Summary Review for Regulatory Action

Date	May 29, 2008
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA	NDA 21-830
Applicant Name	Procter and Gamble Pharmaceuticals, Inc.
Date of Submission	Original Submission October 24, 2004 Resubmission October 22, 2007
PDUFA Goal Date	April 22, 2008
Proprietary Name / Established (USAN) Name	Asacol®800 Delayed Release tablet Mesalamine
Dosage Forms / Strength	800 mg tablet
Proposed Indication(s)	Treatment of moderately active ulcerative colitis
Proposed Regimen	1600 mg orally three times a day for 6 weeks
Action/Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Anil Rajpal, MD/John Hyde, MD
Statistical Review	Milton Fan, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Sushanta Chakder
CMC Review/OBP Review	Maria Ysern, MSc./Moo-Jhong Rhee, PhD
Microbiology Review	NA
Clinical Pharmacology Review	Insook Kim, PhD/Sue-Chih Lee, PhD
DSI	Khairy Malek
OSE/DMETS	Walter Fava, R.Ph., Linda Kim-Jung, Pharm D.
Division of Adverse Events Analysis I	Anne Corken Mackey RPh MPH/Mark Avigan, MD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation

Division Director Review

1. Introduction

The applicant has submitted a complete response to the approvable action that they received on August 29, 2005 for their first submission of NDA 21-830.

The major issue cited in the approvable letter was: Insufficient proof of 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 approvable letter stated that this issue could be addressed by:

1) providing 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.
2) explaining why Asacol 800 mg at 4.8 g/day was more efficacious than Asacol 400 mg at 2.4 g/day in male patients.

The applicant has submitted a randomized phase 3 study in response to that letter. This review will focus on the adequacy of the data from this new study to address the major review issue identified in the first review cycle.

2. Background

Proctor and Gamble Pharmaceuticals, Inc (P&G) submitted an NDA (NDA 21-830) for Asacol 800 (mesalamine) Delayed-Release Tablets for the indication of moderately active ulcerative colitis on October 24, 2004 and received an approvable action letter on August 29, 2005.

The original NDA submission included two major trials ASCEND I (2000083) and ASCEND II (2000082). Both studies enrolled patients with minimally or moderately active ulcerative colitis and were designed with the same primary endpoint and analysis plan. The eligibility and primary endpoint were anchored in the Physician's Global Assessment (PGA), which in these studies included four components: (1) rectal bleeding scored 0-3, (2) stool frequency scored 0-3, (3) sigmoidoscopy score of 0-3, and (4) Patient Functional Assessment scored 0-3. In both studies Asacol 800 mg dosed at 4.8/day (two tablets dosed three times a day, TID) was compared to Asacol 400 mg dosed at 2.4g/day (two tablets dosed TID). The primary analysis was a comparison of proportion of patients in each arm that experienced "treatment success", which was defined as complete response (Physician's Global Assessment score of 0) or improvement in at least 1 of the 4 components of the Physician's Global Assessment (stool frequency, rectal bleeding, sigmoidoscopy score, and Patient Functional Assessment) by at

least one point, with no worsening of the remaining 3 components of the Physician's Global Assessment (PGA).

Study 2000083 was the first study completed, and a statistically significant difference was not observed between the two Asacol arms. However, in a subset analysis of the patients with moderately active ulcerative colitis, the Asacol 800 mg arm appeared to yield superior results relative to the Asacol 400 mg arm. A further subset analysis revealed that the treatment effect favoring Asacol 800 mg was driven by the male population.

In response to these observation ins Study 2000083, P&G changed the primary analysis plan of the ongoing Study 2000082 to evaluate treatment success in the patients on study who had moderately active ulcerative colitis. The targeted enrollment was increased to enroll more patients with moderately active disease. The superior outcome in the moderate disease group observed on the Asacol 800 mg arm at study completion was questioned by the FDA reviewers because the analysis had been revised very late in the conduct of the study (after approximately 96% of the originally planned patients had been enrolled). The subset analysis by gender again found that the difference favoring the 800 mg arm was driven by the male subpopulation.

