appear to have slightly higher incidence in the 4.8 g/day Asacol 800 group than in the Asacol 2.4 g/day group (6.4% in the Asacol group versus 7.3% in the Asacol 800 group). These are mainly accounted for by upper respiratory infections which are higher in the 4.8 g/day Asacol 800 group than in the Asacol 2.4 g/day group (3.1% Asacol group versus 4.0% in the Asacol 800 group). The higher incidence of upper respiratory infections is in turn accounted for by a higher incidence of nasopharyngitis in the 4.8 g/day Asacol 800 group (1.4% in the Asacol group versus 2.5% in the Asacol 800 group).

Incidence of colitis is slightly higher in the Asacol 2.4 g/day group than in the 4.8 g/day Asacol 800 group (3.0% in the Asacol group versus 2.5% in the Asacol 800 group).

Renal Function

Creatinine levels were measured at Baseline and Week 6. The mean change was +1% in both arms. The number of subjects with a normal to high shift was 4 in the 2.4 g/day arm and 1 in the 4.8 g/day arm. One case of nephritis was described in Study 82 with Asacol 400 (see Section 7.1.2). No additional cases of change in renal function were identified based on the studies submitted; this may be because the duration of follow-up was not long enough and because there may not have been enough patients to identify more than one patient with a change in renal function.

7.1.1 Deaths

No deaths occurred in any of the three studies (82, 83, and 2006444) or in Study 2004112.

7.1.2 Other Serious Adverse Events

Nineteen patients (13 in the 2.4 g/day group, 6 in the 4.8 g/day group) experienced 30 SAEs (22 in the 2.4 g/day group; 8 in the 4.8 g/day group) during this clinical program. These SAEs are summarized in the table below by treatment group.

Table 22. SAE's by Treatment Group

Number of SAEs		
MedDRA PT Term	2.4g/day Asacol (400mg Tablet) (N=732)	4.8g/day Asacol (800mg Tablet) (N=727)
Total number of Patients Experiencing SAEs [n (%)]	**13 (1.8%)**	**6 (0.8%)**
Total number of SAEs	**22**	**8**
Drug Hypersensitivity	0	1
Nephritis	1	0
Colon cancer	0	1
Vomiting	1	0
Nausea	1	0
Gastroenteritis	1	0
Abdominal pain (left)	1	0
Abdominal pain (right upper quadrant)	1	1
Cholecystitis	2	0
Pancreatitis	1	0
Vasovagal syncope	0	1
Chest pain	0	1
Pericarditis	0	1
Musculoskeletal pain	0	1
Uterine Leiomyoma	1	0
Ovarian cyst	1	0
Enterocolitis	1	0
Ulcerative Colitis	5	1
Diarrhea	2	0
Abdominal pain (lower)	2	0
Rectal hemorrhage	1	0

N = number of patients within specified treatment.
n(%) = number and percentage of patients in category and treatment group.
(Values in table above were compiled by this reviewer using data on pages 12-14 of the Applicant's Summary of Clinical Safety.)

Although the majority of SAEs were events described in the Asacol package insert, four serious AEs occurred that are not described in the Asacol package insert nor known to be events associated with mesalamine use. These four events (two in each dose group) are summarized below:

(1) Dysfunctional uterine bleeding (DUB): A 49 year old female had a hysterectomy for DUB secondary to pre-existing fibroids and ovarian cyst; the study was completed. [2.4 g/day group]
(2) Enterocolitis: A 30 year old male had enterocolitis of unknown etiology; he recovered and completed the study. [2.4 g/day group]
(3) Colon cancer: A 66 year old male was hospitalized with colon cancer at study exit; the colon was resected and the event resolved. [4.8 g/day group]
(4) Vasovagal syncope: A 44 year old male had a vasovagal syncopal episode; he recovered and completed the study but study drug was interrupted during hospitalization. [4.8 g/day group]

The majority of SAEs primarily involved the gastrointestinal system; these included the following:

(1) signs and symptoms (rectal bleeding, diarrhea, abdominal pain) suggestive of UC
(2) worsening UC
(3) nausea and vomiting
(4) epigastric pain
(5) enterocolitis
(6) gastroenteritis
(7) cholecystitis
(8) pancreatitis

Onset of gastrointestinal SAEs occurred primarily in the first three weeks of treatment. It should be noted that the incidence of worsening UC was higher in the Asacol 2.4 g/day group (5 worsening UC in the Asacol 2.4 g/day group versus 1 worsening UC in the Asacol 800 4.8 g/day group) and that the incidence of signs and symptoms suggestive of UC were higher in the Asacol 2.4 g/day group (2 diarrhea, 2 abdominal pain, and 1 rectal bleeding in the Asacol 2.4 g/day group versus none in the Asacol 800 4.8 g/day group).

Other SAEs reported in the Phase III studies that are described in the Asacol package insert included single reports of the following:

(1) nephritis
(2) pericarditis

The case of nephritis is described below:

- Nephritis: One case of nephritis was described in Study 82 with Asacol 400 mg tablets. A 54-year old Caucasian female patient with proctosigmoditis of more than 30 years duration, who had been previously treated with sulfasalazine (intolerant) and steroids, received study drug for seven days with initial improvement in symptoms, followed by worsening symptoms that resulted in hospitalization for worsening ulcerative colitis. While hospitalized, the patient was diagnosed with nephritis (2+ protein on admitting urinalysis only), which was considered medically significant (serious). Study drug was discontinued and the patient was withdrawn from the study. She was treated with intravenous antibiotics and recovered from the events, although no information was provided with respect to the patient's ulcerative colitis disease status or subsequent therapy.

The etiology is not clear. The possibility that this event was related to the study agent cannot be excluded.

The majority of SAEs were moderate or severe.
All patients had recovered from the events by the time of their last study contact, with the exception of three patients described below by treatment group:

- Worsening UC: two patients remained under treatment for worsening UC (Asacol 2.4 g/day)
- Hypersensitivity: one patient experienced drug hypersensitivity (Asacol 800 4.8 g/day)

A similar percentage of patients in Study 2006444 reported serious AEs as in Studies 2000083 and 2000082, and the serious AEs reported did not suggest any new trends or patterns. (The SAEs are listed in Section 10.2.1.)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Fifty-nine patients (31 in the 2.4 g/day group, 28 in the 4.8 g/day group) were withdrawn from the Phase III studies due to AEs.

The percentage of patients who withdrew due to AEs was similar between treatment groups (4.2% in the Asacol [2.4 g/day] group; 3.9% in the Asacol 800 [4.8 g/day] group). The majority of withdrawals due to AEs occurred as a result of events described in the Asacol package insert, and primarily involved the gastrointestinal system.

A similar percentage of patients in Study 2006444 were withdrawn due to AEs as in Studies 2000083 and 2000082. Although drug hypersensitivity was cause for withdrawal in Study 2006444 and not in Studies 2000083 and 2000082, the distribution of this AE (3 in the 2.4 g/day group and 2 in the 4.8 g/day group) did not suggest a dose-related pattern.

The percentage of patients with moderately active disease who were withdrawn from the studies due to AEs was similar to those in the intent-to-treat population (4.4% in the Asacol [2.4 g/day] group; 4.0% in the Asacol 800 [4.8 g/day] group).

7.1.3.2 Adverse events associated with dropouts

AEs that led to the withdrawal of fifty-nine patients (31 in the 2.4 g/day group, 28 in the 4.8 g/day group) from the Phase III studies are summarized in the table below and are listed in Section 10.2.2.

Table 23. Adverse Events that Led to Withdrawal (Pooled data from Studies 82, 83, and 2006444; ITT)

Adverse Event	2.4g/day Asacol (400mg Tablet) (N=732)	4.8g/day Asacol (800mg Tablet) (N=727)
Total patients withdrew due to AEs	**31 (4.2%)**	**28 (3.9%)**
Colitis ulcerative	12	11
Nausea/vomiting	6	7
Abdominal pain /distension†	6	4
Headache	1	3
Diarrhea	6	2
Drug hypersensitivity	3	2
Upper abdominal pain#	0	3
Arthralgia	0	2
Fever	1	1
Myalgia	1	1
Dyspnea	1	0
Lung disorder‡	0	1
Colitis	1	1
Gastroenteritis	1	1
Rectal hemorrhage	1	0
Others*	2	4

* Others include: chest pain (n=1) and pancreatitis (n=1) in 2.4 g/day group; dizziness (n=1), flatulence (n=1), dehydration (n=1), allergic dermatitis (n=1) in 4.8 g/day group.
†,# "Abdominal pain/distention" is a combined category of the MedDRA PT's "abdominal pain" and "distention"; upper abdominal pain is a separate category that only includes the MedDRA PT of "upper abdominal pain".
‡ The "lung disorder" case was appeared to be musculoskeletal pain.
(Table above compiled by this reviewer from data in Pages 20 to 22 of the Applicant's Summary of Clinical Safety.)

Narratives of selected cases (the five hypersensitivity cases, the dyspnea case, and the allergic dermatitis case) are briefly described below. (More detailed narratives of these cases are provided in Section 10.2.3)

The five hypersensitivity cases were as follows:

- The first hypersensitivity case was in a 60 year old female who experienced a rash, pruritus, and flushing after receiving two doses of Asacol tablets (2.4 g/day); the symptoms moderated when the study drug was interrupted, but two days later, the study drug was resumed, and the symptoms returned. Treatment included cetirizine hydrochloride. Symptoms resolved approximately one week later.
- The second hypersensitivity case was in a 34 year old male who developed increase in stool frequency and flushing after study drug dose 2.4 g/day dose for approximately one week. The event resolved a day after the drug was discontinued.
- The third hypersensitivity case was in a 24 year old male with a history of gastroesophageal reflux that developed a maculopapular skin eruption after 3 days of 2.4 g/day Asacol. The event resolved the next day after the study agent was discontinued; treatment included methylprednisolone, and loratadine.

- The fourth hypersensitivity case was in a 39 year-old Caucasian female who received approximately one week of Asacol 800 mg at 4.8 g/day. She developed hives and itching on both legs, and discontinued study drug the following day. Treatment included chloropyramine hydrochloride.
- The fifth hypersensitivity case was in a 41 year-old Caucasian female who received approximately one week of Asacol 800 mg at 4.8 g/day. She had a medical history of activated protein C resistance, former deep vein thrombosis, hepatic and urinary cysts, myoma of the uterus, Leiden mutation- heterozygote type, and urticaria approximately seven years prior; she had no known drug allergies. The patient experienced skin eruptions in the form of a rash, without maculo-papular changes, on upper and lower extremities. The patient was hospitalized and withdrew from the study. She had elevated ESR and fever; these resolved. Treatment included methylprednisolone and loratadine.

No predictive factors for drug hypersensitivity reactions were appreciated in the case histories of these five patients.

The case of dyspnea/lung disease is described below.

- This was a 58 year old female on a number of medications (including hormone replacement therapy, a thiazide antihypertensive) and with a known allergy to sulfa drugs. She developed muscle pain/chest pain/shortness of breath after receiving Asacol 2.4 g/day for eight days. The patient had normal labs in the emergency room, and received paracetamol/hydrocodone for pain. A chest x-ray also revealed no acute pathology. She interrupted the study agent for two days, and experienced symptom improvement. She re-started the study agent for one day, but discontinued shortly after.

The etiology of this case is not clear, but it does not appear to be related to pneumonia or an infectious process. It is possible that the case may be related to polypharmacy.

The case of allergic dermatitis is described below:

- This was a 29 year old female who had a known allergy to penicillin and medical history significant for Osgood-Schlatter's disease of the left knee, eczema, chronic sinusitis, tonsillectomy, and bloody diarrhea. She had 4.8 g/day on two days, and developed allergic cutaneous rash, vomiting and dehydration. The patient was also found to have sinusitis and was treated with antibiotics. The study agent was discontinued.

The etiology is not clear. The possibility that this was a drug hypersensitivity reaction cannot be excluded.

7.1.3.3 Other significant adverse events

No other significant adverse events were appreciated that are not already in the current labeling for Asacol (400 mg tablets).

7.1.4 Other Search Strategies

No other search strategies were performed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

An adverse event was defined as any undesirable event that occurred to a participant during the course of the study (or a reasonable time after study termination), whether or not that event was considered study drug related.

All adverse events, whether or not related to the study drug, and whether non-serious or unexpected were required to be fully and completely documented on the Adverse Event page of the CRF and in the patient's medical chart. The following attributes must have been assigned: description, dates of onset and resolution, severity, assessment of relatedness to study drug (either related or not related), serious criteria if applicable, and action taken. The Investigator may have been asked to provide follow-up information.

Also, in the event that a subject was withdrawn from the study because of an adverse event, it had to be recorded on the CRF as such. The Investigator had to report all directly observed adverse events and all spontaneously reported adverse events.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The adverse event categorization and preferred terms were deemed to be appropriate. Treatment-emergent adverse events were reported using Medical Dictionary of Regulatory Activities (MedDRA), Version 6.0. In all cases, tables show the incidence of events using preferred terms (PTs). Within MedDRA, the PT level represents distinct medical concepts.

7.1.5.3 Incidence of common adverse events

The tables below summarize commonly occurring AEs (AEs occurring in $\geq$ 2% of patients in either treatment group) for the intent-to-treat patients in the Phase III studies. Based on the combined population from the three studies, the incidence of nausea and vomiting symptoms appears to be of similar magnitude in both treatment groups (3.3% in both groups). The finding of a higher incidence of nausea and vomiting in the 4.8 g/day Asacol 800 group than the Asacol 2.4 g/day group from the previous review (based on Studies 82 and 83) appears to not be present in the larger combined dataset that also includes Study 2006444 (see tables below).

Infections appear to have slightly higher incidence in the 4.8 g/day Asacol 800 group than in the Asacol 2.4 g/day group (6.4% in the Asacol group versus 7.3% in the Asacol 800 group). These are mainly accounted for by upper respiratory infections which are higher in the 4.8 g/day Asacol 800 group than in the Asacol 2.4 g/day group (3.1% Asacol group versus 4.0% in the Asacol 800 group). The higher incidence of upper respiratory infections is in turn accounted for by a higher incidence of nasopharyngitis in the 4.8 g/day Asacol 800 group (1.4% in the Asacol group versus 2.5% in the Asacol 800 group). (See tables below.)

