CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019651/S005

MEDICAL REVIEW(S)

Pages: 51 through 63

APPENDIX 2. Study 87086.

List of Non-Compliant Patients.

Topical Ophthalmics	3 (4.8%)	1 (1.5%)	1 (1.7%)

Table 12 - Continued
Most Commonly Prescribed Concomitant Medications - Completed Patients

Other & Miscellaneous drugs	13 (20.6%)	21 (30.1%)	18 (31.0%)
No concommitant medications	9 (14.3%)	6 (8.8%)	3 (5.2%)

Patients could be taking multiple medications.
N = total number of patients exposed to treatment. n = number of patients exposed who took specific medication. % = n/N.
Supporting data can be found in Appendix 5, Table 24.2.

5.1.4 Patient Compliance With Treatment Regimen

The study protocol defined non-compliance with study treatment as missing more than 15% of the study medication over the length of treatment or more than 50% of the study medication for 4 consecutive days (for reasons other than intolerance or adverse events). Twenty-one study participants were determined to be non-compliant with study treatment on the basis of these criteria, as detailed below (and in Appendix 8, Tables 15 & 17). Sixteen patients were discontinued from the study because of dosing non-compliance, five were discontinued for dosing non-compliance and other protocol violations.

Treatment Group	Patient #	Description of Non-Compliance
Placebo	16330205	Baseline therapy violation, no tablets taken for 4 consecutive days.
	16330218	No tablets taken for 4 consecutive days.
	18800209	No tablets taken for 8 consecutive days.
	18800216	No tablets taken for 4 consecutive days.
	35120202	No tablets taken for 5 consecutive days, concomitant medication violation.
	36810203	Overall tablet compliance = 83%.

Treatment Group	Patient #	Description of Non-Compliance
Asacol 0.8 g/day	15050201	Unknown number of tablets taken for duration of study participation (122 days).
	15050221	No tablets taken for 5 consecutive days.
	15580213	Unknown number of tablets taken for 21 consecutive days, missed proctosigmoidoscopy exam.
	16330241	Unknown number of tablets taken for 20 consecutive days.
	18800205	Baseline therapy violation, no tablets taken for 4 consecutive days.
	19780205	Less than 50% of study medication taken per day for 4 consecutive days.
	29170201	Historical diagnosis violation, no tablets taken for 6, 12, and 5, consecutive days as per diary.
	34090201	Baseline therapy violation, unknown number of tablets taken for duration of study participation (178 days).
	34090206	Unknown number of tablets taken for 22 consecutive days.
	34090222	No tablets taken for 15 consecutive days.
	34090242	Less than 50% of study medication taken per day for 4 consecutive days.
Asacol 1.6 g/day	15050202	Tablet compliance count at Month 1.0 = 186%, tablet compliance count at Month 3.0 = 84%.
	15580205	No tablets taken for 9 consecutive days.
	34090207	Unknown number of tablets taken for 3, 9, and 16 consecutive days.
	34090245	No tablets taken for 4 consecutive days.

APPENDIX 3

March 31, 1997 Letter to P&G Requesting Information.

Dr Prizont-

NDA 19-651/S-005

MAR 3 1 1997

Procter & Gamble Pharmaceuticals
Attention: Melanie Bruno, Ph.D., M.B.A.
11450 Grooms Road
Cincinnati, OH 45242

Dear Dr. Bruno:

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

To complete our review of the clinical and statistical sections of your application, we have the following comments and requests regarding pivotal Study# 87086 entitled, "An Oral Preparation Of Mesalamine As Long-Term Maintenance Therapy For Ulcerative Colitis: A Randomized, Placebo-Controlled Trial," in which patients were administered Asacol 0.8 gm/day, Asacol 1.6 gm/day, or placebo (PBO):

1. According to the application, the following patients were declared ineligible for the trial but were given patient number assignments and study medication. We could not locate them in the Intent-To-Treat (ITT) analysis:

   #34090209
   #34090216
   #19780203
   #19780206
   #18800219
   #15580211

   Please provide the following information:

   a. The reason each patient was ineligible for the trial.

   b. If these patients were randomized, please indicate the treatment group to which they were assigned and perform an ITT efficacy analysis which includes them. If ineligibility was due to non-endoscopic reasons, please perform the ITT analysis by using these patients' baseline endoscopy endpoint readings and carrying them forward to the subsequent three visits, i.e. Last Observation Carried Forward (LOCF).

   c. Please provide original case report forms for these patients which include their baseline endoscopy (Visit 1).

