CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-830

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: *21-830	Submission Date(s): original submission: October 22, 2004 Resubmission: October 22, 2007
Brand Name	* Asacol® 800 Delayed-release tablet
Generic Name	* Mesalamine
Reviewer	* Insook Kim, Ph.D.
Team Leader	* Sue-Chih Lee, Ph.D.
OCP Division	* Division of Clinical Pharmacology 3
ORM division	* Division of Gastroenterology product
Sponsor	* Procter and Gamble
Formulation; Strength(s)	800 mg delayed-release tablet
Dosage regimen	1600 mg three times daily
Indication	* treatment of moderately active ulcerative colitis patients

1 Executive Summary

To support a marketing approval of Asacol 800 mg tablet, the original NDA 21-830 was submitted on October 22, 2004. Included in the original submission were three pharmacokinetic studies; a single-dose study (study 2000027), a multiple dose study (study 2001025) and food effect study (study 2001095). The studies were previously reviewed by Dr. Suliman I. Al-Fayoumi of the Office of Clinical Pharmacology and found acceptable. However, due to clinical efficacy issues the Agency issued a complete response letter and the sponsor submitted additional clinical study results on October 22, 2007 as amendment 20. With the additional study results, the clinical division is moving toward the approval action for Asacol 800 mg tablet. This review will provide recommendations on the proposed labeling in PRL format while detailed information is referred to the original review of clinical pharmacology and biopharmaceutics.

2 Labeling

Major recommendations on labeling changes are as below.

b(4)

Reviewer's comment: *Asacol 800 mg tablet is a different formulation from 400 mg tablet and the study was not conducted with the new formulation of 800 mg tablet, thus there is no direct supporting evidence for this statement although it may be generally true.*

b(4)

2 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox-_____

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/s/

Insook Kim
5/21/2008 04:33:27 PM
BIOPHARMACEUTICS

The same review was also linked to N021830 22-Oct-2004 and signed-off by the team leader. No new Clin. Pharm. information was submitted in this resubmission.

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-830

Letter Date: 10/22/04

Proposed Brand Name: Asacol 800

Generic Name: Mesalamine (5-ASA)

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Team Leader: Suresh Doddapaneni, Ph.D.

ORM Division: Gastrointestinal & Coagulation Drug Products

OCPB Division: Division of Pharmaceutical Evaluation 2

Sponsor: Procter & Gamble Pharmaceuticals

Submission Type: Original NDA

Formulation, Strength(s): Delayed-Release Tablet, 800 mg

Proposed Indications & Dosage Regimens: Treatment of moderately active ulcerative colitis (2 X 800 mg TID for a total daily dose of 4.8 g)

1. Executive Summary

The sponsor sought to utilize an 800 mg tablet formulation with *in vitro* dissolution characteristics and an *in vivo* pharmacokinetic profile that are similar to those of the 400 mg tablet formulation, subsequently the —— tablet formulation was selected for further clinical development as it was the closest of the three 800 mg pilot tablet formulations to the 400 mg tablet with respect to the comparative *in vitro* dissolution performance and the Cmax and AUC values of 5-ASA and N-Ac-5-ASA. b(4)

Single dose administration of the 800 mg Delayed Release Tablet in a relative bioavailability study indicated that the mean tmax value of 5-ASA was significantly delayed while mean Cmax and AUC values decreased by 36% and 25%, respectively, with administration of the 800 mg tablets relative to the 400 mg tablet.

The results of a multiple dose PK study of the 800 mg tablet indicated that the Cmax and AUC values of 5-ASA and N-Ac-5-ASA increase significantly with multiple dose administration suggesting that significant accumulation of 5-ASA and N-Ac-5-ASA takes place at the TID regimen.

The results of a population PK analysis in patients with moderately active ulcerative colitis showed that the steady-state plasma concentrations of 5-ASA and N-Ac-5-ASA increased in a dose-related manner.

