CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

CROSS DISCIPLINE TEAM LEADER REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Gastroenterology Products
HFD-180

Date: **May 29, 2008**

From: **John Hyde, Ph.D., M.D., Clinical Team Leader, DGP**

Subject: **Clinical Team Leader Summary Review of Resubmission to NDA 21-830, Asacol 800 for Ulcerative Colitis**

To: **NDA 21-830 File**
Donna Griebel, M.D., Division Director, DGP

Identifying information

NDA#:	21-830
Applicant:	Proctor and Gamble Pharmaceuticals, Inc.
Established name:	Mesalamine
Proposed trade name:	ASACOL 800
Submission date:	Original: October 22, 2004; Resubmission: October 22, 2007
Stamp date:	Resubmission: October 22, 2007
PDUFA goal date:	April 22, 2008
Formulation:	800 mg delayed-release tablet for oral administration.
Proposed indication:	Treatment of moderately active ulcerative colitis.
Proposed regimen:	1600 mg orally three times a day for six weeks.

Recommended regulatory action: Approval under 21 CFR 314, with proprietary name to be determined.

Introduction and Regulatory Background

General Background

This resubmission, received October 22, 2007, is a complete response to the Approvable (AE) Letter sent by the Division on August 29, 2005, and represents the second review cycle for this product. Please refer the Team Leader memo dated August 26, 2005, and other primary review memos from the initial review cycle for more complete information about the regulatory history and the FDA's conclusions from that review cycle.

This NDA is for a delayed-release oral tablet formation of mesalamine. Mesalamine is a 5-aminosalicylate. It is thought to act in the gastrointestinal tract as a topical anti-inflammatory

agent through inhibition of cyclooxygenase and 5-lipoxygenase. The formulation in Asacol 800 involves an outer coat designed with the intent to delay the release of mesalamine until the product reaches the terminal ileum and colon.

The Applicant's currently approved mesalamine formulation, Asacol, is a 400 mg delayed-release tablet indicated for mildly to moderately active ulcerative colitis at a dose of 2.4 g/d in divided doses for six weeks. The indication also includes the maintenance of remission of ulcerative colitis at a dose of 1.6 g/d in divided doses. The Applicant has not been able to demonstrate bioequivalence between Asacol 800 and Asacol, and the available data suggest that the two might not be bioequivalent. (See Clinical Pharmacology Issues, below.)

The Applicant proposes that Asacol 800 be indicated for the treatment of moderately active ulcerative colitis (in contrast to *mildly to moderately* active disease, as for Asacol). Asacol 800 is to be administered at a dose of 1.6 g three times per day (total of 4.8 g/d) for six weeks. The Applicant has proposed labeling in PLR format that is largely similar in content to that of the labeling for Asacol. In particular, the labeling includes a contraindication for hypersensitivity to Asacol and other salicylate products, warnings and precautions for renal impairment, exacerbation of UC, hypersensitivity, and use in patients with pyloric stenosis. The proposed pregnancy category is B. No pediatric use recommendations are proposed.

Asacol 800 was approved in Canada in July 2005, and it was approved in the U.K. in January 2008.

Presubmission Communications between FDA and the Applicant

The original NDA submission was dated 10/22/04, and it was received on 10/29/04. It was given Standard (ten month) review priority. An AE (approvable) Letter was issued on August 29, 2005. See the reviews from the initial review cycle for more information about the regulatory history leading up to the original NDA submission.

In response to the recommendations in the AE Letter, the Applicant initiated a new study (Study 2006444) with the objective of showing superiority of Asacol 800 4.8 g/d over Asacol 2.4 g/d in moderately active ulcerative colitis.

On 1/16/07 the Division approved Lialda, a once daily oral mesalamine formulation, at daily doses of both 2.4 and 4.8 g/d, without requiring a demonstration of superior efficacy with the 4.8 g/d dose. The Applicant of the present NDA met with the Division on 3/16/07 to discuss revising Study 2006444 to be a non-inferiority study in view of the efficacy requirements for a 4.8 g/d dose implicit in the Lialda approval. The Division recommended maintaining the objective of superiority, but indicated that demonstration of efficacy by non-inferiority might be sufficient. However, the Division did not agree with the Applicant's proposed 10% non-inferiority margin and stated that the margin to be used would need to be justified. The Applicant proceeded with plans to convert the new study to a non-inferiority design, and revised the sample size upward to obtain adequate power under an assumption of equivalence.