2. According to Table 22, **(Volume 43, Page 65)**, the number of relapses which occurred in the PBO, Asacol 0.8 gm, and Asacol 1.6 gm treatment groups was 37, 29, and 24, respectively. The number of patients withdrawn due to adverse events was 4, 4, and 2, respectively. Therefore, the number of treatment failures of ITT patients for the PBO, Asacol 0.8 gm, and Asacol 1.6 gm groups should be 41, 33, and 26, respectively. In Table 17 **(Volume 43, Page 60)**, however, the number of treatment failures from the ITT analysis is shown as 45, 33, and 26, respectively.

   a. Please explain the reason for the four additional treatment failures in the PBO group.

   b. If the four additional treatment failures in the PBO group were incorrectly included in the ITT analyses, please redo the analyses, excluding these four PBO patients.

3. We note that numerous unscheduled endoscopies were conducted throughout the study. In addition, it appears that many visits occurred after the final 6-month visit (24 weeks).

   a. For both the ITT and the primary analysis efficacy data set, please tabulate the frequency distribution for each treatment group, by the prospectively established scheduled visits. In addition, please perform an analysis of group comparability, based on the frequency of scheduled endoscopies. Define the scheduled visit windows as follows: Visit 2=from week 3 to week 5; Visit 3=from week 11 to week 13; Visit 4=from week 23 to week 25. Please provide treatment comparison analyses of relapses by visit by counting relapses only if the endoscopies were done within the visit window.

   b. For all patients who relapsed within each visit window, please provide a list of patient numbers, drug assignments, and endoscopy grade at relapse.

4. Please provide the prospective randomization plan, the date created, and seed number.

We would appreciate your prompt written response so we can continue our ongoing evaluation of your supplemental application. Your response should be submitted in triplicate (Archival [blue], Clinical [tan], and Statistical [green] copies). In addition, please provide the data from any analyses on SAS diskettes, as 6.10 files (extension .sd2).

If you have any questions, please contact Melodi McNeil, Consumer Safety Officer, at (301) 443-0483.

Sincerely yours,

/S/ 3/28/97

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 19-651/S-005
HFD-180/Div. Files
HFD-180/CSO/M.McNeil
HFD-180/Prizont
HFD-720/Huque
HFD-720/Chen

/S/ 3/27/97

Drafted by: mm/March 26, 1997/c:\wpfiles\cso\n\19651703.ir
Initialed by: KJohnson 3/26/97
RPrizont 3/27/97, 3/28/97
SFredd 3/28/97
final: March 28, 1997

INFORMATION REQUEST (IR)

from all of these events, backache within 1 day, headache and insomnia within 2 days, and numbness/weakness with dragging of left foot within 8 months.

Asacol 0.8 g/day: Patient #15580201 was a 50-year-old Caucasian female with ulcerative colitis who entered the study on 15 July 1988 and received Asacol 0.8 g/day until 16 November 1988. Her past medical history was significant for gastritis, hypertension, angina, migraine headaches, knee pain, hysterectomy, and poor visual acuity. She was allergic to penicillin (causing hives); and Bellergal, Chloromycetin, and Lomotil (reactions unknown). Concomitant medications during the study included Pepcid and Carafate (for gastritis); Xanax (for esophageal reflux per CRF); Lopressor (for hypertension); Isordil and Cardizem (for angina); Cafergot, Sectral, Tylenol #3 and Elavil (for migraine headache); Tylenol and Motrin (for knee pain); Premarin (estrogen replacement therapy); Alka-Seltzer (for a head cold); and Co-Tylenol (for headache and fever). From 14 August 1988 to 15 November 1988, the subject experienced 18 episodes of mild headache. The subject felt she improved on study medication and that it did not contribute to her headaches. The investigator stated "I don't believe headache is related to study medication." However, because of these headaches, the subject's primary physician requested that the study medication be discontinued.

Patient #16330210 was a 44-year-old Black male with ulcerative colitis who entered the study on 30 January 1989 and received Asacol 0.8 g/day until 7 March 1989. His past medical history was significant for poor visual acuity, hypertension, enlarged prostate, anemia secondary to a bleeding ulcer, and pruritus. After one day of therapy, the subject complained of mild itching (for which he received hydroxyzine for an unknown number of days) throughout the study period. On 7 March 1989, the subject decided to discontinue the study, as he believed that his itching was due to the study medication. The investigator commented that "the patient had itching prior to the study which continued following the study."