A significant food-effect was observed on the PK of the 800 mg Asacol tablet. In particular, mean Cmax of 5-ASA decreased by 47% under fed conditions. In addition, a

marked delay in tmax was observed under fed conditions with mean tmax increasing by 14 hours relative to fasting conditions.

Safety and effectiveness in pediatric patients have not been established.

1.1 Recommendation

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-830 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. See Appendix 3.2 for the package insert incorporating the Agency proposed changes to the labeling (See ***Detailed Labeling Recommendations*** on page 16).

1.2 Phase 4 Commitments

None.

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1.3 Summary of CPB Findings

Ulcerative colitis is an idiopathic chronic disease associated with mucosal inflammation that can extend throughout the colon. Products that deliver mesalamine (5-ASA) to the disease site are the first line of treatment for mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis.

Procter & Gamble Pharmaceuticals (P&GP) currently markets 400 mg mesalamine Delayed-Release Tablets (Asacol) that are enteric-coated (Eudragit S) to delay the release of the active drug until the intact tablet reaches the terminal ileum (pH 7.2). Asacol 400 mg Delayed-Release Tablet was first approved for marketing in the US in 1992 and is currently indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis at a total daily dose of 2.4 g.

Asacol 800 is a novel Delayed-Release tablet formulation of Asacol at the 800 mg strength. The sought indication for Asacol 800 is the treatment of moderately active ulcerative colitis at a total daily dose of 4.8 g.

In this application, data was submitted from 4 Clinical Pharmacology and Biopharmaceutics-related studies, including a relative bioavailability study, a food-effect study, a multiple dose PK study, and steady state pre-dose concentrations from a Phase III study. In addition, two clinical safety and efficacy studies were submitted comparing the safety and efficacy of Asacol 4.8 g/d (2 X 800 g TID) to Asacol 2.4 g/d (2 X 400 mg TID) for the treatment of mildly to moderately active ulcerative colitis.

The sponsor sought to utilize an 800 mg tablet formulation with *in vitro* dissolution characteristics and an *in vivo* pharmacokinetic profile that are similar to those of the 400 mg tablet formulation, subsequently the ——— tablet formulation was selected from amongst three pilot 800 mg tablet formulations for further clinical development as it was the closest to the 400 mg tablet with respect to the comparative *in vitro* dissolution performance and the Cmax and AUC values of 5-ASA and N-Ac-5-ASA. b(4)

The single dose PK of Asacol 800 mg Delayed-Release Tablet were characterized in study 2000027, a relative bioavailability study comparing three pilot 800 mg Asacol tablet formulations to 2 X 400 mg Asacol tablets in healthy male and female subjects. In summary, the mean tmax value of 5-ASA was significantly delayed while mean Cmax and AUC values decreased by 36% and 25%, respectively, with administration of the 800 mg tablet relative to the 400 mg tablet.

The multiple dose PK of the 800 mg Asacol tablet were characterized in study 2001025, an open label study in healthy subjects (n = 16) where two Asacol 800 mg tablets were administered TID for 7 days. The results of the study indicate that significant accumulation of 5-ASA and N-Ac-5-ASA takes place with the TID regimen.

The steady-state pre-dose plasma concentrations of 5-ASA and N-Ac-5-ASA were evaluated in patients with moderately active ulcerative colitis following administration of 2.4 g/d (400 mg tablet) and 4.8 g/d (800 mg tablet) for 6 weeks in Phase III study 2000082. However, it was not clear if this pre-dose blood sample collection time is identical in all patients with respect to time after dosing of the current dose. The

coefficient of variation for 5-ASA ranged from 467% and 419% at baseline to 130% and 115% during steady state for the 4.8 mg/day and 2.4 mg/day doses.

The study results indicate that the steady state pre-dose plasma concentrations of 5-ASA and N-Ac-5-ASA in patients with moderately active ulcerative colitis increased with dose with the ratio of pre-dose Css (4.8 g/d relative to 2.4 g/d) for 5-ASA ranging from 1.36 at baseline {2.01 (week 3)} to 2.25 (week 6) and from 1.44 at baseline {1.52 (week 3)} to 1.74 (week 6) for N-Ac-5-ASA. The study results indicate that the steady-state plasma concentrations of 5-ASA and N-Ac-5-ASA in patients with moderately active ulcerative colitis increased with dose.