The approvable letter was issued and a series of meetings were held with P&G to discuss their proposals for addressing the issue outlined in the letter. A summary of these meetings is provided below:

November 28, 2005 Meeting: This meeting was held in response to the August 29, 2005 Approvable action letter. [redacted] The FDA recommended that P & G perform a well-controlled phase 3 study that stratified by gender for patients with moderate disease. Consistent with the recommendation in the August 29, 2005 approvable letter, the FDA said that P&G needed to provide at least one additional adequate and well-controlled study that demonstrated 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.

February 3, 2006 Meeting: This meeting was requested by P&G to discuss their proposals to support registration of Asacol 800 mg 1) at a dose 4.8 g/day for treatment of moderately active ulcerative colitis [redacted]

March 16, 2007 Meeting: This meeting was requested by P&G to discuss "alternate registration path for approval of Asacol 800 tablets dosed 4.8 g/day for treatment of [redacted] moderate ulcerative colitis". P&G cited the approval of two doses of [redacted] without evidence of dose response (both compared to placebo within the same study) as a reason to pursue demonstrating comparable efficacy between Asacol 2.4 g/day and 4.8 g/day as basis of approval for treatment of ulcerative colitis, instead of the "added clinical benefit" stated in the August 29, 2005 approvable letter. The Division stated that they recommended demonstration of incremental clinical benefit, i.e. superiority, but that demonstration of noninferiority "might be sufficient". P&G proposed showing comparability of Asacol 800mg dosed at 4.8 g/day and Asacol 400 mg dosed at 2.4 g/day via a primary noninferiority analysis of Studies 20000083 and 2000082 and results of amended ASCEND III (Study 2006444). The Division responded that either a superiority or noninferiority approach could be used to support the complete response to the August 29, 2005 approvable letter for treatment of moderate ulcerative colitis. A noninferiority approach would raise statitistical concerns. A noninferiority approach based on the ongoing ASCEND III (Study 2006444) would necessitate amending the protocol, and the Division voiced concerns regarding making such changes near study completion. The previously completed studies 2000083 and 2000082 could not be used to establish noninferiority because they were not designed as noninferiority trials, however, the Division stated that these studies, "may be supportive".

P&G proposed a noninferiority margin of 10%. The Division stated that they could not agree to that margin and that the margin should be based on historical evidence of the efficacy of the active control. P&G stated that they would use statistical testing hierarchy, which in the protocol amendment would be noninferiority first, and then superiority. They planned to proceed with the amended protocol, as submitted, using the 10% noninferiority margin of 10%, and would rely on study 2000082 as one of the two "pivotal trials" demonstrating noninferiority.

3. CMC/Device

I concur with the conclusions reached by Maria Ysern, the chemistry reviewer, regarding the acceptability of the manufacturing of the drug product and drug substance. The manufacturing site inspections were repeated this review cycle and were acceptable. The mesalamine drug substance in this product is the same as that approved for the applicant's approved and marketed Asacol 400 mg tablets. The product proposed for marketing in this NDA contains 800mg of the mesalamine drug substance.

4. Nonclinical Pharmacology/Toxicology

The applicant did not submit non-clinical studies in support of this NDA, however, they did reference their IND and NDA for their Asacol (mesalamine) 400 mg product. Dr. Chakder reviewed the applicant's proposed labeling and I concur with his recommendations for modifying the non-clinical sections.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer, Insook Kim, PhD, that there are no outstanding clinical pharmacology issues that preclude approval. She recommended revisions to the applicant's proposed labeling to reflect the variability in timing of blood sampling that occurred in the pharmacokinetic studies and the limitations of the data used to calculate the proposed labeled estimated terminal half-life.