Submission and Review

The NDA resubmission was dated October 22, 2007, and it was received on that same date. It was classified as a six-month resubmission with a PDUFA deadline of April 22, 2008. On 4/18/08 the Applicant was sent a letter stating that the proposed proprietary name of "Asacol 800" was not acceptable.

No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines for this review cycle have all written review documents. The primary review documents relied upon for the current review cycle are the following:

Clinical Review, by A. Rajpal, dated 5/29/08.
Statistical Review and Evaluation, by M. Fan, dated 5/23/08.
Pharmacologist's Review, by S. Chakder, dated 5/23/08
Office of Clinical Pharmacology Review, by I. Kim, dated 5/21/08.
OSE/DMEP Proprietary Name Review for Asacol 800, by W. Fava, dated 4/18/08.
OSE consult memo for mesalamine by A. Mackey, dated 3/19/08 (archived under NDA 19-619).
DSI Clinical Inspections Summary, by Khairy Malek, dated 4/16/08.
CMC Review, by M. Ysern, dated 4/17/08.

The reviews should be consulted for more specific details of the application. The reader is also referred to the Team Leader Review Memo dated August 26, 2005, for the initial review cycle, as well as to the primary review documents from that cycle. This memorandum summarizes selected information from the review documents, with primary emphasis on the issues to be resolved in the current review cycle.

Clinical Background

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology. Peak age of onset is in the early twenties, but age of onset can vary widely. UC is more common in whites vs. non-whites and in women vs. men. The disease is manifest as mucosal inflammation and mucosal ulceration that occurs in the colon in a continuous segment beginning with the rectum. Extent of involvement varies, but it can include the entire colon. Involved areas classically show inflammatory changes that are limited to the mucosa, and, depending on severity, there may be extensive, broad-based ulceration. Clinically, UC presents as a chronic relapsing disease with variable-length bouts of bloody mucoid diarrhea and lower abdominal pain, but there may be long quiescent periods between attacks. There may also be systemic manifestations of the disease, with involvement of joints, eyes, skin, or the hepatobiliary system. Potential serious complications include severe bleeding, toxic megacolon, and perforation. There is a very significant risk of colon cancer with longstanding disease, such that pancolitis of 10 years duration or longer has a 20- to 30-fold increased risk of cancer compared to the general population.

Approved therapies for UC include corticosteroids to "tide the patient over a critical period" of UC, and aminosalicylates, which are available in rectal formulations (Canasa and Rowasa

[mesalamine]) and oral formulations (Azulfadine [sulfasalazine]; Asacol, Pentasa, and Lialda [mesalamine]; Dipentum [osalazine]; and Colazal [balsalazide]) as limited-term therapy to treat mildly or moderately active UC. Azulfadine, Asacol, and Dipentum are also approved as chronic therapy to maintain remission in UC. Also used, but unapproved, therapies include azathioprine and 6-mercaptopurine. Use of any of the preceding has come to be considered part of "conventional therapy." Remicade (infliximab) is a TNF blocker approved for induction and maintenance of remission in moderately to severely active UC with inadequate response to conventional therapy.

Chemistry, Manufacturing, and Controls Issues

No CMC issues were included in the FDA's AE Letter of 8/29/05. The reader is referred to the reviews by M. Ysern dated 5/18/05 and 4/17/08.

Conclusions from the Initial Review Cycle
During the first review cycle the Product Reviewer concluded that the product was acceptable pending adequate results from the plant inspections.

Current Cycle Review
There were no new CMC issues in the current review cycle. New manufacturing site inspections were requested because more than two years had passed. They received an acceptable recommendation on 3/19/08.

Final Conclusions and Recommendations
The Product Reviewer recommended the product for approval.

No Phase 4 CMC requirements were recommended.

Pre-clinical Pharmacology and Toxicology Issues

No pre-clinical pharmacology and toxicology issues were included in the FDA's AE Letter of 8/29/06. The reader is referred to the initial cycle Pharmacology/Toxicology Review and Evaluation by R. Honchel, dated 7/22/05, and to the Pharmacologist's Review by S. Chakder, dated 5/23/08.

