CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-830

Procter and Gamble Pharmaceuticals, Inc.
Attention: Mark S. Leusch, Ph.D.,
U.S. Regulatory Affairs
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Leusch:

Please refer to your new drug application (NDA) dated October 22, 2004, received October 29, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol 800® (mesalamine) Tablets.

We acknowledge receipt of your submissions dated November 2 and December 9, 2004 and January 14, February 17, February 24, February 28, March 3, March 9, March 28, April 27, May 9, May 12, May 13, May 17, June 9, June 16, July 11, July 13, August 2, August 12, and August 15, 2005.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to resolve 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.

Studies 2000082 and 2000083 were randomized, active-controlled trials to study patients with mildly to moderately active ulcerative colitis. Study 2000083 was carried out as planned and overall superiority of the 4.8 g/day regimen relative to the 2.4 g/day regimen was not shown ($p= 0.4$). Subgroup analyses showed a modest benefit for patients with moderate disease but not for mild disease. After these results were known, Study 2000082 was amended to recruit additional patients with moderately active ulcerative colitis shortly before enrollment would have finished. In this study, overall superiority of the 4.8 g/day regimen was not demonstrated for mild and moderate patients. Patients with moderate disease again showed a modest benefit, however, this result appeared to be driven by unexplained efficacy in male patients. Also, there is an inconsistency in outcome when the pre- and post- amendment populations are compared. Therefore, we conclude that Study 2000082 is not robust enough to stand on its own as a single study in support of the proposed 4.8 g/day regimen for treatment of moderately active ulcerative colitis. In addition, we consider Study 2000083 to be a failed study overall. In our view, the subgroup analyses of moderately affected patients in these studies do not provide confirmatory evidence of efficacy of the higher dose regimen. More specific comments follow.

We note that both trials were started at approximately the same time. If the goal was to use one study to provide exploratory information to adjust design parameters of a second study, such as sample size, then there are two possible ways that this could have been accomplished (i.e., either of the two studies could have finished first and been used to adjust the other study's design). Therefore, there is some concern that an adjustment for the multiple chances of producing one definitive study is needed.

Study 2000083 was completed first. It 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. Your 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. 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 (p = 0.29). 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% vs. 55%), but not in post-amendment enrollees (76% vs. 71%). Again, we do not consider the analysis of moderately affected patients in this study to be definitive.

The following are our recommendations for resolution of your 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 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.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Kristen Everett, RN, Regulatory Project Manager, at (301) 443-8347.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
8/29/2005 11:45:20 AM
for Dr. Brian Harvey