Of note, the clinical pharmacology/biopharmaceutics reviewers found that the Asacol 800 mg tablet is not bioequivalent to two Asacol 400 mg tablets, the applicant's currently marketed product. The mean Cmax of Asacol 800mg tablet was 36% lower than two Asacol 400 mg tablets and the mean AUC was 25% lower. These conclusions are based on systemic exposure, but the product is believed to act locally on the colonic epithelium. Approximately 25% of the orally administered dose of Asacol 800mg is systemically absorbed, based on cumulative urinary recovery of mesalamine and its N-Ac-5-ASA metabolite in healthy volunteers administered a single dose. Metabolism occurs by acetylation in the gut wall and liver.

Food effect studies have demonstrated that high fat meals cause a 47% decrease in mesalamine Cmax and a 14 hour delay in Tmax.

6. Clinical Microbiology

NA

7. Clinical/Statistical-Efficacy

Study 2006444 is the randomized, controlled trial submitted in response to the August 29, 2005 approvable letter that stated the initial application had provided insufficient proof of superiority of Asacol 800 mg dosed at 4.8 g/day compared to Asacol 400 mg dosed at 2.4 g/day to support the proposed indication of treatment of moderately active ulcerative colitis. That letter stated that this issue could be addressed by providing 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 and explaining why Asacol 800 mg at 4.8 g/day was more efficacious than Asacol 400 mg at 2.4 g/day in male patients.

Study 2006444 was originally designed as a superiority study comparing Asacol 800 mg (4.8g/day) to Asacol 400 mg (2.4g/day), but the protocol was amended to revise it to a noninferiority design in early March 2007. The amendment increased the sample size from 470 to 770, and at the time of the amendment there were 552 patients who had enrolled in the trial. Dr. Fan states in his review that the study failed superiority, p value=0.4595 at the time of the amendment - treatment difference was 3% at that point, with a 95% CI (-4.8, 10.8). The analysis plan for the primary endpoint was a noninferiority comparison of the proportion of the patients with "treatment success", which in this study was defined as improvement of PGA score, with no worsening of component subscales (Patient Functional Status not included). If

noninferiority was established in the first analysis, the second step-wise comparison was an analysis of superiority.

The observed outcome was 70.2% of the Asacol 800 mg (4.8g/day) patients experienced treatment success compared to 65.5% of the Asacol 400 mg (2.4g/day) arm, a difference of 4.6% (95% CI = -1.9%, 11%). In response to FDA's previous comments that the treatment effect of the active control arm, Asacol 400 mg, relative to placebo would need to be established in order to interpret the outcome of this study, the applicant presented an analysis of data from a placebo-controlled trial of Asacol 400 mg. Because that study enrolled both patients with mildly and moderately active ulcerative colitis, the applicant presented analyses of treatment effect of Asacol 400 mg (2.4 g/day) relative to placebo in two populations: 1) the study's eligible population of combined mildly and moderately active ulcerative colitis and 2) the subset of the study with moderately active disease. The latter population is the population studied in the noninferiority study presented for review in this complete response. The treatment effect relative to placebo for the combined mild to moderately active disease (N=105) in the reference placebo-controlled trial was 20% (95% CI = 3%,38%) and for the moderately active subset (total N = 48) was 29% (95% CI = 2%,56%).

The biostatistical reviewer Dr. Fan stated that a proposed 10% noninferiority margin could not be justified. He conducted a number of sensitivity analyses of the noninferiority study and the reference placebo-controlled trial. He concluded that because the lower limit of the 95% confidence interval for the difference between arms in the noninferiority trial ranged from -1.1% to -2.5%, the results of the applicant's analysis, which had a lower limit of the 95% confidence interval of -1.9%, could be considered robust. This lower limit is close to 2%, the lower bound of the confidence interval for the treatment difference in the moderately active disease subgroup of the reference placebo-controlled trial. Fifty per cent of that lower bound is 1%. In that low range, Dr. Fan stated that 1.9% is close to 1%, and certainly less than the proposed 10% noninferiority margin. The biostatistics reviewers concluded that the Asacol 800 mg (4.8g/day) product should be considered efficacious compared to placebo.