Conclusions from the Initial Review Cycle
No new pre-clinical toxicology studies were submitted for this NDA; the Applicant relied on pre-clinical toxicology studies from the Applicant's approved NDA 19-651 for Asacol and the Applicant's IND 26,093. The Pharmacology/Toxicology Reviewer recommended the product for approval with recommendations for labeling changes. In particular, he advised that comparisons of animal doses to human doses be based on body surface area and that the comparisons should all reflect the human dosing recommended for this product (as opposed to the lower human dosing recommended for the currently approved Asacol). The Reviewer also proposed that the dog data be deleted from the OVERDOSAGE section.

Current Cycle Review
No new pre-clinical data were provided for the current review cycle. The Reviewer for the current cycle concurred with the previous recommendation to relate animal dosing to human dosing based on body surface area, and he provided additional comments on the labeling.

Final Conclusions and Recommendations
The Reviewer for the initial cycle concluded that the product was approvable. Both he and the current cycle Reviewer recommended labeling changes as noted above.

No Phase 4 pre-clinical requirements were recommended.

Clinical Pharmacology Issues

No Clinical Pharmacology issues were included in the FDA's AE Letter dated 8/29/05. The reader is referred to the initial cycle Clinical Pharmacology Review by S. Al-Fayoumi, dated 8/1/05, and to the Office of Clinical Pharmacology Review, by I. Kim, dated 5/21/08.

Initial Review Cycle Findings and Conclusions
In the initial review cycle the Clinical Pharmacology Reviewer evaluated three studies. In a 20-patient, single-dose, relative bioavailability study it was seen that one Asacol 800 tablet resulted in 36% lower mesalamine C_{max} and 25% lower mesalamine AUC compared to two Asacol (400 mg) tablets, and t_{max} was delayed by 2 hours. The variability was too large to permit a definitive conclusion that the formulations were not bioequivalent.

In a repeated-dose PK study there was significant accumulation of mesalamine and its N-acetyl metabolite (N-Ac-5-ASA) under a TID regimen. In a food-effect study, it was seen that under fed conditions mesalamine C_{max} was decreased 47% and t_{max} was delayed 14 hours relative to fasting conditions.

No pediatric PK data with Asacol 800 were provided.

The Reviewer concluded that the NDA was acceptable provided agreement was reached between the Division and Applicant regarding labeling. The Reviewer noted that despite a large food effect, Asacol 800 was administered without regard for food in the clinical studies, and therefore could be labeled for administration without regard for food. The Reviewer recommended that the labeling include a statement that bioequivalence between Asacol 800 and Asacol has not been demonstrated, and that therefore the products were not exchangeable.

No Phase 4 Clinical Pharmacology requirements were recommended.

Current Cycle Review
There were no Clinical Pharmacology issues in the AE Letter and no new Clinical Pharmacology studies were submitted for this review cycle. The Reviewer for the current cycle provided additional recommendations for labeling changes, including the following:

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Final Conclusions and Recommendations
The Clinical Pharmacology Reviewer for the initial cycle concluded that the NDA was acceptable and made labeling recommendations. The Reviewer for the current cycle provided additional labeling recommendations as noted above.

No Phase 4 Clinical Pharmacology requirements were recommended.

Clinical/Statistical Issues

The AE Letter of 8/29/05 cited insufficient proof of the superiority of Asacol 800 over Asacol as the issue needing resolution prior to approval. The Applicant's Complete Response submission provided the results of an additional clinical study to address the issue. The reader is referred to the Statistical Review and Evaluation by M. Fan dated 5/23/08, and the Clinical Review by A. Rajpal dated 5/29/08, as well as to the clinical and statistical reviews of the initial review cycle.

Clinical Data from the Initial Review Cycle
In the initial NDA submission, the Applicant provided results of two Phase 3 efficacy studies, designated Study 82 and Study 83. Both were six-week, multi-site, randomized, double-blind, active-controlled trials comparing Asacol 800 4.8 g/d (given as 1.6 g TID) to Asacol 2.4 g/d (given as two 400 mg tablets TID). Both studies were initially designed to enroll patients with mildly to moderately active UC. Activity was assessed by a protocol-defined physician global assessment (PGA), which categorized disease severity on a discrete four-point scale (0 to 3) that incorporated the factors of stool frequency, stool blood, sigmoidoscopic findings, and patient functional assessment. The primary study endpoint was "success" defined in terms of improvement in PGA score.