Incidence of ulcerative colitis is slightly higher in the Asacol 2.4 g/day group than in the 4.8 g/day Asacol 800 group (3.0% in the Asacol group versus 2.5% in the Asacol 800 group; see tables below).

Table 24. Adverse Events occurring in ≥2% by SOC & HLT (82, 83, & 2006444)

SOC HLT	2.4g/day (400) (N=732)	4.8g/day (800) (N=727)
GI Disorders	13.9%	13.8%
Nausea and vomiting symptoms	3.3%	3.3%
GI and abdominal pains	3.3%	3.2%
Colitis (excluding infective)	3.0%	2.5%
Infections	6.4%	7.3%
Upper Respiratory Infections	3.1%	4.0%
Nervous system disorders	6.6%	6.2%
Headaches	5.1%	4.8%
General disorders	3.3%	3.3%
Musculoskeletal & connective tissue	2.5%	2.9%
Respiratory, thoracic and mediastinal	3.1%	2.1%
Skin and subcutaneous tissue	2.5%	1.8%

SOC: MedDRA System Organ Class
HLT: MedDRA High Level Term
(Table above is modified from Page 8 of the Applicant's Summary of Clinical Safety.)

Table 25. Selected Adverse Events Occurring in ≥2% by SOC, HLT, & PT (82, 83, & 2006444)

SOC HLT PT	2.4g/day (400) (N=732)	4.8g/day (800) (N=727)
GI disorders	13.9%	13.8%
Colitis (excl infective)	3.0%	2.5%
Ulcerative Colitis	2.7%	2.3%
Infections	6.4%	7.3%
URI's	3.1%	4.0%
Nasopharyngitis	1.4%	2.5%

SOC: MedDRA System Organ Class
HLT: MedDRA High Level Term
PT: Preferred Term
(Table above is modified from Page 8 of the Applicant's Summary of Clinical Safety.)

7.1.5.4 Common adverse event tables

Therapy with Asacol 800 was similar in overall incidence of adverse reactions compared to that seen with the Asacol 400 mg tablet. The most common reactions reported (greater than 1% of all patients treated in either dose group) were nausea, abdominal pain, nasopharyngitis, headache, and exacerbation of ulcerative colitis (see table below). The methods used in generating the table are provided in Sections 7.1 and 7.1.5.1.

Table 26. Adverse Reactions Occurring in ≥ 1% in All Treated Patients (Studies 2000082, 2000083, and 2006444 combined; ITT)

MedDRA Preferred Term	Asacol 2.4g/day (N=732) (%)	Asacol 800 4.8g/day (N=727) (%)
Headache	5%	5%
Nausea	3%	3%
Nasopharyngitis	1%	2%
Abdominal pain	2%	2%
Colitis ulcerative	3%	2%
Diarrhea	2%	2%
Dyspepsia	1%	2%
Vomiting	2%	1%
Flatulence	1%	1%
Influenza	1%	1%
Pyrexia	1%	0.7%
Cough	1%	0.3%

N = number of patients within specified treatment.
% =percentage of patients in category and treatment group

7.1.5.5 Identifying common and drug-related adverse events

Adverse events that occurred frequently in Asacol 800-treated patients and Asacol-treated patients in the studies conducted (Studies 82, 83, and 2006444 are likely to be drug-related. Thus, the table in Section 7.1.5.4 that displays adverse reactions in the studies should be added to the Adverse Reactions section of the labeling.

7.1.5.6 Additional analyses and explorations

No additional analyses and explorations were performed.

7.1.6 Less Common Adverse Events

Review of uncommon adverse events in the entire safety database did not identify additional safety concerns not addressed elsewhere in the review. Less common but clinically significant adverse events are discussed in Section 7.1.2 of this review.

7.1.7 Laboratory Findings

Laboratory data for serum chemistry, hematology, and urinalysis parameters measured in Studies 2000083 and 2000082 were previously submitted (NDA 21-830) and were reviewed by Dr. Fathia Gibril. She concluded that group mean results at Screening and at Week 6 were not clinically different between treatments for any of the parameters evaluated. (see Dr, Fathia Gibril's review dated August 26, 2005)

7.1.7.1 Overview of laboratory testing in the development program

Serum creatinine was the only clinical laboratory parameter evaluated in the Study 2006444 study; therefore it is the only parameter discussed in this review. Creatinine values in each of the Phase III studies (Studies 82, 83, and 2006444) were determined by visit.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Descriptive statistics for change and percent change from baseline in creatinine for intent-to-treat patients from each of the three studies (Studies 82, 83, and 2006444) are summarized by treatment group.

7.1.7.3 Standard analyses and explorations of laboratory data

Descriptive statistics for creatinine values by visit, and descriptive statistics for percent change from baseline in creatinine are presented in the tables below. Both treatment groups showed similar mean changes and percent changes from baseline in serum creatinine, with no evidence of a dose-related increase (see tables below).

Table 27. Creatinine: Descriptive Statistics by Visit (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Lab Test Visit Statistic	2.4g/day Asacol (400 mg Tablet) (N=732)	4.8g/day Asacol (800 mg Tablet) (N=727)
Creatinine (µmol/L)*		
Baseline		
n	725	718
Mean (SD)	76.0 (15.9)	76.2 (15.8)
Median	71.0	71.0
25, 75	62.0, 88.0	62.0, 88.0
10, 90	53.0, 97.2	53.0, 97.2
Min, Max	44.0, 150.0	35.0, 124.0
Week 6		
n	621	619
Mean (SD)	76.2 (15.3)	76.3 (15.2)
Median	71.0	79.6
25, 75	62.0 88.0	62.0, 88.0
10, 90	61.9, 97.2	61.9, 97.2
Min, Max	44.0, 132.6	35.4, 123.8
Withdrawal		
n	61	58
Mean (SD)	75.4 (16.5)	74.2 (18.7)
Median	71.0	70.7
25, 75	62.0, 88.4	61.9, 88.0
10, 90	53.0, 97.2	53.0, 106.0
Min, Max	35.4, 106.1	35.0, 115.0

(Table above is modified form Page 29 of the Applicant's Summary of Clinical Safety.)

Table 28. Creatinine Percent Change from Baseline (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Lab Test Visit Statistic	2.4g/day Asacol (400 mg Tablet) (N=732)	4.8g/day Asacol (800 mg Tablet) (N=727)
Creatinine (% change)		
Baseline		
n	725	718
Mean (SD)	76.0 (15.9)	76.2 (15.8)
Median	71.0	71.0
25, 75	62.0, 88.0	62.0, 88.0
10, 90	53.0, 97.2	53.0, 97.2
Min, Max	44.0, 150.0	35.0, 124.0
Week 6		
n	614	611
Mean (SD)	1.19 (13.9)	1.21 (13.1)
Median	0.0	0.0
25, 75	-8.6, 10.0	-9.1, 11.1
10, 90	-12.7, 14.5	-14.3, 16.7
Min, Max	-45.4, 140.9	-41.5, 42.9
Withdrawal		
n	61	58
Mean (SD)	1.59 (19.1)	-2.77 (13.5)
Median	0.000	0.0
25, 75	-10.0, 10.0	-12.5, 10.0
10, 90	-14.5, 20.5	-18.2, 16.7
Min, Max	-33.8, 80.0	-33.3, 30.7

(Table above is modified form Page 31 of the Applicant's Summary of Clinical Safety.)

The table below shows individual patient shifts from baseline to Week 6 and final value in serum creatinine among intent-to-treat patients in the Phase III studies. There was no evidence of shifts to higher serum creatinine levels with Asacol 800 (4.8 g/day) as compared to Asacol (2.4 g/day); see table below.

Table 29. Creatinine Shift Table for Baseline vs. Week 6 and Final Value (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Lab Test Visit	Baseline	2.4g/day Asacol (400 mg Tablet) (N=732)			4.8g/day Asacol (800 mg Tablet) (N=727)		
		Total	Normal n (%)	**High n (%)**	Total	Normal n (%)	**High n (%)**
Creatinine							
Week 6	**Normal**	604	600 (99%)	**4 (<1%)**	604	603 (100%)	**1 (<1%)**
	High	10	5 (50%)	5 (50%)	7	6 (86%)	1 (14%)
Final Result	**Normal**	668	663 (99%)	**5 (<1%)**	666	662 (99%)	**4 (<1%)**
	High	10	5 (50%)	5 (50%)	7	6 (86%)	1 (14%)

(Table above is modified form Page 32 of the Applicant's Summary of Clinical Safety.)

7.1.7.4 Additional analyses and explorations

No additional analyses and explorations are indicated.

7.1.7.5 Special assessments

Although no evidence of change in renal function was identified based on the studies submitted, a longer duration of follow-up and more patients may be needed to identify change in renal function and renal failure.

7.1.8 Vital Signs

Vital signs and physical findings were not collected for Study 2006444; therefore, these data are not presented for any study. Vital signs and physical findings measured in Studies 2000083 and 2000082 were previously submitted (NDA 21-830) and are discussed in the review of that submission by Dr. Fathia Gibril. In that review, she found that examination of the vital signs data from Studies 82 and 83 revealed no adverse event signal; there were no marked outliers or dropouts due to vital signs abnormalities in this clinical program (see Dr. Fathia Gibril's Review).

7.1.9 Electrocardiograms (ECGs)

The applicant did not provide any clinical or adverse event data regarding ECGs in this application.

7.1.10 Immunogenicity

The applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

7.1.11 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application. Results from preclinical carcinogenicity studies have been previously reviewed and are reflected in the current Asacol product label.

7.1.12 Special Safety Studies

No special safety studies were conducted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no clinical information with respect to the potential for abuse, withdrawal, or rebound effects with use of the Asacol 800 mg tablet formulation at a dose of 4.8 g/day in patients with active UC. Additionally, there is no new information with respect to the potential for these effects associated with the active ingredient, mesalamine.

7.1.14 Human Reproduction and Pregnancy Data

There is not new information on pregnancy, use in labor and delivery, or lactation. Information about mesalamine had been adapted for this product from the labeling of Asacol 400 mg tablets.

7.1.15 Assessment of Effect on Growth

Asacol 800's effect on growth has not been studied. Asacol 800 has not been studied in patients younger than age 18.

7.1.16 Overdose Experience

There is no clinical experience with overdose of the Asacol 800 formulation.

However, two cases of pediatric overdosage have been reported with mesalamine tablets and are described in the currently approved Asacol (400 mg tablets) labeling, and the label also had information on lethal doses in animals.

7.1.17 Postmarketing Experience

Asacol 800 has been marketed in Canada since April 2005, at a dose of 4.8 g/day. Since then, 10 spontaneous reports have been received.

One case of each of the following was reported:

- dysphagia
- ulcerative colitis flare and alopecia
- diarrhea
- nausea, fatigue, and insomnia
- ulcerative colitis flare with abdominal pain and bloody diarrhea; this patient was taking Asacol 800 but switched back to 400 mg tablets due to unavailability of Asacol 800.

In addition, five cases of medication residue were reported.

All of the adverse reactions were non-serious.

Of these adverse reactions, only dysphagia is unlisted in the current Asacol package insert.

Since April 2005, Asacol 800 at a dose of 4.8 g/day has been marketed in Canada; the Applicant estimates that the exposure is approximately 11,000 patient-years.

Periodic data review and annual Periodic Safety Update Reports (PSURs, last submitted 08 August 2007) indicate that Asacol's post-marketing safety profile remains consistent overall with the clinical trials experience with Asacol, as reflected in the current product label for Asacol 400 mg tablets.

7.1.17.1 Deaths

No deaths were reported in the Asacol 800 experience from Canada since April 2005, at a dose of 4.8 g/day.

7.1.17.2 Other Serious Adverse Events

No other serious adverse events were reported in Asacol 800 experience from Canada since April 2005, at a dose of 4.8 g/day.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Across the three studies (Studies 82, 83, & 2006444), 727 patients received Asacol 800 at a dose of 4.8 g/day for a mean duration of exposure of approximately six weeks. (See description of studies in Section 4.2.)

7.2.1.2 Demographics and Baseline Characteristics

Demographic and baseline characteristic data, ulcerative colitis history data, and baseline disease state characteristics data for the intent-to-treat population for the three Phase III studies combined are shown in the tables below.

Table 30. Demographic and Baseline Characteristics (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Parameter Statistic/Category	2.4 g/day Asacol (400 mg tablet) (N=732)	4.8 g/day Asacol (800 mg tablet) (N=727)	p-value
Age			0.0443
n	732	727	
Mean (SD)	42.7 (13.68)	44.1 (13.31)	
Median	42.0	44.0	
Min,Max	18,75	18,76	
Age Group	732 (100.0%)	727 (100.0%)	0.5398
<65 years	674 (92.1%)	663 (91.2%)	
>=65 years	58 (7.9%)	64 (8.8%)	
Height (cm)			0.5860
n	381	389	
Mean (SD)	171.43 (9.238)	171.07 (9.266)	
Median	171.00	171.00	
Min,Max	145.0,202.0	152.0,200.0	
Weight (kg)			0.6829
n	729	727	
Mean (SD)	76.03 (17.163)	76.34 (16.901)	
Median	74.40	75.00	
Min,Max	42.0,149.8	37.0,140.3	
Race	732 (100.0%)	727 (100.0%)	0.8580
Caucasian	640 (87.4%)	636 (87.5%)	
Black	41 (5.6%)	45 (6.2%)	
Hispanic	31 (4.2%)	24 (3.3%)	
Indian (Asian)	10 (1.4%)	8 (1.1%)	
Asian (Oriental)	3 (0.4%)	4 (0.6%)	
Multi-Racial	7 (1.0%)	10 (1.4%)	
Sex	732 (100.0%)	727 (100.0%)	0.8723
Male	379 (51.8%)	374 (51.4%)	
Female	353 (48.2%)	353 (48.6%)	
Smoking History	732 (100.0%)	727 (100.0%)	0.5660
Currently	72 (9.8%)	67 (9.2%)	
Never	437 (59.7%)	421 (57.9%)	
Previously	223 (30.5%)	239 (32.9%)	

(Table above is taken from Page 39 of the Applicant's Summary of Clinical Safety.)