Patient #19430203 was a 66-year-old Caucasian male with ulcerative colitis who entered the study on 25 November 1989 and received Asacol 0.8 g/day until 29 December 1989. His past medical history was significant for degenerative arthritis of the spine, post-traumatic stress syndrome, intermittent skin rash, and amoebic dysentery. He had no known drug allergies. Concomitant medications at study entry included diazepam (for anxiety). He had erythematous patches of skin on his right and left forearms at study entry; no treatment was noted for this. From the onset of the study, the subject complained of severe, periodic, migrating muscle and joint pain affecting the fingers, knees, and right shoulder. He was treated with acetaminophen and Tylenol #3, with some relief. At the Month 1 visit (21 December 1989), the subject continued to experience migratory joint and muscle pains. The areas involved included the small joints of the hands (with some swelling) and occasionally the elbow, knee, and jaw. On 29 December 1989, the subject was discontinued from the study by the investigator who stated, "Apparently, the withdrawal of sulfasalazine unmasked this patient's rheumatoid arthritis which was inapparent at study entry." The investigator also commented that the unmasking of rheumatoid arthritis required the reinstitution of sulfasalazine and non-steroidal anti-inflammatory medications. Follow-up information obtained 4 May 1990 revealed that the patient was still experiencing migratory synovitis consistent with rheumatoid arthritis.

Patient #36810204 was a 34-year-old Caucasian male with a history of ulcerative colitis who entered the study on 23 December 1991 and received Asacol 0.8 g/day until 19 February 1992. His past medical history was significant for Gilbert's disease and herpes keratitis (of the right eye). He was allergic to Azulfidine (causing fever and rash). Concomitant medications at study entry included Viroptic ophthalmic solution, Pred Forte drops, and FML Liquifilm drops (for herpes keratitis); and aspirin (for sore mouth and cold). From 23 December 1991 to 2 February 1992, the patient reported

a moderate decrease in sex drive. Consequently, study medication was discontinued on 19 February 1992 and the patient recovered.

Asacol 1.6 g/day: Patient #19430212 was a 66-year-old Caucasian female with a history of ulcerative colitis who entered the study on 13 May 1991 and received Asacol 1.6 g/day until 11 September 1991. Her past medical history was significant for asthma, bladder incontinence, migraine headaches, hysterectomy, cholecystectomy, and appendectomy. She was allergic to theophylline. Concomitant medications taken during the study include Proventil inhaler (for asthma); Naldecon and allergy shots (for allergies); Premarin (for post-menopausal symptoms); Cipro (for cystoscopy prophylaxis), oxybutynin (for incontinence); and Alternagel (for stomach pain). On 11 September 1991, the investigator stated the patient was dropped from the study secondary to an "anxiety state related to being a study patient and to the natural coping strategy of this patient."

Patient #28100210 was a 60-year-old Caucasian female with ulcerative colitis who entered the study on 19 December 1988 and received Asacol 1.6 g/day until 24 May 1989. Her past medical history was significant for hypertension, cystic breast disease, and a flame (-shaped) hemorrhage in her left eye. She was allergic to phenobarbital (reaction unknown). Concomitant medications taken during the study include Dyazide and Inderal (both for hypertension); Estrace and Provera (both for post-menopausal hormone replacement); aspirin and Tylenol (both for aching hands); Robitussin (for cough); and tetracycline and oral nystatin (for treatment of an unknown facial condition). The patient voluntarily discontinued study medication on 24 May 1989, and returned for her final visit on 11 June 1989. At that time, the investigator advised patient to discontinue experimental drug as the patient presented with signs which the investigator thought to be "similar to those of Stevens-Johnson syndrome" (unexplained sore throat with small ulcers, tiredness). A follow-up progress report stated that "her symptoms of sore mouth, malaise have subsided, colon remains quiescent" and it has been documented that symptoms have not recurred. Additionally, the patient entered the study with a clinically significant low WBC which remained significantly low throughout the study. In a follow-up letter the investigator also stated that "the overall reaction was probably due to Asacol since the patient had been taking Azulfidine for 25 years without incident prior to taking Asacol, but it's a little unclear why she would have a reaction to 5-ASA in the form of Asacol but not Azulfidine."