Study 83 was completed first. There was no statistically significant difference in success rates between the treatment groups (56% for Asacol 800 vs. 51% for Asacol, p=0.44). In exploratory analyses, it was found that the subset of patients with moderate disease at baseline appeared to show a greater difference between treatments (72% vs. 57%, p=0.038 [sponsor], p=0.055 [exact test performed by this reviewer], p=0.16 [dropouts treated as failures]). On the basis of this finding, the Applicant modified the protocol for the then ongoing Study 82 to base the primary analysis on the subgroup with moderately active UC at baseline, and to increase enrollment with up to 100 additional patients with moderately active disease. There was also slight relaxation of some eligibility criteria, presumably to enhance enrollment. At the time of the amendment, Study 82 was 96% enrolled for its original objective and was still blinded.

By the amended primary analysis, the results of Study 82 showed a benefit of Asacol 800 4.8 g/d over Asacol 2.4 g/d (72% vs. 59%, p = 0.036, [p = 0.0487 exact test performed by this reviewer]) in patients with moderately active UC at baseline. However, it was also seen that the observed benefit was limited to males 65% vs. 46%, whereas females had slightly lower success rates with Asacol 800 than with Asacol (51% vs. 54%). The Statistical Reviewer also noted that the superiority of Asacol 800 was not seen in the subset of patients enrolled following the protocol amendment. A table of key results abstracted from previous reviews is shown below:

Treatment Success Rates at Week 6 (ITT population) for Studies 83 and 82

	Asacol 2.4 g/d	Asacol 800 4.8 g/d	p-value	Difference (Asacol 800 – Asacol)	95% C. I.
Study 83					
Total	51.3% (77/150)	55.9% (76/136)	0.441	4.6%	(-7%, 16%)
Moderate	57.0% (53/93)	72.4% (55/76)	0.038[+]	15.4%	(1.2%, 30%)
Mild	42.1% (24/57)	35.0% (21/60)	0.430	-7.1%	(-25%, 11%)
Study 82					
Total	53.8% (98/182)	59.3% (108/182)	0.290	5.5%	(-5%, 16%)
Moderate	59.2% (77/130)	71.8% (89/124)	0.036*	12.6%	(1.0%, 24%)
Mild	40.4% (21/52)	32.8% (19/58)	0.406	-7.6%	(-26%, 10%)

[+] p=0.055 using exact test; tabulated p-value is Applicant's result using uncorrected Chi-square.
* p=0.049 using exact test; tabulated p-value is Applicant's result using uncorrected Chi-square.

The Clinical Reviewer's review of adverse events found that the overall safety profile for Asacol 800 4.8 g/d was similar to that of Asacol 2.4 mg/d, but the incidence of nausea and vomiting appeared to be higher with Asacol 800, particularly in women.

Conclusions from the Initial Review Cycle

The Statistical Reviewer concluded that neither study showed a statistically significant difference between the Asacol 800 and Asacol arms. He did not consider the finding in the moderately active subgroup in Study 83 to be valid, because it was a finding from one of many secondary analyses without adjustment for multiplicity. He also had concerns about the amendment of Study 82 so late in the study, as well as concerns about internal inconsistencies in that study's results. He regarded the finding in the moderate subset of Study 82 to be *post hoc* and not statistically persuasive. He recommended that the finding in moderately active UC patients be confirmed in a subsequent Phase 3 trial.

The secondary Statistical Reviewer concurred that the results of Study 83 should be considered exploratory. She differed from the primary Statistical Reviewer in that she concluded that the results of the primary analysis of Study 82 could be considered valid. However, she did not feel that Study 82 was adequate to stand on its own as a single definitive study, and concurred with the recommendation that another study in moderately active UC be conducted.

The Clinical Reviewer concluded that the application provided insufficient evidence of efficacy to support the proposed indication for treatment of moderately active UC and that an additional adequate and well-controlled study would be required to confirm the findings of Study 82. Further, she concluded that the results indicated that Asacol 800 at 4.8 g/d should not be indicated for patients with mild disease. She noted that the treatment benefit appeared to be mainly in males; in both Study 83 and 82 there appeared to be little difference between the two treatment arms in females with moderately active UC. The Clinical Reviewer recommended that the Applicant also be asked to address the inconsistent results for males vs. females.

Issues for the Current Cycle

The AE Letter of 8/29/05 cited the issue needing resolution prior to approval as the following:

> 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.