The effect of a standard FDA high-fat breakfast on the bioavailability of the 800 mg Asacol tablet formulation was assessed in study 2001095. A significant food-effect was observed on the PK of the 800 mg Asacol tablet. In particular, Cmax of 5-ASA decreased by 47% under fed conditions. In addition, a marked delay in tmax was observed under fed conditions with tmax increasing by 14 hours relative to fasting conditions.

The approved dissolution method and dissolution specifications for the 400 mg dose strength will be utilized for the 800 mg dose strength.

2 *Question-Based Review*

2.1 General Attributes

Mesalamine (5-aminosalicylic acid; 5-ASA) is an anti-inflammatory agent. Mesalamine is thought to exert topical anti-inflammatory effects on the colon through inhibition of prostaglandin and leukotriene synthesis.

Asacol 400 mg Delayed-Release Tablet is currently marketed by Procter and Gamble in the US for the treatment and maintenance of remission of mildly to moderately active ulcerative colitis at a total daily dose of 1.6-2.4 g (NDA 19-651).

In this NDA, Procter and Gamble seeks approval of the use of Asacol 800 mg Delayed-Release Tablet for the treatment of moderately active ulcerative colitis at a total daily dose of 4.8 g. The dose of 4.8 g/day was chosen for development based on a previously reviewed study (study C.3, Schroeder, et al., 1987) in NDA 19-651, which evaluated the safety and efficacy of 400 mg Asacol tablets in 87 patients with mildly to moderately active ulcerative colitis at dosages of 1.6 g/day and 4.8 g/day versus placebo for 6 weeks. The majority of these patients (77%) had moderately active disease. Asacol 4.8 g/day was associated with enhanced efficacy (74% response rate for 4.8 g/day compared to 27% response rate of 18% for placebo). To facilitate patient compliance at a dose of 4.8 g/day, the 800 mg dose strength was developed to allow patients to take six 800 mg tablets instead of twelve 400 mg tablets a day. The pharmacokinetics, safety and effectiveness of the Asacol 800 mg delayed-release tablet for treatment of moderately active ulcerative colitis at 4.8 g/day are the subject of this NDA.

Three Clinical Pharmacology and Biopharmaceutics studies characterizing the relative bioavailability (study 2000027), multiple dose pharmacokinetics (study 2001025), and food effect (study 2001095) were submitted in this NDA. In addition, steady state pre-dose concentrations were also evaluated from patients participating in Phase III study 2000082.

Two Phase III Clinical safety and efficacy studies compared Asacol 4.8 g/day to Asacol 2.4 g/day in newly- and previously-diagnosed mildly to moderately active ulcerative colitis patients. Based on the results of Study 2000083, study 2000082 was subsequently amended to evaluate the 800 mg formulation in patients with moderately active ulcerative colitis patients.

2.2 General Clinical Pharmacology

2.2.1. What is the relative bioavailability of the new 800 mg Asacol Delayed-Release Tablet compared to the currently approved 400 mg Delayed-Release Tablet?

The mean Cmax and AUC of the to-be-marketed 800 mg Asacol tablets compared to two 400 mg tablets were 35% and 25% lower, respectively. Tmax and Tlag are longer by about 4 hours and 2 hours, respectively.

In study 2000027, the bioavailability of the three pilot 800 mg Asacol tablets were assessed relative to 2 X 400 mg Asacol tablets in a randomized, open-label, single center, four-way crossover study in healthy male and female subjects (n = 20, age 18-45 years). Plasma and urine concentrations of 5-ASA and N-Ac-5-ASA were determined up to 72 hrs post-dose. A 7-day washout period separated successive treatments. The study results indicated that tmax was delayed while Cmax and AUC decreased considerably with administration of the 800 mg tablets relative to the 400 mg tablet. This might be expected given the higher content of the protective enteric coating in the pilot 800 mg tablets. Overall, the [redacted] tablet formulation appeared to be the closest of the three 800 mg tablet formulations to the 400 mg tablet with respect to Cmax and AUC values of 5-ASA and N-Ac-5-ASA (Refer to Table 1). b(4)