Evaluation of the treatment outcomes in the noninferiority study for each individual component of the PGA, including the separately evaluated PFA, demonstrated improvement that exceeded 70% in both Asacol treatment arms in each component except sigmoidoscopy, in which the proportion that experienced improvement was 30.7% in the Asacol 400 mg arm and 30.2 % in the Asacol 800 mg arm. The proportion that experienced improvement was higher in the Asacol 800 mg arm than the 400 mg arm in the other PGA components, although the differences were not found to be statistically significant. A post-hoc analysis of clinical remission at week 6, defined as having achieved a rectal bleeding and stool frequency score of 0, found that clinical remission was achieved in 42.8% of patients treated with Asacol 800 mg tablets and in 35.4% of those treated with the 400 mg tablets. The difference was 7.3% (95% CI = 0.1, 14.5).

An issue that concerned the FDA reviewers in the initial NDA review was the subset analysis by gender of Study 2000082, which suggested that the efficacy observed in the Asacol 800 mg treatment arm was confined to the males in the study. The treatment success observed in women in that trial treated with Asacol 400 mg (2.4g/day) was numerically higher than women

treated with Asacol 800 mg (4.8g/day). The analysis of treatment success by gender in the current noninferiority study, however, did not detect differences in efficacy by gender. The proportion of patients who experienced treatment success was higher in the Asacol 800 mg arm in both men and women. The difference was 3.0 (95% CI= -5.0, 12.7) in men and 5.6 (95% CI= -4.2, 15.5) in women.

8. Safety

The safety database for this product includes 727 patients treated with Asacol 800 mg (4.8g/day) in the two randomized, controlled trials submitted in the original NDA submission and in the noninferiority study submitted in this complete response. The mean duration of exposure in the original two trials was 40 days and the mean in the recent study was 51 days. In the combined safety data base for these three studies, there was a similar proportion of adverse events in patients treated with Asacol 800mg (4.8g/day) relative to the already approved Asacol 400 mg product, dosed at 2.4 g/day. The proportion of patients with Serious Adverse Events (SAEs) was slightly higher in the Asacol 400 mg (2.4g/d) group – 1.8% vs. 0.8%. There was a somewhat higher proportion of moderate adverse events on the higher dose level, 37% vs. 30%. The most common adverse events for the Asacol 800 and Asacol 400mg groups were headache (5% in each), nausea (3% in each), vomiting (1% and 2%, respectively), abdominal pain (2% in each), ulcerative colitis (2% and 3%, respectively), and diarrhea (2% each). The clinical review of the original NDA submission detected no safety concerns.

Dr Rajpal gave special attention to changes in renal function in the safety database for the submitted study. A mean change in creatinine of 1% was observed in both treatment groups. The number of patients whose creatinine shifted from normal to high during the course of the study was higher on the 2.4g/day arm than on the 4.8 g/day arm – 4 vs. 1 patient. One case of nephritis was observed in the 2.4 g/day dose group.

In his review of the Serious Adverse Events in the database, Dr. Rajpal identified 19 patients, 13 treated with the Asacol 400 mg 2.4g/day product and 6 treated with Asacol 800 mg 4.8 g/day who experienced SAEs. He noted that the majority of the SAEs were gastrointestinal events related to ulcerative colitis, nausea and vomiting, gastroenteritis, cholecystitis, and pancreatitis. Single events each of nephritis and pericarditis were observed. Nephritis and pericarditis are described in the Asacol 400 mg product labeling. There was one case of hypersensitivity that occurred in a patient treated with Asacol 800 mg. Events reported as SAEs that have not been identified in the previous Asacol 400 mg product label included a case of dysfunctional uterine bleeding in a woman with pre-existing fibroids, a case of enterocolitis of unknown etiology that resolved, a case of colon cancer, and an episode of vasovagal syncope in a 44 year old male.