The AE Letter recommended that the Applicant provide at least one additional adequate, well-controlled study to demonstrate the added benefit of Asacol 800 at 4.8 g/day compared to Asacol at 2.4 g/d in moderately active UC, and asked that the Applicant explain why the effect was seen only in male patients. The letter also requested a safety update with the response, as described in 21 CFR 314.

In response to the recommendations in the AE Letter, the Applicant initiated a new study (Study 2006444) with the objective of showing superiority of Asacol 800 4.8 g/d over Asacol 2.4 g/d in moderately active colitis, but this was amended to a non-inferiority design with a larger sample size after discussions with the Division indicated that a non-inferiority approach could be considered (see the section: Presubmission Communications between FDA and the Applicant, above).

Current Cycle Review

In the Complete Response resubmission of 10/22/07, the Applicant provided the results of the amended Study 2006444 together with updated safety data. The reader is referred to the Clinical Review by A. Rajpal, dated 5/29/08, and the Statistical Review by M. Fan, dated 5/23/08, for details of the results of that study.

Study 2006444 (also referred to as ASCEND III by the Applicant) was a six-week, multi-center, randomized, double-blind, active-controlled study comparing Asacol 800 4.8 g/d (given as 1.6 g TID) to Asacol 2.4 g/d (given as 800 mg TID). To be eligible, patients had to be at least 18 years old with an endoscopically confirmed diagnosis of UC extending beyond 15 cm from the anal verge. The disease activity was required to be moderate as defined by a physician's global assessment (PGA) score of 2. (For this study the PGA score was a discrete four-point scale [0 to 3] incorporating factors of stool frequency, stool blood, and sigmoidoscopy findings. Unlike Studies 83 and 82, the PGA for this study did not incorporate a patient functional assessment.) Patients were excluded for recent treatment with aminosalicylate compounds, topical rectal therapy, systemic steroids, or biologic therapy. Patients were also excluded if they had creatinine greater than 1.5 times upper limit of normal or liver enzymes (AST or ALT) more

than twice the upper limit of normal (see Clinical Review for study eligibility details).

Patients were randomized with equal probability to receive six weeks of treatment with either Asacol 800 4.8 g/d or Asacol 2.4 g/d; both were divided into TID dosing. Clinical assessments, excluding sigmoidoscopy, were obtained at the end of Week 3, and assessments including sigmoidoscopy were obtained at the end of Week 6. The primary endpoint was "success" at Week 6, defined as improvement in PGA score.

A total of 772 patients were enrolled. The mean age was 43 years, 8% were over 65, 56% were male, and 97% were Caucasian. More than 90% completed the study in both arms; slightly under half of the discontinuations were due to adverse events. The primary efficacy results, as well as the success rates by gender, are given in the table below:

Treatment Success Rates at Week 6 (ITT population) in Study 2006444

	Asacol 2.4 g/d	Asacol 800 4.8 g/d	p-value	Difference (Asacol 800 – Asacol)	95% C. I.
Study 2006444					
Total	65.5% (251/383)	70.2% (273/389)	0.168	4.6%	(-1.9%, 11%)
Males	65.3% (141/216)	69.1% (150/217)		3.8%	(-5%, 13%)
Females	65.9% (110/167)	71.5% (123/172)		5.6%	(-4%, 16%)

The difference in success rates for Asacol 800 and Asacol was not statistically significant, but the non-inferiority margin was just under -2% in magnitude. The Statistical Reviewer noted that agreement had not been reached on the Applicant's proposed non-inferiority margin of -10%. The Statistical Reviewer conducted his own evaluation of a relevant placebo-controlled study of Asacol 2.4 g/d, and determined that a lower limit in the range of -1.1% to -2.5% appeared to represent an appropriate margin. He concluded that the findings from Study 2006444 could be considered robust. The Clinical Reviewer noted that, in a *post hoc* analysis, 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). He also commented that a gender difference in treatment effect was not seen in the present study.

In reviewing the combined safety data from this study and the Applicant's other studies, the Clinical Reviewer concluded that overall the safety profile of Asacol 800 at 4.8 g/d was similar to that of Asacol at 2.4 g/d, although there were some variations in particular subcategories of adverse reactions. He noted that there were numerically fewer serious adverse events in the Asacol 800 arms, partly accounted for by a lower incidence of UC exacerbations with Asacol 800 4.8 g/d. The finding of a higher incidence of nausea and vomiting in the Asacol 800 arms seen in the first review cycle did not appear to be present in the larger combined data set that included the larger new study. No evidence of an effect on creatinine was noted in these studies, but the Clinical Reviewer noted that these studies involved only relatively brief (six weeks) exposure.

