

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

APPROVABLE LETTER

McNeil

NDA 19-651/SE1-005

Procter & Gamble Pharmaceuticals
Attention: Melanie A. Bruno, Ph.D., M.B.A.
11450 Grooms Road
SW GR DNW-36 Box# C30
Cincinnati, OH 45252-1408

JUN - 5 1997

Dear Dr. Bruno:

Please refer to your supplemental new drug application dated June 4, 1996, received June 5, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) Tablets.

We acknowledge receipt of your submissions dated July 11, 16, 29, and 30, August 2, September 26, October 11 and 21, November 8 and 18, December 18 and 20, 1996, January 24, February 21 and 24, March 10, April 4, 10, and 14, May 6 and 16, 1997. The User Fee goal date for this application is June 5, 1997.

The supplemental application provides for a new indication, the maintenance of remission of ulcerative colitis.

Your application, as submitted with draft labeling, proposed low and high doses of 0.8 and 1.6 gm/day, respectively. The following pivotal studies were submitted in support of the application:

1. Study# 87086 was a six month, multicenter, double-blind trial which randomized 270 patients to daily doses of Asacol 0.8 gm, 1.6 gm, or placebo (PBO), but only treated 264 patients. The 264 patients included 3 placebo patients enrolled while in endoscopic ulcerative colitis relapse. In an adjusted Intention To Treat (ITT) analysis which excluded only 1 of these 3 patients, the efficacy of Asacol at a dose of 0.8 gm/day was not statistically significant when compared to PBO ($p=0.068$). In contrast, an adjusted comparison between Asacol 1.6 gm/day and PBO, with inclusion of All-Randomized 179 patients, demonstrated a significant difference in favor of the high Asacol dose ($p=0.005$).
2. In support of your claim, you also submitted the pooled results of 4 small maintenance trials (C.1, C.2, C.6, and C.15) in which the efficacy of Asacol, 0.8 to more than 2.4 gm/day, was compared to that of daily doses of 2.0 to 4.0 gm of sulfasalazine. Study duration ranged from 4 months to one year. The pooled efficacy analysis of these studies, i.e., treatment success, was 59/68 (59%) for Asacol and 70/102 (69%) for sulfasalazine. Using a 90% confidence interval of $\pm 20\%$ to reject the null hypothesis that Asacol treatment was inferior to sulfasalazine, the difference in efficacy between Asacol and sulfasalazine was 21%, favorable to sulfasalazine.

Based on the submitted results, we conclude that the claim for the efficacy of Asacol for the maintenance of remission of ulcerative colitis is only supported by the single multi-center placebo-controlled trial (Study# 87086). Hence, the application is approvable for the maintenance of remission at a dose of 1.6 gm/day.

Before this supplement may be approved, it will be necessary for you to submit final printed labeling (FPL). The labeling should be identical in content to the enclosed marked-up draft labeling. In addition, all previous revisions as reflected in the most recently approved package inserts must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Melodi McNeil, Regulatory Health Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 6-5-97

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ON ORIGINAL

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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cc:

Original NDA 19-651/S-005
HFD-180/Div. Files
HFD-002/ORM
HFD-103/Office Director
HFD-101/L. Carter
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-180/CSO/M. McNeil
HFD-180/Prizont
HFD-180/Duffy
HFD-180/Shaw
HFD-180/Choudary
HFD-720/Huque
HFD-720/Chen
HFD-720/Rashid

Drafted by: mm/June 3, 1997/c:\wpfiles\cso\n\19651706.ae

Initialed by: KJohnson 6/4/97, 6/5/97

LTalarico 6/4/97

RPrizont 6/4/97

Final: June 5, 1997

APPROVABLE (AE)