5.3.2.9 Patients with Recorded UC Symptomatology Without Significant Proctosigmoidoscopy Findings

Eight patients, at the time of their last visit, had recorded symptomatology that could be related to active ulcerative colitis not accompanied by specific proctosigmoidoscopic findings (i.e., score = 0, according to the amended protocol). Three patients (1 from the Placebo group and 2 from the Asacol 1.6 g/day group) were classified as voluntary withdrawals according to the criteria described in Table 3 (symptomatic-only relapse). Of the remaining 5 patients, 2 patients were uncooperative due to the lack of adherence to study procedures (both from the Asacol 0.8 g/day group), 1 patient was a concomitant medication violator (from the Asacol 0.8 g/day group), 1 patient was lost to follow-up (from the Placebo group), and 1 patient violated inclusion criteria (from the Asacol 1.6 g/day group). Narratives for these eight patients are presented below and are cited in Appendix 6.

Placebo: Patient #28100212 was a 28-year-old Caucasian male with an 8 year history of ulcerative colitis who entered the study on 25 January 1989 and received Placebo until 20 March 1989. His past medical history was significant for tonsillectomy/adenoidectomy. He had no known allergies, and no concomitant medications were taken during the study. He voluntarily discontinued study medication on 20 March 1989 after reporting three weeks of mild symptoms of active ulcerative

colitis; specific symptoms included gas, bloating, and loose bowel movements once a day. Symptoms on 20 March included cramping with minimal mucus and traces of blood. The patient returned for a final visit on 21 March 1989. His proctosigmoidoscopy findings indicated "rectal mucosa had edema, erythema, no friability or bleeding. Transition zone at 8 cm. Mucosa of sigmoid is normal". All laboratory test results were normal. Follow-up indicated that the patient's symptoms resolved following return to pre-study therapy (Azulfidine, 2.0 g/day). The patient was finally classified as a voluntary withdrawal from the study.

Patient #36870228 was a 38-year-old Caucasian female with a 6 year history of ulcerative colitis who entered the study on 3 November 1990 and received Placebo until 31 January 1991. Her past medical history was significant for depression, hypercholesterolemia, and degenerative cervical disc disease. She had no known drug allergies. Concomitant medications received during the study included amitriptyline (for depression), ibuprofen (for degenerative disc disease), Questran (for high cholesterol), Tussi-Organidin (for cough), Seldane and Trimox (for nasal drip and congestion), and Talacen (for ear and throat pain). On 3 December 1990, the patient's proctosigmoidoscopy was "0". At which time, the investigator commented that "patient symptomatically ~ 24 hours of low abdominal cramps and increased flatus no change in number of stools/(hematochemia); mild in nature." Investigator further commented on 14 February 1991 that the "patient did not return after 12/3/90 visit. Patient stated that she want to discontinue study participation on 1/31/91." The patient did not return for her follow-up visits and was finally classified as lost to follow-up.

Asacol 0.8 g/day: Patient #34090218 was a 51-year-old Caucasian female with a 1 year history of ulcerative colitis who entered the study on 28 September 1989 and received Asacol 0.8 g/day until 27 March 1990. Her past medical history was significant for palindromic rheumatism, goiter, peptic ulcer, and a repair of an anal fistula in 1986. The patient reported allergies to tetracycline (unknown reaction), penicillin (unknown reaction), and sulfasalazine (causes cracking and swelling of first CMC joints). Concomitant medications received during the study included Depo Provera (for hormone replacement-menopause), erythromycin (for cold symptoms), Pepto-Bismol and Imodium AD (for diarrhea), and cortisone (for wrist joint). On 27 March 1990, the patient's proctosigmoidoscopy score was "0". At this time, the investigator commented that there was "little inflammation present. Some patchy hyperemia, this is unchanged from previous examination. Thickening and induration in the anal canal with possible recurrent fissure." The patient experienced increased diarrhea and abdominal cramping that started three weeks prior to this last visit. The patient took erythromycin during study participation for 11 days, and was finally classified as a concomitant medication violator.

Patient #15580213 was a 31-year-old Indian male with a 7 year history of ulcerative colitis who entered the study on 3 June 1989 and received Asacol 0.8 g/day (unknown number of tablets/day) from 3 June 1989 to 23 June 1989. His past medical history is significant for increased anal sphincter tone and an anal fissure. He has no known drug allergies. On 13 June 1989, the patient had a rectal exam, which revealed an acute anal fissure, which the investigator felt explained the patient's report of hematochezia. The 13 June 1989 proctosigmoidoscopy was normal. At the month 1 visit, 23 June 1989, the patient and his wife were convinced that the patient was experiencing a flare of his disease and that he was being treated with placebo. At that time, the patient elected to drop from the study and be placed on active medication, even though the investigator could not find evidence of relapse. The patient did not keep a patient diary, therefore the number of Asacol tablets taken is unknown. The patient was finally classified as uncooperative due to the lack of adherence to study procedures.