FDA's Division of Scientific Investigations (DSI) inspected study sites in Toronto, ON, Canada; Orange County, CA; and Shreveport, LA. The inspector concluded that the data from the study sites were valid and could be used in support of the NDA.

Final Conclusions and Recommendations
The Statistical Reviewer concluded that Asacol 800 at 4.8 g/d should be efficacious as compared to placebo.

The Clinical Reviewer concluded that non-inferiority had been demonstrated for Asacol 800 4.8 g/d compared to Asacol 2.4 g/d, and he recommended that Asacol 800 be approved for treatment of moderately active UC at a dose of 4.8 g/d for six weeks. He concluded that the database allowed for an adequate assessment of safety.

The Clinical Reviewer recommended modifications to proposed labeling to the describe the lack experience with the product beyond six weeks in INDICATIONS and DOSAGE AND ADMINISTRATION, to add updated postmarketing information to the ADVERSE REACTIONS section, to revise recommendations in the OVERDOSAGE section, and to add information on comparative PK parameters to the CLINICAL PHARMACOLOGY section. He also recommended several modifications to the study descriptions in the CLINICAL STUDIES section of the labeling (see Clinical Review for details).

No Phase 4 requirement was recommended beyond a pediatric study (see Pediatrics, below).

Office of Surveillance and Epidemiology Consults

Conclusions from the Initial Review Cycle
DMETS review of the proposed proprietary name "ASACOL 800" during the initial review cycle raised concerns about use of "800" as a modifier and about the potential for substitution with the approved product Asacol, to which bioequivalence had not been demonstrated. However, based on the Division's assessment that substitution did not pose a safety risk, DMETS concluded that it had no objections to the name "Asacol 800." DMETS also made some recommendations for improvement in the container labels and carton labeling.

Current Cycle Review
In consideration of the current NDA as well as an interest in other mesalamine products, the Division requested from OSE's Division of Adverse Event Analysis (DAEA I) a search of AERS reports with mesalamine, with attention to the question of whether there was any evidence that renal impairment or hypersensitivity reactions with mesalamine were related to dose. The OSE Reviewer also conducted a literature search. (See OSE review by A. Mackey dated 3/19/08 and filed in DFS under NDA 19-619.) The Reviewer concluded that the AERS data could not address the issue of dose-relatedness of those adverse reactions, but she noted that from reports in the literature, mesalamine-induced renal impairment did not appear to be dose related.

The proprietary name was reviewed again for the current review cycle. DMEP felt it was highly probable that substitution errors would occur between Asacol 800 and Asacol and that the "800" modifier would not communicate the difference. Although the clinical review team for the

present review cycle felt that the medical risk that might result from a substitution was not large, they were concerned with the expected high probability of substitution errors and the problems inherent with numerical modifiers. DMEP concluded that it objected to the proprietary name "Asacol 800." DMEP also provided updated recommendations for container labels and carton labeling.

Final Conclusions
From available literature, renal impairment due to mesalamine does not appear to be related to dose.

DMEP objected to the proprietary name "Asacol 800."

Pediatrics

No pediatric data were provided in this application. For the initial submission, the Applicant had requested a deferral of pediatric studies for patients aged 5 to 16 years and a waiver for patients under 5 years, stating that ulcerative colitis is uncommon in children less than 5 years of age. The Review Team for the initial review cycle was in agreement with those requests. However, no decision on the waiver or deferral requests was communicated in the AE Letter of 8/29/05. Subsequent to the AE action, in a letter dated 10/19/05, the Division granted a waiver for pediatric patients less than 5 years and a deferral for patients 5 to 17 years.