Table 31. Ulcerative Colitis History (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Parameter Category	2.4 g/day Asacol (400 mg tablet) (N=732) (n%)	4.8 g/day Asacol (800 mg tablet) (N=727) (n%)	p-value
Disease Extent History	728 (100.0%)	722 (100.0%)	0.7048
Proctitis	63 (8.7%)	63 (8.7%)	
Proctosigmoiditis	290 (39.8%)	273 (37.8%)	
Left-Sided Colitis	234 (32.1%)	252 (34.9%)	
Pancolitis(Pancolitis + Extensive)	141 (19.4%)	134 (18.6%)	
Length of Disease History	728 (100.0%)	725 (100.0%)	0.2997
<1 year	248 (34.1%)	220 (30.3%)	
1 to 5 yrs	204 (28.0%)	229 (31.6%)	
>5 to 10 yrs	131 (18.0%)	141 (19.4%)	
>10 yrs	145 (19.9%)	135 (18.6%)	
Steroids (oral or IV)	732 (100.0%)	727 (100.0%)	0.6221
No	463 (63.3%)	468 (64.4%)	
Yes	269 (36.7%)	259 (35.6%)	
Immunomodulators	732 (100.0%)	727 (100.0%)	0.7682
No	705 (96.3%)	698 (96.0%)	
Yes	27 (3.7%)	29 (4.0%)	
Sulfasalazine	732 (100.0%)	727 (100.0%)	0.8140
No	408 (55.7%)	408 (56.1%)	
Yes	324 (44.3%)	319 (43.9%)	
Sulfa-free oral 5-ASAs	732 (100.0%)	727 (100.0%)	0.1347
No	358 (48.9%)	326 (44.8%)	
Yes	374 (51.1%)	401 (55.2%)	
Any oral 5-ASAs	732 (100.0%)	727 (100.0%)	0.4447
No	205 (28.0%)	189 (26.0%)	
Yes	527 (72.0%)	538 (74.0%)	
Rectal Therapies	732 (100.0%)	727 (100.0%)	0.9408
No	411 (56.1%)	406 (55.8%)	
Yes	321 (43.9%)	321 (44.2%)	
Relapse Frequency	730 (100.0%)	727 (100.0%)	0.4659
Newly diagnosed	195 (26.7%)	177 (24.3%)	
Less than once a year	132 (18.1%)	141 (19.4%)	
Once every 6-12 months	176 (24.1%)	184 (25.3%)	
Once every 6 months	159 (21.8%)	172 (23.7%)	
More than once a month	68 (9.3%)	53 (7.3%)	

(Table above is taken from Page 41 of the Applicant's Summary of Clinical Safety.)

Table 32. Baseline Disease State Characteristics (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Parameter Statistic/Category	2.4 g/day Asacol (400 mg tablet) (N=732)	4.8 g/day Asacol (800 mg tablet) (N=727)	p-value
Stool Frequency Score	731 (100.0%)	727 (100.0%)	0.0630
0 (Normal Frequency)	35 (4.8%)	36 (5.0%)	
1 (1 to 2 greater than normal)	224 (30.6%)	196 (27.0%)	
2 (3 to 4 greater than normal)	359 (49.1%)	405 (55.7%)	
3 (>= 5 greater than normal)	113 (15.5%)	90 (12.4%)	
Rectal Bleeding Score	731 (100.0%)	727 (100.0%)	0.3145
0 (none)	72 (9.8%)	58 (8.0%)	
1 (Streak, less than 1/2 time)	228 (31.2%)	238 (32.7%)	
2 (Obvious, most of time)	405 (55.4%)	414 (56.9%)	
3 (Blood alone)	26 (3.6%)	17 (2.3%)	
Patient's Functional Assessment Score	731 (100.0%)	727 (100.0%)	0.9117
0 (Generally well)	96 (13.1%)	96 (13.2%)	
1 (Fair)	363 (49.7%)	366 (50.3%)	
2 (Poor)	261 (35.7%)	257 (35.4%)	
3 (Terrible)	11 (1.5%)	8 (1.1%)	
Physician Global Assessment Score	731 (100.0%)	727 (100.0%)	0.2054
1 (Mild disease)	113 (15.5%)	125 (17.2%)	
2 (Moderate disease)	618 (84.5%)	602 (82.8%)	
Sigmoidoscopy Score	349 (100.0%)	338 (100.0%)	0.1808
1 (Mild)	102 (29.2%)	121 (35.8%)	
2 (Moderate)	218 (62.5%)	191 (56.5%)	
3 (Severe)	29 (8.3%)	26 (7.7%)	
Sigmoidoscopy Score with CFT	383 (100.0%)	389 (100.0%)	0.3022
1 (Mild)	2 (0.5%)	0 (0.0%)	
2 (Moderate)	364 (95.0%)	368 (94.6%)	
3 (Severe)	17 (4.4%)	21 (5.4%)	
Baseline UCDAI			0.5180
n	731	727	
Mean (SD)	7.0 (1.62)	7.0 (1.59)	
Median	7.0	7.0	
Min,Max	3,11	2,11	
Number of days in Flare	721 (100.0%)	720 (100.0%)	0.7968
0 to 14	65 (9.0%)	61 (8.5%)	
15 to 28	129 (17.9%)	138 (19.2%)	
>28	527 (73.1%)	521 (72.4%)	

(Table above is taken from Page 42 of the Applicant's Summary of Clinical Safety.)

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure across the three studies (Studies 82, 83, & 2006444) is summarized in the table below.

Table 33. Extent of Exposure to Study Drug (Studies 2000082, 2000083 and 2006444 Combined; ITT)

Parameter	2.4g/day Asacol (400mg Tablet) (N=732)	4.8g/day Asacol (800mg Tablet) (N=727)
Mean number of patient-days of exposure		
n	724	721
Mean(SD)	40.13 (8.79)	40.05 (9.13)
Min	2	1
25%-tile	41	41
Median	42	42
75%-tile	44	44
Max	61	62
Duration of Treatment		
>0 Weeks	732 (100%)	727 (100%)
>3 Weeks	674 (92%)	670 (92%)

(Table above is taken from Page 3 of the Applicant's Summary of Clinical Safety.)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Another study (Study 2004112) was conducted in the United States (under IND 26,093) and Europe comparing Asacol 4.8 g/day (800) ; 169 more patients received Asacol 4.8 g/day (800) for a mean duration of exposure of approximately seven weeks. (See table below.) b(4)

Table 34. Extent of Exposure to Study Drug Among Patients Taking 4.8 g/day (Study 2004112)

Exposure	Asacol 4.8 g/day (N=169)
n	169
Total patient-days of exposure	8615
Mean patient-days of exposure	51.0
Total Patient-years of exposure	23.6

(Table above is taken from Page 3 of the Applicant's Summary of Clinical Safety.)

7.2.2.2 Postmarketing experience

An estimation of patient-years exposure for Asacol 800 is based on the Applicant's shipment data to Canada and on the assumption that patients are treated with the maximum daily dose for the tablet formulation. There were tablets (800 mg) shipped since approval in Canada (April 2005). The maximum dose per day is six 800 mg tablets, such that the supply shipped would account for an estimated patient-days (11,635 patient-years). (See also Section 7.1.17.) b(4)

7.2.2.3 Literature

This safety review does not contain a significant review of the scientific literature on either mesalamine or UC.

7.2.3 Adequacy of Overall Clinical Experience

The database is sufficiently large to allow for adequate assessment of the safety profile of Asacol 800, although events that occur rarely (in fewer than 1/1000 patients) may not have been detected. In addition, the median length of exposure to Asacol 800 does not permit the adequate assessment of the rate and risk of events that may need long exposures to develop.

The demographics of patients treated with Asacol 800 in UC trials are adequate for the purposes of analyzing the safety of Asacol 800 for the treatment of patients with moderately active UC. The number of non-Caucasian patients exposed to Asacol 800 in clinical trials was small, but the known characteristics of neither Asacol 800 nor UC suggest that the safety profile of Asacol 800 would be appreciably different in non-Caucasian populations.

There has been no experience with Asacol 800 in the pediatric population and negligible experience with Asacol 800 in the geriatric population. It must be noted that the safety profile of Asacol 800 may be different in patients younger than 18 and older than 64. The safety data currently available cannot necessarily be extrapolated to children, adolescents, and older patients.

The Division of Gastroenterology Products requested Ann Corken Mackey, RPh, MPH, from the Division of Adverse Event Analysis 1, to conduct a search of the Adverse Event Reporting System (AERS) for evidence that hypersensitivity and renal impairment associated with mesalamine use are dose-related. The safety evaluator also conducted a literature search. The safety evaluator concluded that the AERS database cannot identify dose-related adverse events due to lack of confirmation that the AE is due to increased or decreased dose, due to incomplete data submission on dosage for each case, and due to a lack of denominator for each dose and AE. The safety evaluator concluded based on reports in the medical literature, that the risk of mesalamine-induced renal impairment does not appear to be dose-related. (See Safety Evaluator Review dated March 19, 2008 included in Section 10.4 of this review; filed under NDA [redacted] in DFS.) b(4)

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No additional animal or in vitro testing has been submitted with this application. The protocol defined clinical testing and safety assessments were adequate given the extensive safety experience with mesalamines.

7.2.5 Adequacy of Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate. The methods for acquisition of laboratory and adverse event data in the development program are described in the relevant sections (7.1.5, Common Adverse Events; and 7.1.7, Laboratory Findings). The routine clinical testing that was done was adequate to assess the safety of Asacol 800.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Based on the results of the previous two studies conducted using Asacol 800 that were submitted for the previous review cycle, no significant findings were found with regard to laboratory parameters or ECG changes. Thus, additional laboratory measurements or ECGs were not required for the current study submission. The clinical pharmacology data submitted by the Applicant as a part of the application was considered adequate by the Clinical Pharmacology Team (see Section 5.)

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The database is sufficiently large to allow for adequate assessment of the safety profile of Asacol 800, although events that occur rarely (in fewer than 1/1000 patients) may not have been detected. In addition, the median length of exposure to Asacol 800 does not permit the adequate assessment of the rate and risk of events that may need long exposures to develop.

Although no evidence of change in renal function was identified based on the studies submitted, a longer duration of follow-up and more patients may be needed to identify change in renal function.

7.2.8 Assessment of Quality and Completeness of Data

The primary source data provided was complete and of good quality.

7.2.9 Additional Submissions, Including Safety Update

Data from the following additional submissions have been included in this safety review:

- Responses to FDA queries and requests, including responses with FDA received date of:
  - December 11, 2007
  - February 13, 2008
  - February 25, 2008
  - March 4, 2008
  - April 3, 2008
  - April 11, 2008
  - May 8, 2008
  - May 14, 2008
  - May 19, 2008

See Section 4.1 also.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Across the three studies (Studies 82, 83, & 2006444), 727 patients received Asacol 800 (4.8 g/day) and 732 patients received Asacol 2.4 g/day for a mean duration of approximately six weeks. Overall, a comparable safety profile between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day was found with some notable points.

SAEs were less common in the Asacol 800 (4.8 g/day) group than in the Asacol group (0.8% vs. 1.8%); this is partly accounted for by a lower incidence of UC exacerbations in the Asacol 800 (4.8 g/day) group than in the Asacol 2.4 g/day group (2.3% vs. 2.7%). The majority of SAEs were described in the currently approved Asacol (400 mg tablets) labeling, and primarily involved the gastrointestinal system.

Moderate AEs were more common in the Asacol 800 (4.8 g/day) group than the Asacol 2.4 g/day group (37% vs. 30%). Mild AEs were more common in the Asacol 2.4 g/day group than the Asacol 800 (4.8 g/day) group (55% vs. 63%).

Withdrawals due to AEs were similar between treatment groups, 4.2% in the Asacol 2.4 g/day group and 3.9% in the Asacol 800 (4.8 g/day) group. The majority of withdrawals due to AEs occurred as a result of events described in the currently approved Asacol (400 mg tablets) labeling, and primarily involved the gastrointestinal system.

Overall incidence of adverse events seen with Asacol 800 therapy (27.7%) was similar to the overall incidence of adverse reactions seen with the Asacol 400 mg tablet (28.8%). The most common adverse events reported (> 1% in either group) were nausea, abdominal pain, nasopharyngitis, headache, and exacerbation of ulcerative colitis.

Upper respiratory infections were more common in the Asacol 800 (4.8 g/day group than in the Asacol 2.4 g/day group (4.0% vs. 3.1%); this is largely accounted for by a higher incidence of nasopharyngitis in the Asacol 800 (4.8 g/day) group than in the Asacol 2.4 g/day group (2.5% vs. 1.4%).

The incidence of nausea and vomiting symptoms appears to be of similar magnitude in both treatment groups (3.3% in both groups). The finding of a higher incidence of nausea and vomiting in the 4.8 g/day Asacol 800 group than the Asacol 2.4 g/day group from the previous review (based on Studies 82 and 83) appears to not be present in the larger combined dataset that also includes Study 2006444.

The mean change in creatinine was +1% from Baseline to Week 6 in both treatment groups; the number of subjects with a normal to high shift was 4 in the 2.4 g/day arm and 1 in the 4.8 g/day arm. Although no evidence of change in renal function was identified based on the studies submitted, a longer duration of follow-up and more patients may be needed to identify change in renal function.

Since April 2005, Asacol 800 at a dose of 4.8 g/day has been marketed in Canada; the Applicant estimates that the exposure is approximately 11,000 patient-years. Ten spontaneous reports have been received, all of which were non-serious AEs. All except one AE, dysphagia, is currently listed in the currently approved Asacol (400 mg tablets) labeling.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Across the three studies (Studies 82, 83, & 2006444), 727 patients received Asacol 800 at a dose of 4.8 g/day for a mean duration of exposure of approximately six weeks and 732 patients received Asacol (400 mg tablets) at a dose of 2.4 g/day.

7.4.1.1 Pooled data vs. individual study data

Conclusions of the safety review are primarily based on the pooled data from the three studies (Studies 82, 83, & 2006444). The pooled data was primarily used for assessing the incidence of adverse events in the Asacol 800 and the Asacol groups.

7.4.1.2 Combining data

This review pools studies by simple combination of numerators and denominators and does not employ other pooling procedures.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Overall, a comparable safety profile between treatment groups (Asacol 800 4.8 g/day vs. Asacol 2.4 g/day) was found with some notable points.