Patient #15050221 was a 52-year-old Caucasian female with a 5 year history of ulcerative colitis who entered the study on 14 April 1990 and received Asacol 0.8 g/day until 7 October 1990. Her

past medical history was significant for a hysterectomy and arthralgias. She has no known drug allergies. Concomitant medication received during study participation included Natrum Murcabum, Ignatia, Staphisagria, Silicea, Scrophularia Nodosa (reason unknown), phosphorus, MVI, calcium, and Vitamin B12 (supplement), Premarin (hormone replacement), Motrin and Tylenol (sinus headache), and amoxicillin (trachitis and flu). At the last visit, 8 October 1990, the patient's proctosigmoidoscopy was "0" (no specific description was provided by the investigator). The patient experienced cramping and diarrhea at this time per the diary. The case report form noted there were no Asacol tablets taken from 6/12/90 - 6/25/90. The patient was finally classified as uncooperative due to the lack of adherence to study procedures.

Asacol 1.6 g/day: Patient #15050210 was a 40-year-old Caucasian female with a 9 year history of ulcerative colitis who entered the study on 16 August 1989 and received Asacol 1.6 g/day until 28 August 1989. Her past medical history was significant for chronic sinusitis, heart murmur, arthritis (hands, knees, neck), hysterectomy, acne, low back pain (status post-motor vehicle accident, with neck and back injury), endometriosis, and gastritis (with abdominal pain and nausea). She was allergic to codeine and Demerol. Patient contacted the investigator on 28 August 1989 with report of 7 days of symptoms of active ulcerative colitis; specific complaints included increased abdominal cramps with looser stools, mucus, and increased urgency with stomach "growls". The patient's final visit exhibited normal physical exam and laboratory test results. Proctosigmoidoscopy findings included "increased symptoms and worse mucosal appearance. Procto. exam revealed 1+ edema, trace granularity indicative of baseline changes. Evidence of mild flare for this patient although not as defined by protocol" (no friability noted). The patient's study participation was ended, and she was started on Asacol 1.6 g/day (open-label study). The patient was treated for three months at that dose with no adverse events or worsening of disease. She continued open-label study participation until May 1992, with no serious adverse events noted and was finally classified as a voluntary withdrawal from the study.

Patient #16330209 was a 35-year-old Caucasian female with a 22 year history of ulcerative colitis who entered the study on 23 January 1989 and received Asacol 1.6 g/day until 23 March 1989. Her past medical history was significant for an upper gastrointestinal bleed, toxic colon, cesarean section, transitional zone surgery for Class IV pap smear, and one small kidney. The subject is intolerant to sulfonamides (causing hematuria and proteinuria) and aspirin (hematemesis). Concomitant medications received during the study included Motrin (for menstrual cramps), acetaminophen and Rynatan (for nasal congestion). The investigator stated, "Patient is intolerant of most ulcerative colitis meds, she had a recent flare which was controlled on prednisone and was in remission at beginning of study. At the time she was put into the study impression was that those with recent flare were eligible." On 10 March 1989, the subject reported that she had felt some symptoms of relapse, but proctosigmoidoscopy was normal at that visit. Twelve days later (22 March 1989), the subject returned to the investigator, complaining that she was feeling much worse. Proctosigmoidoscopy at that visit revealed some slight distal granularity and irregularity, with the investigator's impression of probable mild distal inflammatory bowel disease (no friability noted). The following day, 23 March 1989, the subject again returned feeling worse. At that time, the subject felt that she was beginning to flare and elected to discontinue from the study and start active medication. This patient was taking oral prednisone 1 month prior to study entry and was finally classified as a study entry violator.

Patient #15050216 was a 39-year-old Caucasian male with a 1 year history of ulcerative colitis who entered the study on 18 December 1989 and received Asacol 1.6 g/day from 18 December 1989 to 11 February 1990 (4 tablets/day). His past medial history is significant for no other diseases and no known drug allergies. Concomitant medications received during the study included Extra Strength Tylenol (for headache) and Maalox (reasons unknown). The investigator noted, on 12 February

1990, that the patient did well until 2 February 1990, when the patient noted blood on stool and toilet paper. Stool culture, tests for ova/parasites, and Clostridium difficile toxin analysis were all negative, and the patient's proctosigmoidoscopy was "0". The investigator commented that the patient "feels like colitis is starting. Bowel movements are formed, approximately 2-4/day. Increased complaining of gas with flare." The patient was finally classified as a voluntary withdrawal from the study.