Dr. Rajpal notes in his review that the Asacol 800 mg product has been marketed in Canada since 2005, at a dose of 4.8g/day. Ten spontaneous adverse events have been reported for the product since that time, all non-serious. These included single reports of dysphagia, diarrhea, nausea/fatigue/insomnia, ulcerative colitis flare, ulcerative colitis flare with alopecia, and five cases of medication residue. The estimated patient-years of exposure in Canada based on the applicant's shipment data to that country is approximately 11,000 patient-years.

Dr. Rajpal examined the safety database for evidence of drug-demographic interactions and noted no clear relationship between age or sex and specific adverse events. However, with regard to special populations, the ability to draw meaningful conclusions from these analyses was limited by the relatively small numbers in subgroups. The majority of patients in the safety database were Caucasian and less than 9% of the study population was aged 65 or older. Analysis of safety by sex revealed that slightly more males experienced diarrhea on the Asacol 400 mg (2.4g/day) than on Asacol 800 mg – 2.1% vs. 0.8%.

Anne Corken Mackey RPH MPH reviewed the AERS database for adverse events associated with the mesalamine products currently marketed, in particular exploring the database for evidence of a relationship of mesalamine dose with adverse events of renal impairment and hypersensitivity. The database was examined for the period between 1992 and February 12, 2008. No evidence of a dose relationship was identified. Ms Mackey did note that the database was limited in its ability to identify a dose response relationship as the dose information was not consistently provided in reports. Only 90 of the 224 cases of renal impairment reported the dose. Sixty of the 90 occurred at doses of ≤2.4 g/day and the remaining 30 occurred at doses >2.4 g/day. A literature search conducted by Ms. Mackey also did not find evidence that dose was associated with risk of renal impairment.

9. Advisory Committee Meeting

There was no advisory committee meeting for this application.

10. Pediatrics

There were no pediatric data provided in this application. The applicant's request to defer pediatric studies in children aged 5-16 years and for a waiver in children under age of 5 years (because ulcerative colitis is rare in that age group) was presented to the Pediatric Review Committee (PeRC) on April 9, 2008. The committee concurred with the waiver and recommended that the applicant's Asacol 400 mg tablet should be viewed as the age-appropriate formulation of mesalamine for pediatric use. The committee recommended that the applicant's proposed randomized study in children ages 5-17 with ulcerative colitis would be appropriate to require as a pediatric study under PREA for the current NDA for its mesalamine 800 mg product.

11. Other Relevant Regulatory Issues

DSI inspected three study sites – two U.S. sites and one Canadian site – and concluded that the data from the sites could be used to support the NDA.

The applicant certified that it didn't enter into financial agreements with the clinical investigators whereby the value of their compensation could affect outcome of the studies.

12. Labeling

The DMETS review team recommended against accepting the proposed product name "Asacol 800" because they felt it was highly probable that substitution errors would occur between the Asacol 800 and Asacol 400 mg product. They did not believe that the modifier "800" would prevent such errors. The same proprietary name had been reviewed in the previous review cycle, and although initially was found to be unacceptable for the same reason, the final recommendation was that DMETS did not object to "Asacol 800" , a recommendation based on the clinical reviewers' conclusion that substitution would not pose a safety risk. In the current review cycle the clinical review team concurred with DMETS that there was significant risk of substitution and although the risk associated with substitution is not large, the clinical reviewers supported the DMETS recommendation since the Asacol 800 mg product is not bioequivalent to the Asacol 400 mg product.

I concur with the labeling recommendations of the clinical review team and the Pharmacology/Toxicology and Clinical Pharmacology reviewers.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  - I concur with the reviewers' recommendations for approval of this mesalamine 800 mg product for treatment of moderately active ulcerative colitis at a dose of 4.8g/day in three divided doses (two tablets per dose). Dr. John Hyde's Clinical Team Leader Summary Review provides an excellent summary discussion of the issues that the clinical and statistical review teams weighed when they considered the strength of evidence of effectiveness to make a final recommendation of approval. He has clearly delineated the issues of superiority, noninferiority, lowest effective dose, and the balance of risk/benefit that were carefully considered during this review.