- Asacol 800 4.8 g/day had a lower incidence of SAEs (0.8% vs. 1.8% with Asacol 2.4 g/day); this was partly accounted for by a lower incidence of UC Exacerbations (2.3% vs. 2.7% with Asacol 2.4 g/day)
- Asacol 800 4.8 g/day had a higher incidence of upper respiratory infection (4.0% vs. 3.1% with Asacol 2.4 g/day); this was mainly accounted for by a higher incidence of nasopharyngitis (2.5% vs. 1.4% with Asacol 2.4 g/day)
- Asacol 800 4.8 g/day had a higher proportion of moderate AEs (37% vs. 30% with Asacol 2.4 g/day) but a lower proportion of mild AEs (55% vs. 63% with Asacol 2.4 g/day)

7.4.2.2 Explorations for time dependency for adverse findings

No particular explorations for time dependency of adverse events were conducted.

7.4.2.3 Explorations for drug-demographic interactions

Subgroup analyses of AE data for sex, age, and race were performed on data from the Phase III studies.

Sex
In the intent-to-treat population, the AE profile for male patients showed that more males in the Asacol (2.4 g/day) group reported diarrhea than in the Asacol 800 (4.8 g/day) group (2.1% and 0.8%, respectively). Female patients reported nasopharyngitis less frequently in the 2.4 g/day (400 mg tablet) than in the Asacol 800 (4.8 g/day) group (1.1% and 3.1%, respectively). In patients with moderately active disease, males reported pyrexia more frequently in the Asacol (2.4 g/day) group than in the Asacol 800 (4.8 g/day) group (2.2% and 0.3% respectively). As in the intent-to-treat population, females reported nasopharyngitis less frequently the Asacol (2.4 g/day) group than in the Asacol 800 (4.8 g/day) group (1.0% and 2.7%, respectively). See also Section 10.2.4.

Age
Approximately 122 of the 1459 ITT patients (and 102 of the 1220 moderate disease population) in the Phase III studies were 65 years of age or older. Events were generally similar between the ≥65 years old and the <65 years old populations (ITT and moderate disease population). No clear relation of age with occurrence of particular adverse events was appreciated. The age subgroup analysis is in Section 10.2.5.

Race
Of the Phase III studies, approximately 1276 of the ITT patient population were Caucasian, approximately 86 were Black, and approximately 97 were other races. Events were generally similar between the three groups. No clear relation of race with occurrence of particular adverse events was appreciated. The age subgroup analysis is in Section 10.2.6.

7.4.2.4 Explorations for drug-disease interactions

No particular explorations for drug-disease interactions were conducted.

7.4.2.5 Explorations for drug-drug interactions

There are no known drug interactions with Asacol, and no drug-drug interaction studies were performed in this clinical development program.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This reviewer recommends that the dose of Asacol 800 tablets be two Asacol 800 mg tablets (1.6 g) to be taken three times a day for a total daily dose of 4.8 g for six weeks.

One Asacol 800 mg tablet is not interchangeable with two Asacol 400 mg tablets, because the relative bioavailability study showed that the mean C_{max} was 36% lower and the mean AUC was 25% lower with administration of the 800 mg tablet relative to two 400 mg tablets.

8.2 Drug-Drug Interactions

There are no known drug interactions with Asacol, and no drug-drug interaction studies were performed in this clinical development program.

8.3 Special Populations

Asacol 800 has not been studied in enough patients with renal insufficiency, hepatic insufficiency, age $\geq$ 65, age < 18, or in women who are pregnant or nursing to assess safety and efficacy in these populations. Asacol 800 should be used during pregnancy only if clearly needed.

It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol 800 and periodically while on therapy. Caution should be exercised when using Asacol 800 in patients with known renal dysfunction or history of renal disease.

Reports from uncontrolled clinical studies and postmarketing reporting systems for Asacol (mesalamine) suggested a higher incidence of blood dyscrasias, i.e., agranulocytosis, neutropenia, pancytopenia, in patients who were 65 years or older. Caution should be taken to closely monitor blood cell counts during mesalamine therapy.

8.4 Pediatrics

Safety and efficacy have not been established in pediatric patients.

Partial waiver was granted for patients age 0 to 4 years old during the first review cycle of this NDA with the rationale stated in the "PREA Partial Waiver Granted" Letter dated October 19, 2005, as "...studies are impossible or highly impractical because the number of patients is so small and geographically dispersed."

During the first review cycle of this NDA, the Applicant was granted a partial waiver for patients age 0 to 4 years old from enrollment in future UC pediatric studies with Asacol 800. Based on the information submitted, this reviewer recommends that pediatric studies in age 5 to 17 years old UC patients be deferred, that the Asacol 400 mg tablets be the age-appropriate formulation for Asacol 800, and that a required Phase 4 commitment for Asacol 800 be the completion of the following postmarketing study:

(1) A randomized, double-blind study of six weeks of at least two dose levels in pediatric patients ages 5 to 17 years to evaluate the safety and effectiveness of those doses and to compare with results seen in adults. The study should include at least 40 patients in each dosage arm; in each arm, five patients should be age 5 years to 8 years. A protocol should be submitted by August 15, 2008, study should start by October 15, 2008, study

should be completed by November 13, 2009, and study report should be submitted by January 15, 2009.

8.5 Advisory Committee Meeting

There was no Advisory Committee meeting required for this NDA because there is considerable experience with other mesalamine products such as Asacol 800, and because there are no concerns related to safety or efficacy of Asacol 800 that would require recommendations from an Advisory Committee.

8.6 Literature Review

A brief review of the scientific literature was conducted with regard to the scoring systems used in UC (see Sections 6.1.2.1, 10.1.1, 10.1.2, and 10.1.3.)

8.7 Postmarketing Risk Management Plan

In this NDA, there are no applicable issues related to risk management.

8.8 Other Relevant Materials

Review of this application included consultation from the Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention (DMEP) formerly known as Division of Medication Errors and Technical Support (DMETS), Study Endpoints and Label Development (SEALD) Labeling Team, and Division of Adverse Event Analysis 1 (DAEA1).

The Division of Gastroenterology Products requested Ann Corken Mackey, RPh, MPH, from DAEA1, to conduct a search of the Adverse Event Reporting System (AERS) for evidence that hypersensitivity and renal impairment associated with mesalamine use are dose-related. The safety evaluator also conducted a literature search. The safety evaluator concluded that the AERS database cannot identify dose-related adverse events due to lack of confirmation that the AE is due to increased or decreased dose, due to incomplete data submission on dosage for each case, and due to a lack of denominator for each dose and AE. The safety evaluator concluded based on reports in the medical literature, that the risk of mesalamine-induced renal impairment does not appear to be dose-related. (See Safety Evaluator Review dated March 19, 2008 included in Section 10.4 of this review; filed under NDA — in DFS.) b(4)

Prior to the current proprietary name review by DMEP, there was a proprietary name review dated July 20, 2005 by DMETS. In that review, DMETS summarized that it believes that there is potential for confusion and substitution between the "400" and "800" dosage forms, but that the Division has clarified that such confusion will not pose a safety risk. A Trade Name Acceptable Letter" dated August 1, 2005, was sent to the applicant that stated that the proposed trade name "Asacol 800" is acceptable. On the current review cycle, DMEP has in a review dated April 18, 2008, summarized that it is highly probable that substitution errors would occur between Asacol 800 and Asacol, and that the two products cannot safely co-exist in the marketplace. Although this reviewer believes that the safety concerns posed from such a substitution are minimal, this reviewer agrees with the DMEP reviewers that the potential for

confusion from such substitutions would occur commonly if the product under review was approved as "Asacol 800". DMEP also provided updated recommendations for container labels and carton labeling.

Results of discussions with the SEALD Labeling Team are included within Section 9.4 Labeling Review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy

This reviewer concludes that in Study 2006444, the primary efficacy analysis (treatment success at Week 6) demonstrated non-inferiority between Asacol 800 (4.8g/day) and Asacol (2.4g/day). Treatment success rates were 70.2% in the Asacol 800 group and 65.5% in the Asacol group. The difference (Asacol 800 – Asacol) was 5% (95% confidence interval: [-1.9%, 11.2%]). Treatment success in the Asacol 800 group in Study 82 with moderately active UC was as similar to that of 71.8%. Thus, this reviewer concludes that based on the results of the two studies, Study 2006444 and Study 82, non-inferiority of Asacol 800 (4.8 g/day) and Asacol (2.4 g/day) has been demonstrated. This reviewer recommends that Asacol 800 be approved for the treatment of adult patients with moderately active ulcerative colitis with revisions to the proposed labeling.

This reviewer concludes that in Study 2006444, treatment success at Week 6 was similar for male and female subjects by treatment group; a gender difference in treatment effect was not seen in Study 2006444 as it had been seen in Study 82. The gender difference observed in Study 82 remains unexplained; however, this reviewer does not believe that additional studies are warranted. The applicant has adequately addressed the gender difference by obtaining and analyzing results by gender in Study 2006444..

This reviewer notes that in Study 2006444, a *post hoc* analysis of Week 6 remission rates (defined as stool frequency and rectal bleedings scores of 0) were nominally statistically significantly greater in the Asacol 800 group (43% vs. 35%, nominal p=0.045). This reviewer further notes that the rates of improvement for individual clinical assessments (stool frequency, rectal bleeding, PFA, sigmoidoscopy) and composite scores (PGA and UCDAI) by Week 6 were similar by treatment group.

Safety

Across the three studies (Studies 82, 83, & 2006444), 727 patients received Asacol 800 (4.8 g/day) and 732 patients received Asacol 2.4 g/day for a mean duration of approximately six weeks. Overall, a comparable safety profile between Asacol 800 (4.8 g/day) and Asacol 2.4 g/day was found with some notable points.

SAEs were less common in the Asacol 800 (4.8 g/day) group than in the Asacol group (0.8% vs. 1.8%); this is partly accounted for by a lower incidence of UC exacerbations in the Asacol 800 (4.8 g/day) group than in the Asacol 2.4 g/day group (2.3% vs. 2.7%). The majority of SAEs were described in the currently approved Asacol (400 mg tablets) labeling, and primarily involved the gastrointestinal system.

Moderate AEs were more common in the Asacol 800 (4.8 g/day) group than the Asacol 2.4 g/day group (37% vs. 30%). Mild AEs were more common in the Asacol 2.4 g/day group than the Asacol 800 (4.8 g/day) group (55% vs. 63%).

Withdrawals due to AEs were similar between treatment groups, 4.2% in the Asacol 2.4 g/day group and 3.9% in the Asacol 800 (4.8 g/day) group. The majority of withdrawals due to AEs occurred as a result of events described in the currently approved Asacol (400 mg tablets) labeling, and primarily involved the gastrointestinal system.

Overall incidence of adverse events seen with Asacol 800 therapy (27.7%) was similar to the overall incidence of adverse reactions seen with the Asacol 400 mg tablet (28.8%). The most common adverse events reported (> 1% in either group) were nausea, abdominal pain, nasopharyngitis, headache, and exacerbation of ulcerative colitis.

Upper respiratory infections were more common in the Asacol 800 (4.8 g/day group than in the Asacol 2.4 g/day group (4.0% vs. 3.1%); this is largely accounted for by a higher incidence of nasopharyngitis in the Asacol 800 (4.8 g/day) group than in the Asacol 2.4 g/day group (2.5% vs. 1.4%).

The incidence of nausea and vomiting symptoms appears to be of similar magnitude in both treatment groups (3.3% in both groups). The finding of a higher incidence of nausea and vomiting in the 4.8 g/day Asacol 800 group than the Asacol 2.4 g/day group from the previous review (based on Studies 82 and 83) appears to not be present in the larger combined dataset that also includes Study 2006444.

No evidence of change in renal function was identified based on the studies submitted. The mean change in creatinine was +1% from Baseline to Week 6 in both treatment groups; the number of subjects with a normal to high shift was 4 in the 2.4 g/day arm and 1 in the 4.8 g/day arm.

Since April 2005, Asacol 800 at a dose of 4.8 g/day has been marketed in Canada; the Applicant estimates that the exposure is approximately 11,000 patient-years. Ten spontaneous reports have been received, all of which were non-serious AEs. All except one AE, dysphagia, is currently listed in the currently approved Asacol (400 mg tablets) labeling.

The data are adequate for safety labeling as revised based on recommendations provided in Section 9.4.

9.2 Recommendation on Regulatory Action

This reviewer recommends that Asacol 800 delayed-release tablets at a dose of 4.8 g/day be approved for the treatment of adult patients with moderately active ulcerative colitis with revisions to the proposed labeling. The information in this submission provides substantial evidence to support the proposed indication, and there are data to provide adequate directions for use.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There is no applicable activity related to risk management for this New Drug Application (NDA).

9.3.2 Required Phase 4 Commitments

Safety and efficacy have not been established in pediatric patients. Partial waiver was granted for patients age 0 to 4 years old from enrollment in future UC pediatric studies with Asacol 800 during the first review cycle of this NDA. This reviewer recommends that age 5 to 17 years old patients also be waived from enrollment in future UC pediatric studies with Asacol 800.

9.3.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

9.4 Labeling Review

Discussions between the Applicant and CDER have resolved major issues with regard to the label. Several significant changes have been made to the applicant's proposed labeling. These include the following:

Section 1 Indications and Usage and Section 2 Dosage and Administration

- It was decided to add a statement that the safety and effectiveness of Asacol 800 beyond 6 weeks has not been established in each of the sections.

Section 6.1 Clinical Trials Experience

- It was decided to not explicitly state in this section how the measures of systemic exposure (Cmax and AUC) differed between Asacol 800 and Asacol, but instead to refer to the Section 12.3 Pharmacokinetics section.

Section 6.2 Adverse Reactions Information from Other Sources

- Adverse events were updated to include additional AEs from postmarketing experience with other mesalamine products including Asacol 400 mg tablets, and from clinical trial experience with Asacol 800.

Section 10 Overdosage

- It was decided to remove the description of the two cases of overdosage in children that are described in the Asacol 400 mg tablets label.
- Instead, a statement of the recommended management in case of overdose was provided.

Section 12.3 Pharmacokinetics

- Based on internal discussions between the clinical review team and the clinical pharmacology review team, it was decided to include a statement that informs the reader that the relationship between measures of systemic exposure (e.g., Cmax and AUC) and clinical efficacy are not known because the action of mesalamine is believed to be topical, and not systemic. This statement was added in order to communicate that the 25% lower AUC and 36% lower Cmax of the Asacol 800 tablet compared to two Asacol (400 mg tablets) may not be associated with a change in efficacy.