As part of currently ongoing negotiations regarding a change in a pediatric Written Request for the Applicant's approved oral mesalamine product, Asacol (400 mg tablets), the Applicant has proposed a randomized, double-blind study in UC patients ages 5 through 17 years to evaluate the safety and effectiveness of two different doses of Asacol administered for six weeks. The study would enroll at least 40 patients at each dosage arm, with at least 5 patients in each arm in the age range 5 to 8 years. Effectiveness would be assessed with a non-endoscopic endpoint. When the current NDA was presented at the Pediatric Review Committee (PeRC) meeting on April 9, 2008, the Committee recommended that the 400 mg tablet (Asacol) be viewed as an age-appropriate formulation of Asacol 800 for pediatric use, and they recommended that the pediatric study for Asacol as proposed by the Applicant would be appropriate to require as a pediatric study under PREA for Asacol 800. The PeRC also concurred with the waiver for pediatric patients younger than 5 years. The Applicant agreed to offer the proposed pediatric study of Asacol as the pediatric program for Asacol 800.

Advisory Committee

If approved, Asacol 800 would be the fourth oral mesalamine product approved for treating ulcerative colitis (previously approved oral mesalamine products are Asacol [in 1992], Pentasa [in 1993], and Lialda [in 2007]). This application was not presented to an FDA advisory committee because the safety and efficacy data did not pose unique concerns beyond those applicable for other oral mesalamine products already on the market.

Team Leader Review and Discussion

This Reviewer generally is persuaded by the principal that the recommended dose of a drug should be the lowest effective dose unless there is substantial evidence of a benefit of a higher dose, either overall or for an identifiable, clinically meaningful subset of patients. This is predicated on the presumption that higher doses entail greater risk and therefore should be expected to afford an offsetting benefit. The case for this position is strongest when there are known significant risks of higher doses, almost as strong if the risks are not well characterized, but is admittedly more controversial if the risks are better understood and do not appear to be terribly concerning. While a practitioner is free to use discretion in deciding to user a higher dose, this Reviewer feels the FDA should have an objective basis for recommending it. This approach to the requirements for approval seems to be reflected in the Division's advice to sponsors in meeting minutes regarding oral mesalamine products in the 1990's, after the first oral mesalamine products were approved. This also seems to be the approach reflected in the initial cycle review documents and the August 2005 AE Letter for this NDA.

For the present consideration of this particular NDA, however, additional factors are in play. Although the administrative record is not explicit on the reasons for a modification in the Division's approach to oral mesalamine products as reflected in the 2007 approval of both the 2.4 g/d and 4.8 g/d doses of Lialda (mesalamine) without a demonstration of greater efficacy for 4.8 g/d, reasons are suggested by the observation that the general safety of a 4.8 g/d dose was no worse than a 2.4 g/d dose; and in fact the safety profile of the 4.8 g/d dose appeared slightly better as reflected in a lower rate of UC-like adverse reactions, suggesting (but not establishing) a somewhat improved efficacy. Also, by 2007 there had been almost 15 years of satisfactory market history with oral mesalamine products, providing a greater safety experience than one would have with a typical new molecular entity.

For this particular product, one also needs to take into account the point that no doses of Asacol 800 lower than 4.8 g/d were studied (studies of lower doses using Asacol [400 mg] cannot be considered lower doses of the present product given the lack of established bioequivalence). Therefore, if Asacol 800 is considered efficacious and the risk/benefit of the studied dose of Asacol 800 is deemed acceptable, there are not sufficient grounds to recommend the product be used at a lower dose or deny its approval at the studied dose. Given the similarity in safety between Asacol 800 and Asacol in the controlled clinical studies, and the conclusion from the literature (cf. OSE consult by A. Mackey) that one of the more significant, but infrequent, AE's of renal impairment is most likely not significantly related to dose, it can be concluded that Asacol 800 at 4.8 g/d for six weeks has an acceptable safety profile.

Thus, given the current precedents, and given the generally similar safety profile of Asacol 800 4.8 g/d compared to Asacol 2.4 g/d, the current understanding regarding the safety of oral mesalamine, and the Division's advice to the Applicant in March 2007 that a non-inferiority approach could be acceptable, it does not appear that is reasonable to sustain the requirement that Asacol 800 4.8 g/d be established as superior to Asacol 2.4 g/d. Therefore, despite the deficiencies and requirements cited in the AE Letter of 8/28/05, a demonstration of none-inferiority relative to Asacol 2.4 g/d should now be considered sufficient evidence of efficacy when viewed in conjunction with the results of Study 82.