    The data in this application support that the 800 mg (4.8 g/day) dose of the applicant's mesalamine product is more effective than placebo for treatment of ulcerative colitis. The primary analysis of the data from the noninferiority study submitted in the complete response suggest that the 800 mg tablet dosed at 4.8g/day has a similar treatment effect to the 400 mg Asacol product dosed 2.4 g/day, in patients with moderately active ulcerative colitis. A previously conducted and reviewed comparative trial had suggested that the higher dose might be superior to the lower dose in the subset of that trial with moderately active disease, but this finding of superiority was not reproduced in the trial submitted for review in the complete response. Analyses of secondary efficacy endpoints within the noninferiority trial favored the higher dose, but the differences were not statistically significant.

There is precedent for approving incrementally higher doses of mesalamine products based on demonstration of effectiveness relative to placebo, without demonstration of incremental increase in comparative effectiveness. Mesalamine products work locally on the gut mucosa, and the safety profile has been acceptable and systemic exposure relatively low. There was no evidence within this application's safety database that risk increases with the increased dose, and pharmacokinetics analyses indicate that the systemic exposure with the 800 mg product is less than taking a similar total dose using the 400 mg product formulation. A literature review indicates that the most serious toxicity that has been associated with mesalamine products, nephrotoxicity/interstitial nephritis, has not been established to be dose related, but is thought to be an idiopathic reaction to the 5-ASA products.

The American College of Gastroenterology Practice Guidelines for treatment of ulcerative colitis in adults [Kornbluth A, and Sachar D. Ulcerative Colitis Practice Guidelines in Adults (Update): American College of Gastroenterology, Practice Parameters Committee. American Journal of Gastroenterology 2004, pp1371-1385] state that "effective doses..range….for mesalamine 2-4.8 g per day in three divided doses". This suggests that practicing physicians use a range of mesalamine doses. There are two publications cited by the Guidelines to support the mesalamine dose range. One compared each of two mesalamine doses, 2.4 g/day and 1.6 g/day, to placebo and found them both superior to placebo [Sninsky CA, et al. Annals Internal Medicine 1991, 115(5):350]. The other, which compared mesalamine doses 4.8 g/D and 1.6 g/D to placebo, only found a statistically significant difference relative to placebo in the patients treated with the 4.8g/day dose [Schroeder KW, et al. NEJM. 1987, 317 (26) 1625].

Recent review articles state that studies have not clearly established in head to head dose comparisons that there is added benefit to mesalamine doses above 2.4 g/day (Safdi AV and Cohen RD. Review article: increasing the dose of oral mesalazine therapy for active ulcerative colitis does not improve remission rates. Aliment Pharmacol Ther 2007 26, 1179-1186.) The data submitted in this NDA do not indicate that there is a statistically significant added benefit in escalating the Asacol mesalamine dose beyond 2.4 g/day in patients with moderately active ulcerative colitis. However, the data in this application indicate that Asacol 800 mg (dosed 4.8g/day) is more effective than placebo and there is no evidence of additional risk with the higher dose based on the review of the data in this submission, the AERS database information and literature review. Clearly, based on the practice guidelines, physicians are treating some patients with doses up to at least 4.8 g/day. With that target total dose, the Asacol 800 mg product would be predicted, based on the relative pharmacokinetic profile, to result in a lower systemic exposure than if the Asacol 400 mg dose were administered to achieve that 4.8 g dose.

- Recommendation for other Postmarketing Study Commitments
  The applicant will be required to conduct a randomized, double-blind study of six weeks of therapy with mesalamine at two different doses in pediatric patients ages 5-17

years to evaluate the safety and effectiveness of those doses and to compare with the results seen in adults. The study should include at least 40 patients in each dosage arm, and 5 patients in each arm should be 5-8 years of age. The protocol should be submitted by August 15, 2008. The study should begin by October 15,2008. A study report should be submitted by January 15, 2009.

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/s/

Donna Griebel
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DIRECTOR