Section 14.1 Moderately Active Ulcerative Colitis

- It was decided to not explicitly state in this section how the measures of systemic exposure (Cmax and AUC) differed between Asacol 800 and Asacol, but instead to refer to the Section 12.3 Pharmacokinetics section.
- It was decided not to describe in detail the results of Study 82 because it was not the major basis of the finding of the demonstration of efficacy; it was decided to only include the proportion of moderately active UC patients that met the primary endpoint of treatment success without stating the comparative rate in the control group.
- It was decided to describe the study design and results of Study 2006444 in detail because it was the major basis of the finding of the demonstration of efficacy; and to describe the results of Study 82 in limited detail because it was supportive but not able to stand on its own.
- It was decided to only state the proportion of moderately active UC patients that were treated with Asacol 800 in Study 82 and that met the primary endpoint of treatment success without stating the comparative rate in the control group (Asacol 400 mg tablets), because inclusion of the rate in the control group could be misconstrued as evidence of superiority of Asacol 800 over Asacol 400 mg tablets.

9.5 Comments to Applicant

Additional comments should be conveyed to the applicant regarding the proprietary name.

Prior to the current proprietary name review by DMEP, there was a proprietary name review dated July 20, 2005 by DMETS. In that review, DMETS summarized that it believes that there is potential for confusion and substitution between the "400" and "800" dosage forms, but that the Division has clarified that such confusion will not pose a safety risk.

A Trade Name Acceptable Letter" dated August 1, 2005, was sent to the applicant that stated that the proposed trade name "Asacol 800" is acceptable.

On the current review cycle, DMEP has in a review dated April 18, 2008, summarized that it is highly probable that substitution errors would occur between Asacol 800 and Asacol and that the two products cannot safely co-exist in the marketplace. Although this reviewer believes that the safety concerns posed from such a substitution are minimal, this reviewer agrees with the DMEP reviewers that the potential for confusion from such substitutions would occur commonly if the product under review was approved as "Asacol 800". DMEP also provided updated recommendations for container labels and carton labeling.

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10 APPENDICES

The review of individual study reports has been integrated into the Integrated Review of Efficacy (see Section 6) and the Integrated Review of Safety (see Section 7). Pertinent information from individual study reports that is not integrated into the Integrated Review of Efficacy and the Integrated Review of Safety is summarized in the appendices in the sub-sections below. See Section 4.2 for features of each of the individual studies.

10.1 Study Endpoint Definition and Scoring

10.1.1 Appendix 1: Physician's Global Assessment (PGA)

Table 35. PGA Score Calculation

0	Quiescent disease activity	0 = Stool frequency 0 = Rectal bleeding 0 = Sigmoidoscopy findings
1	Mild disease activity (mostly 1's)	0 or 1 = Stool frequency 0 or 1 = Rectal bleeding 0 or 1 = Sigmoidoscopy findings
2	Moderate disease activity (mostly 2's)	1 or 2 = Stool frequency 1 or 2 = Rectal bleeding 1 or 2 = Sigmoidoscopy findings
3	Severe disease activity (mostly 3's)	2 or 3 = Stool frequency 2 or 3 = Rectal bleeding 2 or 3 = Sigmoidoscopy findings

(Table above is taken from Page 156 of the Applicant's Study Report for 2006444)

10.1.2 Appendix 2: Ulcerative Colitis Disease Activity Index (UCDAI)

Table 36. UCDAI Score Calculation

1. Stool Frequency	**0 = Normal** **1 = 1-2 stools daily > normal** **2 = 3-4 stools daily > normal** **3 = >4 stools daily > normal**
2. Rectal Bleeding	**0 = None** **1 = Streaks of blood** **2 = Obvious blood** **3 = Mostly blood**
3. Mucosal appearance	**0 = Normal** **1 = Mild friability** **2 = Moderate friability** **3 = Exudation, spontaneous bleeding**
4. Physician's rating of disease activity	**0 = Normal** **1 = Mild** **2 = Moderate** **3 = Severe**
Score Range	**0-12**

10.1.3 Appendix 3: Stool Frequency, Rectal Bleeding, Sigmoidoscopy, Patient's Functional Assessment

Table 37. Stool Frequency

Stool Frequency	
0	Normal stool frequency per day
1	1-2 stools greater than normal per day
2	3-4 stools greater than normal per day
3	≥ 5 stools greater than normal per day

(Table above is taken from Page 153 of the Applicant's Study Report for 2006444)

Table 38. Rectal Bleeding

Rectal Bleeding	
0	No blood seen
1	Streaks of blood with stool less than half of the time
2	Obvious blood with stool most of the time
3	Blood alone passed

(Table above is taken from Page 154 of the Applicant's Study Report for 2006444)

Table 39. Sigmoidoscopy Assessment Score

Sigmoidoscopy Assessment Score		
0	Normal	Intact vascular pattern, no friability or granularity
1	Mild	Erythema; diminished or absent vascular markings; mild granularity
2	Moderate	Marked erythema, granularity; absent vascular markings; bleeds with minimal trauma; no ulcerations
3	Severe	Spontaneous bleeding, ulcerations

(Table above is taken from Page 152 of the Applicant's Study Report for 2006444)

Table 40. Friability Assessment

Friability Assessment	
Negative	No bleeding after light touch to the worst affected mucosa
Positive	Bleeding after light touch to the worst affected mucosa between 15 cm and 60 cm from the anal verge

(Table above is taken from Page 152 of the Applicant's Study Report for 2006444)

Table 41. Patient's Functional Assessment (PFA)

Patient's Functional Assessment (PFA)	
0	Generally well
1	Fair
2	Poor
3	Terrible

(Table above is taken from Page 155 of the Applicant's Study Report for 2006444)

10.2 Adverse Event Tabulation

10.2.1 Serious Adverse Events

Table 42. Listing of Serious Adverse Events Studies 2000082, 2000083 and 2006444 Combined (ITT)

Treatment Group Study Number Patient	Age/Sex/Race	Duration in Days First Dose to AE Onset	Investigator's Description of AE	MedDRA PT	Severity	AE Outcome	Action Taken
Asacol 2.4 g/d							
Study 2000082							
71152461	66/M/CAUC	12	CHOLECYSTITIS	Cholecystitis	Severe	Recovered	Drug Interrupted
71242931	61/M/CAUC	1	NAUSEA	Nausea	Moderate	Recovered	Drug Discontinued
		1	VOMITING	Vomiting	Moderate	Recovered	Drug Discontinued
		1	INCREASED DIARRHEA	Diarrhea	Moderate	Recovered	Drug Discontinued
		1	ABDOMINAL CRAMPING	Abdominal pain	Moderate	Recovered	Drug Discontinued
71262699	54/F/CAUC	7	EXACERBATION OF U.C.	Colitis ulcerative	Moderate	Recovered	Drug Discontinued
		11	NEPHRITIS	Nephritis	Moderate	Recovered	Drug Discontinued
71302267	48/F/HISP	19	PANCREATITIS	Pancreatitis	Severe	Recovered	Drug Discontinued
Study 2000083							
37263458	49/F/BLA	38	UTERINE FIBROIDS EXACERBATION	Uterine leiomyoma	Mild	Recovered	No Action Taken
		38	OVARIAN CYST EXACERBATION	Ovarian cyst	Mild	Recovered	No Action Taken
71003796	57/F/BLA	3	WORSENING OF ULCERATIVE COLITIS	Colitis ulcerative	Severe	Ongoing	Drug Discontinued
		3	RECTAL BLEEDING	Rectal hemorrhage	Severe	Ongoing	Drug Discontinued
Asacol 2.4 g/day							
71063246	31/F/HISP	-2	DIARRHEA	Diarrhea	Severe	Recovered	Drug Discontinued
		-2	LEFT SIDE ABDOMINAL PAIN	Abdominal pain	Moderate	Recovered	Drug Discontinued

		9	RIGHT UPPER QUADRANT PAIN	Abdominal pain upper	Moderate	Recovered	No Action Taken
		14	CHOLECYSTITIS	Cholecystitis	Severe	Recovered	No Action Taken
Study 2006444							
1030294003	30/M/CAUC	17	ENTEROCOLITIS OF UNCLEAR ETIOLOGY	Enterocolitis	Moderate	Recovered	No Action Taken
1030294005	19/M/CAUC	23	WORSENING OF ULCERATIVE COLITIS	Colitis ulcerative	Severe	Recovered	Drug Discontinued
1030394001	41/F/CAUC	16	SEVERE LOWER RIGHT QUADRANT ABDOMINAL PAIN	Abdominal pain lower	Severe	Recovered	No Action Taken
1030424022	26/M/CAUC	20	WORSENING OF UC	Colitis ulcerative	Moderate	Ongoing	Drug Discontinued
1030594002	18/F/CAUC	3	ULCERATIVE COLITIS DETERIORATION	Colitis ulcerative	Moderate	Recovered	Drug Discontinued
1031164006	29/M/CAUC	40	ACUTE GASTROENTERITIS BY INFECTION	Gastroenteritis	Moderate	Recovered	No Action Taken
Asacol 800 4.8 g/day							
Study 2000082							
71262708	20/M/CAUC	24	SHOULDER PAIN	Musculoskeletal pain	Moderate	Recovered	No Action Taken
		24	CHEST PAIN	Chest pain	Moderate	Recovered	No Action Taken
		24	PERICARDITIS	Pericarditis	Severe	Recovered	No Action Taken
Study 2000083							
72973876	23/M/CAUC	7	EPIGASTRIC PAIN	Abdominal pain upper	Severe	Recovered	Drug Discontinued
Study 2006444							
1030294006	32/M/CAUC	24	WORSENING OF ULCERATIVE COLITIS	Colitis ulcerative	Severe	Recovered	Drug Discontinued
1030344006	41/F/CAUC	8	DRUG ALLERGY	Drug hypersensitivity	Moderate	Ongoing	Drug Discontinued
1030384001	66/M/CAUC	44	MALGINANT TUMOR OF COLON SIGMOIDEUM	Colon cancer	Severe	Recovered	No Action Taken

1031134002	44/M/MULT	8	VASOVAGAL SYNCOPAL EPISODE(SECONDARY TO MICTRITION)	Syncope vasovagal	Severe	Recovered	Drug Interrupted

BLA=Black; CAUC=Caucasian; HIP=Hispanic; MULT=Multi-Racial
(Table above is taken from Pages 16 to 18 of the Applicant's Summary of Clinical Safety.)

10.2.2 Adverse Events that Led to Withdrawal

Table 43. Adverse Events that Led to Withdrawal Studies 2000082, 2000083 and 2006444 Combined (ITT)

Treatment Group Study Number Patient Number	Duration in Days First Dose to AE Onset	MedDRA PT
Asacol 2.4 g/day 400 mg TAB		
Study 2000082		
27884421	18	Diarrhea
27884427	2	Gastroenteritis viral
29792542	23	Colitis
	27	Nausea
	27	Vomiting
63972002	8	Myalgia
	8	Chest pain
	8	Dyspnea
71152454	12	Stomach discomfort
	12	Nausea
	12	Pyrexia
	12	Diarrhea
	14	Abdominal pain
	29	Vomiting
71242931	1	Nausea
	1	Vomiting
	1	Diarrhea
	1	Abdominal pain
71262699	7	Colitis ulcerative
71302267	19	Pancreatitis
Study 2000083		
20393609	2	Colitis ulcerative
37263452	4	Colitis ulcerative
37263457	10	Colitis ulcerative
70853181	14	Diarrhea
	14	Abdominal pain
71003796	3	Colitis ulcerative
	3	Rectal hemorrhage
71063246	-2	Diarrhea
	-2	Abdominal pain
73353848	1	Headache
73955038	10	Abdominal pain
	10	Frequent bowel movements
Study 2006444		
1030174004	15	Gastrointestinal hemorrhage
1030294005	23	Colitis ulcerative
Asacol 2.4 g/day 400 mg TAB		
Study 2006444		
1030304011	25	Abdominal pain

	25	Diarrhea
1030344010	4	Drug hypersensitivity
1030414007	9	Colitis ulcerative
1030424022	20	Colitis ulcerative
1030454001	2	Drug hypersensitivity
1030454003	2	Drug hypersensitivity
1030464018	24	Colitis ulcerative
1030484003	6	Colitis ulcerative
1030504002	26	Rectal hemorrhage
1030594002	3	Colitis ulcerative
1031304008	15	Nausea
	15	Gastroenteritis viral
1031884002	9	Colitis
1032204004	5	Colitis ulcerative
Asacol 4.8 g/day 800 mg TAB		
Study 2000082		
27884424	20	Colitis ulcerative
29792554	27	Colitis ulcerative
	27	Gastroenteritis
31864226	6	Nausea
	6	Pyrexia
	6	Arthralgia
71152467	1	Colitis ulcerative
71202573	6	Diarrhea
71222361	8	Condition aggravated
71252603	12	Diarrhea
	12	Nausea
	12	Flatulence
	12	Abdominal distension
74824370	3	Headache
	5	Back pain
	5	Neck pain
Asacol 4.8 g/day 800 mg TAB		
Study 2000083		
34933091	2	Nausea
	2	Vomiting
	2	Musculoskeletal chest pain
	2	Lung disorder
	2	Headache
37263455	11	Nausea
	11	Vomiting
61443361	1	Arthralgia
	1	Nausea
	1	Vomiting
	1	Dizziness
	1	Decreased appetite
	1	Headache

72973876	7	Abdominal pain upper
73353842	9	Colitis ulcerative
Study 2006444		
1030174002	6	Drug hypersensitivity
1030294006	24	Colitis ulcerative
1030344006	8	Drug hypersensitivity
1030364003	1	Abdominal pain upper
1030424044	5	Abdominal pain upper
1030584005	22	Colitis ulcerative
1030584010	13	Abdominal pain
	13	Vomiting
1030604016	7	Colitis ulcerative
1030924001	10	Colitis ulcerative
1031054004	8	Colitis
1031084002	2	Dermatitis allergic
	2	Vomiting
	2	Dehydration
1031314023	30	Colitis ulcerative
1031884005	6	Abdominal distension
	6	Abdominal pain
	6	Flatulence
1032204028	5	Colitis ulcerative
1032204029	8	Colitis ulcerative

(Table above is taken from Pages 20 to 22 of the Applicant's Summary of Clinical Safety.)

mutation- heterozygote type, urticaria in 2000. The patient had no known allergies. Onset date was Admission date was The patient experienced skin eruptions in the form of a rash, without maculo-papular changes, on upper and lower extremities and was admitted to the hospital. Admission erythrocyte sedimentation rate (ESR) was 32 mm/hour. b(6)
Fever and malaise developed a few days later and the dermatologist diagnosed a drug allergy to mesalamine. Treatment included methylprednisolone and loratadine and discontinuation of the study drug. On , ESR had improved to 20 mm/hour. Discharge Date was . Discharge Medications were sulfasalazine, budesonide. Concomitant Medications were sulfasalazine. The study drug was discontinued and the patient was withdrawn from the study on 31-Jan-2007.