A remaining point is the question of what should be the criterion for non-inferiority. From a clinical aspect, a non-inferiority margin of 2% certainly seems sufficiently small. However, the more challenging issue is whether that is small enough to provide reasonable assurance that the study actually provides assurance of efficacy. The Statistical Reviewer felt the Applicant's proposed margin of 10% was unsupported, but he referred to a previous placebo-controlled study of Asacol 2.4 g/d and concluded that a margin in the range of 1.1% to 2.5% was appropriate. A more demanding approach might have been to attempt to survey a broader range of trials in currently approved mesalamine products and the use the most rigorous non-inferiority margin that seemed appropriate. However, in this reviewer's view, while that level of rigor may be desirable for demonstrating non-inferiority to an unrelated product, the fact that Asacol 800 therapy involves administration of a higher dose of oral mesalamine than what is in the approved active comparator, affords strong independent priors regarding the efficacy of the product, so that the non-inferiority requirements applied for this particular NDA can be considered sufficient.

The NDA presents only clinical data on short term (six weeks) use in active UC, but UC is a chronic disease. A requirement for adequate instructions for use would lead one to expect to be able to provide instructions for how this product would be used in the chronic management of UC. In this case, the Applicant's other oral mesalamine product (Asacol) can be viewed as providing adequate additional information. Asacol is approved at 2.4 g/d for six weeks for treating active disease, and at a dose of 1.6 g/d for maintenance of remission in UC. The dosing with Asacol 800 is different, but, given the short action and frequency of dosing, the transition from treating active disease with Asacol 800 to a maintenance dose of Asacol does not raise significant additional issues beyond transitioning from the active disease dose of Asacol to the maintenance dose of Asacol. Between the Applicant's two products, there it is reasonable to consider that there is adequate information about how this product can be used as part of an approach to using mesalamine in the chronic management of UC.

The AE Letter asked the Applicant address the issue of an apparent greater effect in males. No explanation was provided for why that result was seen in Studies 83 and 82. However, in the recent clinical study, there was a much larger number of males and females in each group, and no differential effect was seen; the success rates for females was a good or better than that for males. On the basis of those results, it is reasonable to say that the effectiveness of Asacol 800 can be expected to be acceptable for both females and males, and there would be no basis for restricting the indication by gender. Although no explanation was found for the outcome observed in Studies 83 and 83, the gender issue raised in the AE Letter can be considered addressed.

Regulatory Conclusions

Approval Action

Asacol 800 should be approved under 21 CFR 314 for treating ulcerative colitis, but the Applicant should be required to provide a different proprietary name.

The indication statement should limit the target population to those with moderately active disease (as proposed by the Applicant) and should identify the course of therapy as six weeks. The recommended dosing is 4.8 g/day administered in divided dosing three times a day.

Labeling Recommendations

The labeling should carry substantially the same contraindications, warnings, and precautions as in the labeling for the approved product Asacol.

The labeling should take into account the labeling recommendations of the Pharmacology/Toxicology, Clinical Pharmacology, and Clinical Reviewers. Labeling should clearly explain the lack of demonstrated bioequivalence between the current product and Asacol, and this should be identified in those sections of the labeling in which the two products are discussed together. If the proprietary name that is eventually approved can be viewed as having a significant risk of being confused with Asacol, the labeling should clearly disclose the non-interchangeability of the two products wherever the administration of the current product is discussed.

The adverse reaction section should report information not only from the clinical trials, but also from postmarketing experience with Asacol and other mesalamine products. The clinical trials section of labeling should present the results of Study 2006444 as the principal clinical findings for this product. Although supporting evidence comes from Study 82, the results of that study should not be included in any way that would permit an implicit claim of superiority of Asacol 800 4.8 g/d over Asacol 2.4 mg/d.

Phase 4 Requirements

The Applicant should be required to conduct the following postmarketing study:

1) Conduct a study in pediatric patients ages 5 to 17 years with ulcerative colitis using an age-appropriate formulation (i.e., an oral mesalamine formulation appropriate for pediatric dosing), such as your approved product, Asacol®. The study will evaluate the pharmacokinetics, safety, and clinical response of pediatric patients undergoing six weeks of oral mesalamine therapy. The study will be a randomized, double-blind study comparing at least two different dose levels of mesalamine and it will enroll at least 40 pediatric patients in each dosing arm.

The requirement under PREA to conduct studies in pediatric patients younger than 5 years should be waived, as granted in the Division's letter of 10/19/05.

No other additional postmarketing activities are recommended beyond those required under current NDA regulations.

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/s/

John Hyde
5/29/2008 02:26:47 PM
MEDICAL OFFICER