Dyspnea: This was a was a 58 year-old Caucasian female who experienced muscle pain, chest pain, and shortness of breath, resulting in withdrawal due to the adverse events. The patient received Asacol 2.4 g/day (400 mg tablet) from 06-Jul-2001 to 16-Jul-2001. At study entry the physician's global assessment (PGA) score was 1 (mild disease). The patient began taking blinded study drug on 06-Jul-2001, and experienced muscle pain, chest pain, and shortness of breath beginning 13-Jul-2001. Study drug administration was interrupted from 14- to 15-Jul-2001; labs drawn in the Emergency Department were essentially normal. The b(6)
patient received Vicodin (paracetamol/hydrocodone) 1 tablet four times daily orally as needed for muscle pain from 15- to 18-Jul-2001. She experienced improvement in symptoms while study drug administration was interrupted, but when study drug was re-started on 16-Jul-2001, symptoms recurred, and study drug was discontinued on 16-Jul-2001. A chest x-ray done revealed no acute pathology. The patient recovered from the events by 18-Jul-2001. She was withdrawn from the study on 19-Jul-2001, due to the adverse events of muscle pain, chest pain, and shortness of breath; PGA score at withdrawal was unchanged from baseline (1, mild disease). The patient recovered. Study drug was interrupted from 14- to 15-Jul-2001, then re-started before being discontinued on 16-Jul-2001. The patient was withdrawn from the study on 19-Jul-2001 due to the adverse events of muscle pain, chest pain, and shortness of breath. The patient had a history of cigarette use, history of bilateral tubal ligation, rectal polyp, hypertension, and microscopic hematuria. The patient had known allergies to sulfa drugs (fever, rash).

Allergic dermatitis: This was a 29 year-old Caucasian female who experienced qualifying active ulcerative colitis disease and received mesalamine 4.8 g/day as 800 mg tablets from 14-Feb-2007 to 15-Feb-2007. The patient had a medical history significant for migraine, dyspareunia, right carpal tunnel syndrome, Osgood-Schlatter's disease of the left knee, eczema, chronic sinusitis, tonsillectomy, and bloody diarrhea. The patient had a known allergy to penicillin (associated b(6)
with dyspnea). On presented to the emergency department with an allergic cutaneous rash, vomiting and dehydration. Treatment included diphenhydramine hydrochloride, dimenhydrinate, and intravenous rehydration with dextrose and saline. The patient was also found to have sinusitis and began treatment with clarithromycin and paracetamol on the same date. The study drug was discontinued and the patient was withdrawn from the study on 15-Feb-2007.

10.2.4 Sex Subgroup Analysis (AEs Occurring in ≥ 2% in Either Treatment Group)

Table 44. Sex Subgroup Analysis (ITT) - AEs Occurring in ≥2% in Either Treatment Group (Studies 2000082, 2000083 and 2006444 Combined)

	Female		Male	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=353) n (%)	4.8g/day Asacol (800 mg Tablet) (N=353) n (%)	2.4g/day Asacol (400 mg Tablet) (N=379) n (%)	4.8g/day Asacol (800 mg Tablet) (N=374) n (%)
Gastrointestinal disorders	56 (15.9%)	58 (16.4%)	46 (12.1%)	42 (11.2%)
Nausea	11 (3.1%)	15 (4.2%)	10 (2.6%)	5 (1.3%)
Diarrhoea	6 (1.7%)	9 (2.5%)	8 (2.1%)	3 (0.8%)
Abdominal pain	10 (2.8%)	8 (2.3%)	7 (1.8%)	9 (2.4%)
Colitis ulcerative	10 (2.8%)	6 (1.7%)	10 (2.6%)	11 (2.9%)
Infections and infestations	28 (7.9%)	32 (9.1%)	19 (5.0%)	21 (5.6%)
Nasopharyngitis	4 (1.1%)	11 (3.1%)	6 (1.6%)	7 (1.9%)
Nervous system disorders	29 (8.2%)	25 (7.1%)	19 (5.0%)	20 (5.3%)
Headache	20 (5.7%)	20 (5.7%)	16 (4.2%)	14 (3.7%)
General disorders and administration site conditions	11 (3.1%)	12 (3.4%)	13 (3.4%)	12 (3.2%)
Pyrexia	1 (0.3%)	1 (0.3%)	8 (2.1%)	4 (1.1%)
Musculoskeletal and connective tissue disorders	9 (2.5%)	12 (3.4%)	9 (2.4%)	9 (2.4%)
Skin and subcutaneous tissue disorders	11 (3.1%)	11 (3.1%)	7 (1.8%)	2 (0.5%)
Respiratory, thoracic and mediastinal disorders	12 (3.4%)	9 (2.5%)	11 (2.9%)	6 (1.6%)

(Table above is taken from Page 110 of the Applicant's Summary of Clinical Safety.)

Table 45. Sex Subgroup Analysis (Moderate Disease) - AEs Occurring in ≥2% in Either Treatment Group (Studies 2000082, 2000083 and 2006444 Combined)

	Female		Male	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=296) n (%)	4.8g/day Asacol (800 mg Tablet) (N=291) n (%)	2.4g/day Asacol (400 mg Tablet) (N=322) n (%)	4.8g/day Asacol (800 mg Tablet) (N=311) n (%)
Gastrointestinal disorders	45 (15.2%)	50 (17.2%)	38 (11.8%)	35 (11.3%)
Nausea	8 (2.7%)	10 (3.4%)	8 (2.5%)	4 (1.3%)
Abdominal pain	7 (2.4%)	8 (2.7%)	6 (1.9%)	7 (2.3%)
Diarrhoea	6 (2.0%)	8 (2.7%)	6 (1.9%)	2 (0.6%)
Dyspepsia	4 (1.4%)	7 (2.4%)	0 (0.0%)	4 (1.3%)
Colitis ulcerative	8 (2.7%)	6 (2.1%)	10 (3.1%)	11 (3.5%)
Flatulence	3 (1.0%)	6 (2.1%)	2 (0.6%)	1 (0.3%)
Vomiting	5 (1.7%)	6 (2.1%)	3 (0.9%)	3 (1.0%)
Infections and infestations	19 (6.4%)	25 (8.6%)	17 (5.3%)	14 (4.5%)
Nasopharyngitis	3 (1.0%)	8 (2.7%)	5 (1.6%)	6 (1.9%)
Nervous system disorders	23 (7.8%)	19 (6.5%)	13 (4.0%)	16 (5.1%)
Headache	15 (5.1%)	15 (5.2%)	12 (3.7%)	11 (3.5%)
Musculoskeletal and connective tissue disorders	6 (2.0%)	10 (3.4%)	7 (2.2%)	6 (1.9%)
Skin and subcutaneous tissue disorders	8 (2.7%)	10 (3.4%)	6 (1.9%)	1 (0.3%)
General disorders and administration site conditions	9 (3.0%)	8 (2.7%)	11 (3.4%)	7 (2.3%)
Pyrexia	1 (0.3%)	0 (0.0%)	7 (2.2%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	10 (3.4%)	8 (2.7%)	8 (2.5%)	3 (1.0%)

(Table above is taken from Page 111 of the Applicant's Summary of Clinical Safety.)

10.2.5 Age Subgroup Analysis (AEs Occurring in ≥ 2 % in Either Treatment Group)

Table 46. Age Subgroup Analysis: Adverse Events Occurring in >=2% in Either Treatment Group by MedDRA SOC and PT Studies 2000082, 2000083 and 2006444 Combined

(Patients with Moderate Disease [PGA=2] at Baseline)
(Page 1 of 2)

MedDRA SOC MedDRA Preferred Term	<65 years		>=65 years	
	2.4g/day Asacol (400 mg Tablet) (N=569) n (%)	4.8g/day Asacol (800 mg Tablet) (N=549) n (%)	2.4g/day Asacol (400 mg Tablet) (N=49) n (%)	4.8g/day Asacol (800 mg Tablet) (N=53) n (%)
Gastrointestinal disorders	78 (13.7%)	77 (14.0%)	5 (10.2%)	8 (15.1%)
Abdominal pain	13 (2.3%)	15 (2.7%)	0 (0.0%)	0 (0.0%)
Colitis ulcerative	17 (3.0%)	15 (2.7%)	1 (2.0%)	2 (3.8%)
Nausea	16 (2.8%)	11 (2.0%)	0 (0.0%)	3 (5.7%)
Dyspepsia	3 (0.5%)	10 (1.8%)	1 (2.0%)	1 (1.9%)
Diarrhoea	12 (2.1%)	9 (1.6%)	0 (0.0%)	1 (1.9%)
Vomiting	8 (1.4%)	7 (1.3%)	0 (0.0%)	2 (3.8%)
Flatulence	4 (0.7%)	6 (1.1%)	1 (2.0%)	1 (1.9%)
Abdominal pain upper	2 (0.4%)	5 (0.9%)	1 (2.0%)	0 (0.0%)
Anal discomfort	0 (0.0%)	2 (0.4%)	1 (2.0%)	0 (0.0%)
Infections and infestations	32 (5.6%)	37 (6.7%)	4 (8.2%)	2 (3.8%)
Nasopharyngitis	8 (1.4%)	13 (2.4%)	0 (0.0%)	1 (1.9%)
Influenza	6 (1.1%)	6 (1.1%)	1 (2.0%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	2 (0.4%)	1 (2.0%)	0 (0.0%)
Bronchitis acute	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Ear infection	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Nervous system disorders	35 (6.2%)	31 (5.6%)	1 (2.0%)	4 (7.5%)
Headache	26 (4.6%)	24 (4.4%)	1 (2.0%)	2 (3.8%)
Dizziness	3 (0.5%)	1 (0.2%)	0 (0.0%)	2 (3.8%)
General disorders and administration site conditions	17 (3.0%)	15 (2.7%)	3 (6.1%)	0 (0.0%)
Oedema peripheral	1 (0.2%)	3 (0.5%)	1 (2.0%)	0 (0.0%)
Influenza like illness	2 (0.4%)	1 (0.2%)	1 (2.0%)	0 (0.0%)
Pyrexia	6 (1.1%)	1 (0.2%)	2 (4.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	10 (1.8%)	15 (2.7%)	3 (6.1%)	1 (1.9%)
Back pain	3 (0.5%)	6 (1.1%)	1 (2.0%)	0 (0.0%)
Flank pain	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Joint swelling	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	17 (3.0%)	11 (2.0%)	1 (2.0%)	0 (0.0%)
Dyspnoea	1 (0.2%)	3 (0.5%)	1 (2.0%)	0 (0.0%)

Table 47. Age Subgroup Analysis: Adverse Events Occurring in >=2% in Either Treatment Group by MedDRA SOC and PT Studies 2000082, 2000083 and 2006444 Combined

	<65 years		>=65 years	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=569) n (%)	4.8g/day Asacol (800 mg Tablet) (N=549) n (%)	2.4g/day Asacol (400 mg Tablet) (N=49) n (%)	4.8g/day Asacol (800 mg Tablet) (N=53) n (%)
Gastrointestinal disorders	78 (13.7%)	77 (14.0%)	5 (10.2%)	8 (15.1%)
Abdominal pain	13 (2.3%)	15 (2.7%)	0 (0.0%)	0 (0.0%)
Colitis ulcerative	17 (3.0%)	15 (2.7%)	1 (2.0%)	2 (3.8%)
Nausea	16 (2.8%)	11 (2.0%)	0 (0.0%)	3 (5.7%)
Dyspepsia	3 (0.5%)	10 (1.8%)	1 (2.0%)	1 (1.9%)
Diarrhoea	12 (2.1%)	9 (1.6%)	0 (0.0%)	1 (1.9%)
Vomiting	8 (1.4%)	7 (1.3%)	0 (0.0%)	2 (3.8%)
Flatulence	4 (0.7%)	6 (1.1%)	1 (2.0%)	1 (1.9%)
Abdominal pain upper	2 (0.4%)	5 (0.9%)	1 (2.0%)	0 (0.0%)
Anal discomfort	0 (0.0%)	2 (0.4%)	1 (2.0%)	0 (0.0%)
Infections and infestations	32 (5.6%)	37 (6.7%)	4 (8.2%)	2 (3.8%)
Nasopharyngitis	8 (1.4%)	13 (2.4%)	0 (0.0%)	1 (1.9%)
Influenza	6 (1.1%)	6 (1.1%)	1 (2.0%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	2 (0.4%)	1 (2.0%)	0 (0.0%)
Bronchitis acute	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Ear infection	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Nervous system disorders	35 (6.2%)	31 (5.6%)	1 (2.0%)	4 (7.5%)
Headache	26 (4.6%)	24 (4.4%)	1 (2.0%)	2 (3.8%)
Dizziness	3 (0.5%)	1 (0.2%)	0 (0.0%)	2 (3.8%)
General disorders and administration site conditions	17 (3.0%)	15 (2.7%)	3 (6.1%)	0 (0.0%)
Oedema peripheral	1 (0.2%)	3 (0.5%)	1 (2.0%)	0 (0.0%)
Influenza like illness	2 (0.4%)	1 (0.2%)	1 (2.0%)	0 (0.0%)
Pyrexia	6 (1.1%)	1 (0.2%)	2 (4.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	10 (1.8%)	15 (2.7%)	3 (6.1%)	1 (1.9%)
Back pain	3 (0.5%)	6 (1.1%)	1 (2.0%)	0 (0.0%)
Flank pain	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Joint swelling	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	17 (3.0%)	11 (2.0%)	1 (2.0%)	0 (0.0%)
Dyspnoea	1 (0.2%)	3 (0.5%)	1 (2.0%)	0 (0.0%)

Table 48. (cont.) Age Subgroup Analysis: Adverse Events Occurring in >=2% in Either Treatment Group by MedDRA SOC and PT Studies 2000082, 2000083 and 2006444 Combined

(Patients with Moderate Disease [PGA=2] at Baseline)
(Page 2 of 2)

	<65 years		>=65 years	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=569) n (%)	4.8g/day Asacol (800 mg Tablet) (N=549) n (%)	2.4g/day Asacol (400 mg Tablet) (N=49) n (%)	4.8g/day Asacol (800 mg Tablet) (N=53) n (%)
Skin and subcutaneous tissue disorders	12 (2.1%)	10 (1.8%)	2 (4.1%)	1 (1.9%)
Drug eruption	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Rash macular	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Investigations	5 (0.9%)	5 (0.9%)	2 (4.1%)	2 (3.8%)
Alanine aminotransferase increased	1 (0.2%)	1 (0.2%)	1 (2.0%)	0 (0.0%)
Weight decreased	1 (0.2%)	0 (0.0%)	1 (2.0%)	1 (1.9%)
Metabolism and nutrition disorders	2 (0.4%)	4 (0.7%)	0 (0.0%)	2 (3.8%)
Blood and lymphatic system disorders	2 (0.4%)	2 (0.4%)	2 (4.1%)	0 (0.0%)
Platelet disorder	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Splenomegaly	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Hepatobiliary disorders	1 (0.2%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Cholecystitis	1 (0.2%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2%)	0 (0.0%)	1 (2.0%)	1 (1.9%)
Lipoma	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Surgical and medical procedures	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Tooth extraction	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Vascular disorders	1 (0.2%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Aortic arteriosclerosis	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Arteriosclerosis	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)

10.2.6 Race Subgroup Analysis (AEs Occurring in ≥ 2 % in Either Treatment Group)

Table 49. Race Subgroup Analysis: Adverse Events Occurring in >=2% in Either Treatment Group by MedDRA SOC and PT Studies 2000082, 2000083 and 2006444 Combined (Intent-to-treat)

	Caucasian		Black		Others	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=640) n (%)	4.8g/day Asacol (800 mg Tablet) (N=636) n (%)	2.4g/day Asacol (400 mg Tablet) (N=41) n (%)	4.8g/day Asacol (800 mg Tablet) (N=45) n (%)	2.4g/day Asacol (400 mg Tablet) (N=51) n (%)	4.8g/day Asacol (800 mg Tablet) (N=46) n (%)
Gastrointestinal disorders	86 (13.4%)	78 (12.3%)	6 (14.6%)	8 (17.8%)	10 (19.6%)	14 (30.4%)
Colitis ulcerative	18 (2.8%)	17 (2.7%)	1 (2.4%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
Nausea	17 (2.7%)	16 (2.5%)	3 (7.3%)	2 (4.4%)	1 (2.0%)	2 (4.3%)
Abdominal pain	14 (2.2%)	12 (1.9%)	2 (4.9%)	2 (4.4%)	1 (2.0%)	3 (6.5%)
Diarrhoea	11 (1.7%)	10 (1.6%)	1 (2.4%)	0 (0.0%)	2 (3.9%)	2 (4.3%)
Dyspepsia	5 (0.8%)	9 (1.4%)	0 (0.0%)	1 (2.2%)	1 (2.0%)	2 (4.3%)
Vomiting	11 (1.7%)	9 (1.4%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Flatulence	5 (0.8%)	6 (0.9%)	0 (0.0%)	2 (4.4%)	0 (0.0%)	1 (2.2%)
Abdominal distension	6 (0.9%)	4 (0.6%)	0 (0.0%)	1 (2.2%)	1 (2.0%)	0 (0.0%)
Haemorrhoids	5 (0.8%)	3 (0.5%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	2 (4.3%)
Rectal haemorrhage	2 (0.3%)	3 (0.5%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Anal discomfort	1 (0.2%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Constipation	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	2 (3.9%)	0 (0.0%)
Epigastric discomfort	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Gastrooesophageal reflux disease	0 (0.0%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	1 (2.0%)	1 (2.2%)
Pruritus ani	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Anal skin tags	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Dry mouth	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Haematochezia	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Haemorrhoidal haemorrhage	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoaesthesia oral	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Proctalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Infections and infestations	37 (5.8%)	44 (6.9%)	3 (7.3%)	4 (8.9%)	7 (13.7%)	5 (10.9%)
Nasopharyngitis	8 (1.3%)	15 (2.4%)	0 (0.0%)	2 (4.4%)	2 (3.9%)	1 (2.2%)
Influenza	6 (0.9%)	6 (0.9%)	2 (4.9%)	0 (0.0%)	1 (2.0%)	1 (2.2%)
Sinusitis	5 (0.8%)	4 (0.6%)	1 (2.4%)	0 (0.0%)	1 (2.0%)	1 (2.2%)
Bronchitis	2 (0.3%)	2 (0.3%)	0 (0.0%)	2 (4.4%)	1 (2.0%)	1 (2.2%)
Gastroenteritis	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Cellulitis	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Vulvovaginal mycotic infection	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)

Table 50. (cont.) Race Subgroup Analysis: Adverse Events Occurring in >=2% in Either Treatment Group by MedDRA SOC and PT Studies 2000082, 2000083 and 2006444 Combined (Intent-to-treat)

	Caucasian		Black		Others	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=640) n (%)	4.8g/day Asacol (800 mg Tablet) (N=636) n (%)	2.4g/day Asacol (400 mg Tablet) (N=41) n (%)	4.8g/day Asacol (800 mg Tablet) (N=45) n (%)	2.4g/day Asacol (400 mg Tablet) (N=51) n (%)	4.8g/day Asacol (800 mg Tablet) (N=46) n (%)
Nervous system disorders	38 (5.9%)	32 (5.0%)	6 (14.6%)	3 (6.7%)	4 (7.8%)	10 (21.7%)
Headache	29 (4.5%)	24 (3.8%)	3 (7.3%)	3 (6.7%)	4 (7.8%)	7 (15.2%)
Paraesthesia	0 (0.0%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Somnolence	0 (0.0%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypoaesthesia	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Memory impairment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Syncope	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Syncope vasovagal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Musculoskeletal and connective tissue disorders	16 (2.5%)	18 (2.8%)	1 (2.4%)	0 (0.0%)	1 (2.0%)	3 (6.5%)
Back pain	7 (1.1%)	6 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Buttock pain	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Muscular weakness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.2%)
Pain in extremity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.2%)
General disorders and administration site conditions	21 (3.3%)	16 (2.5%)	1 (2.4%)	2 (4.4%)	2 (3.9%)	6 (13.0%)
Pyrexia	8 (1.3%)	4 (0.6%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.2%)
Fatigue	3 (0.5%)	3 (0.5%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Chest pain	3 (0.5%)	2 (0.3%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (2.2%)
Oedema peripheral	2 (0.3%)	2 (0.3%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (2.2%)
Asthenia	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Condition aggravated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Peripheral coldness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Respiratory, thoracic and mediastinal disorders	21 (3.3%)	13 (2.0%)	2 (4.9%)	1 (2.2%)	0 (0.0%)	1 (2.2%)
Pharyngolaryngeal pain	4 (0.6%)	4 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Cough	9 (1.4%)	2 (0.3%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sinus congestion	3 (0.5%)	1 (0.2%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Nasal congestion	2 (0.3%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	17 (2.7%)	9 (1.4%)	1 (2.4%)	1 (2.2%)	0 (0.0%)	3 (6.5%)
Rash	6 (0.9%)	4 (0.6%)	1 (2.4%)	1 (2.2%)	0 (0.0%)	1 (2.2%)
Night sweats	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Eczema	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)

Table 51 (cont.) Race Subgroup Analysis: Adverse Events Occurring in >=2% in Either Treatment Group by MedDRA SOC and PT Studies 2000082, 2000083 and 2006444 Combined (Intent-to-treat)

	Caucasian		Black		Others	
MedDRA SOC MedDRA Preferred Term	2.4g/day Asacol (400 mg Tablet) (N=640) n (%)	4.8g/day Asacol (800 mg Tablet) (N=636) n (%)	2.4g/day Asacol (400 mg Tablet) (N=41) n (%)	4.8g/day Asacol (800 mg Tablet) (N=45) n (%)	2.4g/day Asacol (400 mg Tablet) (N=51) n (%)	4.8g/day Asacol (800 mg Tablet) (N=46) n (%)
Investigations	8 (1.3%)	8 (1.3%)	1 (2.4%)	1 (2.2%)	0 (0.0%)	1 (2.2%)
Blood alkaline phosphatase increased	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Weight decreased	2 (0.3%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Glucose tolerance test abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Psychiatric disorders	3 (0.5%)	7 (1.1%)	2 (4.9%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Insomnia	3 (0.5%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Anxiety	0 (0.0%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Depression	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Metabolism and nutrition disorders	3 (0.5%)	5 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Dehydration	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Cardiac disorders	1 (0.2%)	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.3%)
Palpitations	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Sinus tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Immune system disorders	4 (0.6%)	3 (0.5%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Seasonal allergy	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Blood and lymphatic system disorders	4 (0.6%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Anaemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Uterine leiomyoma	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	1 (0.2%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ovarian cyst	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Vascular disorders	2 (0.3%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypertension	0 (0.0%)	1 (0.2%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

10.3 Line-by-Line Labeling Review

Discussions between the Applicant and CDER have resolved major issues with regard to the label. Several significant changes have been made to the applicant's proposed labeling. These include the following:

Section 1 Indications and Usage and Section 2 Dosage and Administration

- It was decided to add a statement that the safety and effectiveness of Asacol 800 beyond 6 weeks has not been established in each of the sections.

Section 6.1 Clinical Trials Experience

- It was decided to not explicitly state in this section how the measures of systemic exposure (Cmax and AUC) differed between Asacol 800 and Asacol, but instead to refer to the Section 12.3 Pharmacokinetics section.

Section 6.2 Adverse Reactions Information from Other Sources

- Adverse events were updated to include additional AEs from postmarketing experience with other mesalamine products including Asacol 400 mg tablets, and from clinical trial experience with Asacol 800.

Section 10 Overdosage

- It was decided to remove the description of the two cases of overdosage in children that are described in the Asacol 400 mg tablets label.
- Instead, a statement of the recommended management in case of overdose was provided.

Section 12.3 Pharmacokinetics

- Based on internal discussions between the clinical review team and the clinical pharmacology review team, it was decided to include a statement that informs the reader that the relationship between measures of systemic exposure (e.g., Cmax and AUC) and clinical efficacy are not known because the action of mesalamine is believed to be topical, and not systemic. This statement was added in order to communicate that the 25% lower AUC and 36% lower Cmax of the Asacol 800 tablet compared to two Asacol (400 mg tablets) may not be associated with a change in efficacy.

Section 14.1 Moderately Active Ulcerative Colitis

- It was decided to not explicitly state in this section how the measures of systemic exposure (Cmax and AUC) differed between Asacol 800 and Asacol, but instead to refer to the Section 12.3 Pharmacokinetics section.
- It was decided not to describe in detail the results of Study 82 because it was not the major basis of the finding of the demonstration of efficacy; it was decided to only include the proportion of moderately active UC patients that met the primary endpoint of treatment success without stating the comparative rate in the control group.
- It was decided to describe the study design and results of Study 2006444 in detail because it was the major basis of the finding of the demonstration of efficacy; and to

describe the results of Study 82 in limited detail because it was supportive but not able to stand on its own.

- It was decided to only state the proportion of moderately active UC patients that were treated with Asacol 800 in Study 82 and that met the primary endpoint of treatment success without stating the comparative rate in the control group (Asacol 400 mg tablets), because inclusion of the rate in the control group could be misconstrued as evidence of superiority of Asacol 800 over Asacol 400 mg tablets.

10.4 Review from Safety Evaluator

The review from the Safety Evaluator, Ann Corken Mackey, is provided on the following three pages. (It is filed under NDA in DFS.) b(4)

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On Original

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11 REFERENCES

1. Cooney RM et al., "Outcome measurement in clinical trials for Ulcerative Colitis: towards standardization", *Trials* 2007, 8:17.

2. Higgins PD et al., "Patient defined dichotomous end points for remission and clinical improvement in ulcerative colitis", *Gut* 2005;54:782–788.

3. Schroeder et al., "Coated oral 5-aminosalicyclic acid therapy for mildly to moderately active ulcerative colitis", *NEJM* 1987;317:1625-9. Study C3.

4. Sninsky et al., "Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis", *Ann Intern Med* 1991 Sep 1;115(5):350-5. Study C14.

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/s/

Anil K Rajpal
5/29/2008 01:06:58 PM
MEDICAL OFFICER

John Hyde
5/29/2008 02:17:22 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	
To:	Donna Griebel, MD, Director
	Division of Gastrointestinal Products (DGP)
Thru:	Mark Avigan, MD, CM, Director
	Division of Adverse Event Analysis I (DAEA I)
	Lanh Green, PharmD, MPH
	Safety Evaluator Team Leader DAEA I
From:	Ann Corken Mackey, RPh, MPH
	Safety Evaluator DAEA I
Subject:	Renal impairment
Drug Name(s):	Mesalamine (Asacol, Pentasa, Lialda, Canasa, Rowasa)
Application Type/Number:	19-651, 20-049, 22-000, 21-252, 19-618, 19-919
Applicant/sponsor:	Procter and Gamble, Shire, Axcan Scandipharm, Alaven Pharm
OSE RCM #:	2008-301

1 INTRODUCTION

The sponsor for Asacol (Proctor and Gamble) has submitted an NDA for approval of mesalamine at an increased dose (4.8 g/day [current labeled dose is 2.4 g/day]) for the treatment of ulcerative colitis. DGP requested a search of the Adverse Event Reporting System (AERS) for evidence that renal impairment and hypersensitivity associated with mesalamine use are dose related. Hypersensitivity is usually not dose related and will not be discussed in this review.

Mesalamine is a 5-aminosalicylate (5-ASA) product with local effects; other drugs in the class include sulfasalazine, balsalazide, and olsalazine. All 5-ASA products are pharmaco-logically similar.[1] Renal impairment and hypersensitivity reactions are labeled for sulfasalazine, mesalamine, and olsalazine and are proposed for inclusion in the balsalazide label.[2] [3] [4] [5]

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[1] Facts and Comparisons (www.efactsweb.com), accessed on November 21, 2007.

[2] Azulfidine EN-tabs (sulfasalazine) product label, Pharmacia, revised September 2001.

2 MATERIAL REVIEWED

AERS and the medical literature were searched for cases of renal impairment associated with mesalamine use (hypersensitivity is usually not dose related and will not be discussed in this review).

AERS Search: AERS was searched using the MedDRA HLT *renal failure and impairment* from initiation of marketing (January 1992) to February 12, 2008. The AERS search identified 224 cases of renal impairment associated with mesalamine (note raw data). Of these cases, approximately 90 cases listed a daily dose for mesalamine; 60 cases reported a dose of 2.4 grams/day or less and 30 cases reported a dose greater than 2.4 grams per day (doses were identified from a computer-generated printout and were not individually reviewed).

Literature Search: A search of the medical literature identified a review article for renal impairment associated with 5-ASA drugs used to treat inflammatory bowel disease (IBD; note that IBD includes Crohn's disease and ulcerative colitis).[6] The authors reviewed 36 studies in which serum creatinine or creatinine clearance were measured as well as 10 epidemiology studies, and 47 case reports from 1966 to July 2006. The studies with 5-ASA treatment in which serum creatinine or creatinine clearance were measured showed that the risk of renal impairment is rare (mean rate of 0.26% per patient-year); the potential risk was similar for mesalamine and sulfasalazine. Overall, renal impairment did not appear to be dose related. Withdrawal of the 5-ASA drugs led to recovery of renal function in a majority of patients. A couple of individual studies concluded that renal impairment may be due in part to the patient's underlying IBD.

Regarding a dose effect, at least five studies within the review article concluded that there was no relationship between 5-ASA dose and the risk of renal impairment. In addition, one small study found that cumulative dose of 5-ASA was not a predictor for change in renal function. Most of the patients described in the review article developed renal impairment due to interstitial nephritis which is considered an idiosyncratic reaction and not dose related. The authors stated that interstitial nephritis appears to be a delayed, cell-mediated response (as described for other nonsteroidal anti-inflammatory drugs) rather than a type 1 hypersensitivity. Other rarely-reported types of renal impairment associated with 5-ASA use were due to nephropathy, nephritic syndrome, nephrolithiasis, and dehydration.

3 DISCUSSION/CONCLUSIONS

Based on reports in the medical literature as described above, it appears that the risk of 5-ASA-induced renal impairment is not dose related. In addition, as discussed with the medical reviewer for mesalamine, AERS cases cannot be used to identify dose-related adverse events due to 1) lack of confirmation by reporter that the adverse event is due to increased or decreased dose, 2) incomplete data submission on dosage for each case, 3) lack of a denominator for each dose and adverse event; this question is best identified using clinical trial data which contain more detailed information including the three items mentioned above.

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[3] Asacol (mesalamine) product label, Procter & Gamble Pharmaceuticals, revised September, 2006.

[4]Dipentum (olsalazine) product label, UCB Pharma Limited, revised December 2006.

[5] Mackey AC. Balsalazide: Serious adverse events, RCM# 2007-2045, January 14, 2008.

[6] Gisbert JG, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory disease: A systemic review. Inflamm Bowel Dis 2007; 13 (5): 629-38.

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/s/

Ann Corken
3/19/2008 09:05:54 AM
DRUG SAFETY OFFICE REVIEWER

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3/19/2008 11:56:34 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
3/19/2008 06:29:25 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 08/26/2005

FROM: Joyce A Korvick, MD, MPH

DGCDP/ODE III

SUBJECT: Deputy Division Director Approvable Comments
NDA 21-830

APPLICANT: Proctor & Gamble Pharmaceuticals, Inc.

DRUG: **Asacol 800®** (mesalamine 800 mg delayed release tablet)

DIVISION RECOMMENDATION:
The division recommends, and I concur, that Asacol 800® is made approvable for the proposed indication of the treatment of patients with moderately active ulcerative colitis. This action will not be accompanied by finalized labeling this review cycle.

DEFICIENCIES:
Insufficient proof of the superiority of Asacol 800 mg dosed at 4.8 g/day over Asacol 400 mg dosed at 2.4 g/day to support the proposed indication of treatment of moderately active ulcerative colitis.

The following are our recommendations for resolution of the above cited deficiency for the indication of treatment of moderately active ulcerative colitis:

- Provide at least one additional adequate and well-controlled study to demonstrate the added clinical benefit of Asacol 800 mg tablets at a dose of 4.8 g/day compared to Asacol 400 mg tablets at a dose of 2.4 g/day in moderately active ulcerative colitis patients.
- Explain why Asacol 800 mg at 4.8 g/day was more efficacious than Asacol 400 mg at 2.4 g/day in male patients.

BACKGROUND:
Asacol delayed-release tablets contain mesalamine (5-aminosalicylic acid, also referred to as 5-ASA), an anti-inflammatory drug. Although its mechanism of action is not fully elucidated, the available evidence indicates that mesalamine has a topical anti-inflammatory effect on the colon, where it inhibits prostaglandin and leukotriene synthesis. In the United States, Asacol 400 mg tablets were first approved in 1992 for the treatment of mild to moderate, active ulcerative colitis at a dose of 2.4 g/day (NDA

19-651). Later in 1997, Asacol was also approved for the maintenance of remission of mild to moderate, active ulcerative colitis at a dose of 1.6 g/day.

In the original NDA, the treatment of mildly to moderately active ulcerative colitis a higher dose (4.8 g/day) was studied. This study suggested additional activity in the higher dose; however, it was not confirmed with a second study. Thus, the original approved labeling recommends the lower daily dose (2.4 g/day).

NDA 21-830 proposes a new formulation of mesalamine (800 mg delayed release tablet) which would decrease the number of tablets a patient would have to take to attain the 4.8 mg daily dose. The sponsor chose one of three different experimental formulations and attempted to justify similarity based upon *in vitro* dissolution and *in vivo* pharmacokinetics. Based upon these data, the biopharmaceutics reviewer has concluded that the currently studied formulation is not bioequivalent to the 400 mg tablet. That is, twelve 400 mg tablets are not equivalent to six 800 mg tablets. Thus, a clinical trials program was undertaken in order to demonstrate efficacy.

The sponsor chose to perform 2 double-blind, randomized, 6-week, parallel-group design Phase III clinical trials (Studies 200082 and 200083). These studies were designed to compare 2.4 g/day dosing, administered as the currently-marketed 400 mg tablet, to 4.8 g/day dosing, administered as the 800 mg tablet. These studies were designed to demonstrate superiority in the patient population of mildly to moderately active ulcerative colitis patients.

The original studies were conducted during approximately the same time period. Study 200083 was completed prior to 200082. An analysis of study 200083 did not demonstrate superiority of the new formulation and dosing regimen over the approved formulation and lower dosing regimen. However, there appeared to be a favorable result in the subgroup analysis among the patients with moderately active ulcerative colitis. The sponsor amended the 200082 protocol on February 18, 2003. It is of interest to note that most of the intended sample size (96%) had been enrolled by that date. In this amendment, only patients with moderate disease at baseline were to be enrolled. The sponsor changed the sample size and the focus of the primary analysis to the subgroup of patients with moderately active ulcerative colitis at baseline. This is not considered an adaptive design by the Agency. Additional discussion of the results follows in the clinical study section below.

Several other mesalamine preparations are currently available on the US Market:

- ASACOL (currently approved 400 mg product): for the treatment of mildly and moderately active ulcerative colitis and maintenance of remission of ulcerative colitis. Recommended dosage for the treatment of mild to moderate disease use 2 tabs of 400 mg TID for total daily dose of 2.4 g.

- PENTASA: 250 mg capsules and 500 mg capsules, indicated for mildly to moderately active ulcerative colitis. Recommended dosage is 1 gram 4 times per day for a total daily dose of 4 grams.

- ROWASA: rectal suspension enema, 4.0 grams for mildly to moderately active distal ulcerative colitis

- CANASA: rectal suppository 500 mg and 1000 mg; for the treatment of active ulcerative colitis. Recommended dosage, one rectal suppository two times per day may increase to three times per day if needed. Also, 1000mg h.s..

I. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

Originally there were some concerns regarding the proposed proprietary name. The sponsor submitted additional arguments and information during this review. Upon further discussion with the sponsor it was felt that the name "Asacol 800" was acceptable. Since it is not bioequivalent compared to the currently approved 400 mg Asacol formulation it will be important for the sponsor to clearly advertise this difference. It was felt, given, the material that was presented that Proctor and Gamble would be able to make such a distinction. We agree with DMETS recommendations.

B. Chemistry and Manufacturing:

The CMC review found the new formulation in this NDA acceptable.

C. Pre-Clinical Pharmacology/Toxicology:

There were no new studies submitted to this NDA. The reviewers relied upon the pre-clinical data which was reviewed for the approval of the original formulation of Asacol. There were no concerns and the reviewers suggested some changes to the proposed label which were acceptable.

D. Biopharmaceutics:

The biopharmaceutics reviewer found that this formulation was not bioequivalent to the currently marketed 400 mg formulation. The essential characteristics are as follows from the reviewer's summary"

"Single dose administration of the 800 mg Delayed Release Tablet in a relative bioavailability study indicated that the mean tmax value of 5-ASA was significantly delayed while mean Cmax and AUC values decreased by 36% and 25%, respectively, with administration of the 800 mg tablets relative to the 400 mg tablet.

"The results of a multiple dose PK study of the 800 mg tablet indicated that the Cmax and AUC values of 5-ASA and N-Ac-5-ASA increase

significantly with multiple dose administration suggesting that significant accumulation of 5-ASA and N-Ac-5-ASA takes place at the TID regimen."

"The results of a population PK analysis in patients with moderately active ulcerative colitis showed that the steady-state plasma concentrations of 5-ASA and N-Ac-5-ASA increased in a dose-related manner."

"A significant food-effect was observed on the PK of the 800 mg Asacol tablet. In particular, mean Cmax of 5-ASA decreased by 47% under fed conditions. In addition, a marked delay in tmax was observed under fed conditions with mean tmax increasing by 14 hours relative to fasting conditions."

Thus, clinical evidence is necessary to demonstrate efficacy of this new formulation.

II. Clinical/Statistical:

A. Efficacy

The results of study 200082and 200083 did not adequately demonstrate efficacy for the requested indication. This data is summarized in Table 1.

Table 1. Primary Outcome: Treatment Success at Week 6 (Sponsor's ITT Analysis in Patients with Mild and Moderated Disease at Baseline)

Study population	2.4 g/ Asacol (400 mg Tablet) n/N (%)	4.8 g/ Asacol (800 mg Tablet) n/N (%)	p-value[a]	% Difference in Success	Confidence Interval[b]
Study 200082					
Total	98/182 (53.8%)	108/182 (59.3%)	0.29	5.5	(-0.05, 0.16)
Moderate	77/130 (59.2%)	89/124 (71.8%)	0.04	12.6	(1.0, 24.1)
Mild	21/52 (40.4%)	19/58 (32.8%)	0.41	-7.6	(-25.62, 10.37)
Study 200083					
Total	77/150 (51.3%)	76/136 (55.5%)	0.44	4.6	(-0.07, 0.16)
Moderate	53/93 (57.0%)	55/76 (72.4%)	0.04	15.4	(1.2, 29.6)
Mild	24/57 (42.1%)	21/60 (35.0%)	0.43	-7.4	(-0.20, 0.05)

[a]4.8 g/day compared to 2.4 g/day, from Chi-square test for 82 and 83, and stratified by protocol using the Cochran-Mantel-Haenszel test for pooled analysis.
[b]95% confidence interval for the difference in success rates between 4.8 g/day and 2.4 g/day with no stratification.

Study 2000083 was completed prior to study 200082. Study 200083 failed to show superiority of the 4.8 g/day regimen relative to the 2.4 g/day regimen in patients with mildly to moderately active ulcerative colitis. The subgroup analysis of patients with moderate disease showed a difference in rates of treatment success in favor of the 4.8 g/day regimen of 72% vs. 57%, p= 0.04.

However, much of this effect disappears if dropouts are treated as treatment failures (66% vs. 55%, p= 0.16). Moreover, more than a dozen other subgroups were analyzed without adjustment for multiplicity. Thus, we consider the analysis of moderately affected patients in this study to be exploratory

Study 2000082 was amended when most of the intended sample size had been enrolled. This change was "a direct consequence of results just obtained in the companion safety and efficacy study (2000083)" (serial #205, 18 Feb 2003). Under the amended protocol, up to 100 additional patients with moderate disease were to be enrolled, and the proposed indication was changed to moderately active ulcerative colitis. Eighty-two patients were enrolled after the amendment, for a total of 268 moderately affected patients. Overall, the 4.8 g/day regimen missed significance. The subgroup of moderately affected patients showed a difference in rates of treatment success between dosing regimens in favor of 4.8 g/day (72% vs. 59%, p= 0.04) In addition, the efficacy benefit for 4.8 g/day appears to be driven by results in male patients (76% vs. 50%) for reasons that are not readily explained. Similarly, an efficacy benefit at a dose of 4.8 g/day over that of 2.4g/day was seen in pre-amendment enrollees with moderate disease (70% [58/83] vs. 55%[52/95]), but not in post-amendment enrollees (76%[31/41] vs. 71%[25/35]). Again, we do not consider the analysis of moderately affected patients in this study to be definitive. For additional discussion of the design and analysis issues please refer to the biostatistical reviewer and team leader memos.

B. Safety

There were no unexpected additional safety issues raised in this NDA. It should be noted that the higher dosing regimen (4.8 g/day) resulted in a slightly higher adverse event rate for nausea and vomiting. In patients with moderate disease, infection, nausea, vomiting, and headache were reported more frequently by patients receiving 4.8 g/day compared to 2.4 g/day, especially for nausea (4.1% vs. 2.0%) and vomiting (2.1% vs. 1.1%).

III. Pediatric Use:

Wavier and Deferral

A waiver is justified only for pediatric studies in patients less than 5 years of age for Asacol 800® for moderately active ulcerative colitis. The reason for granting the waiver is studies are impossible or highly impractical because the number of patients is so small and geographically dispersed.

A deferral of pediatric studies for patients between 5 to 17 years of age is justified for moderately active ulcerative colitis until December 31, 2010. The reasons for granting the deferral are studies will need to be conducted to identify appropriate doses and based on the estimated time to recruit patients. The requirements for your deferred pediatric studies will be fully addressed upon approval of this product.

IV. Labeling:

Preliminary labeling was sent to the sponsor on July 28, 2005. However, since we are unable to recommend approval at this time without further clinical data, negotiations cannot proceed further during this review cycle.

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/s/

Joyce Korvick
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MEDICAL OFFICER