The dissolution method and dissolution specifications approved for the 400 mg strength are also used for the 800 mg strength as well (Table 2). The pH conditions employed in this method were selected to simulate release of the drug in terminal ileum and beyond. The comparative *in vitro* dissolution profiles (Fig. 1) show that [redacted] tablet formulation has similar dissolution profile compared to the approved 400 mg strength dissolution profile. b(4)

Overall, based on the results of the comparative *in vitro* dissolution profiles and the *in vivo* relative bioavailability study for the 400 mg tablet formulation and three 800 mg tablet formulations, the sponsor selected the [redacted] tablet formulation for further clinical development.

Table 1. Summary of the PK parameters of 5-ASA following administration of 800 mg single doses of three pilot Asacol formulations and 2X 400 mg Asacol tablets

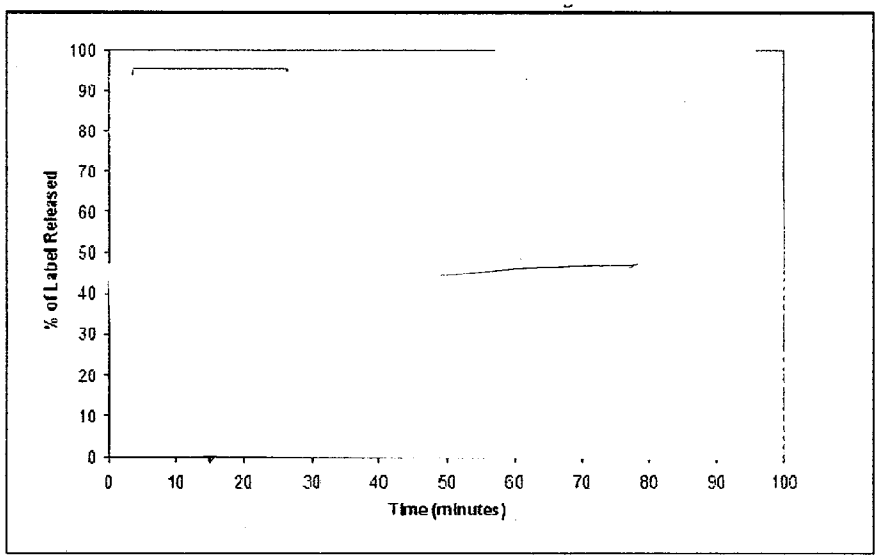
	5-ASA Pharmacokinetics						
	Geometric Mean[a]				Ratio Point Estimate (90% Confidence Interval)		
	[redacted]			2 x 400 mg	[redacted] 2 x 400 mg	[redacted] 2 x 400 mg	[redacted] 2 x 400 mg
AUC_{tlast} (ng•h/mL)	1124.24	789.93	676.01	1496.7	0.75 (0.23, 2.40)	0.53 (0.16, 1.69)	0.45 (0.14, 1.45)
C_{max} (ng/mL)	111.53	122.71	82.55	174.57	0.64 (0.26, 1.56)	0.70 (0.29, 1.71)	0.47 (0.19, 1.15)
	Arithmetic Mean				Mean Differences (95% Confidence Interval)		
	[redacted]		[redacted]	2 x 400 mg	[redacted] 2 x 400 mg	[redacted] 2 x 400 mg	[redacted] 2 x 400 mg
Ae (%)	0.32	0.34	0.28	0.47	-0.16 (-0.40, 0.09)	-0.13 (-0.38, 0.11)	-0.19 (-0.44, 0.05)
t_{max} (h)	19.17	14.40	17.24	15.50	3.87 (-4.44, 12.18)	-1.21 (-9.76, 7.35)	1.94 (-6.48, 10.37)
t_{lag} (h)	9.60	7.02	8.80	7.55	2.13 (-0.36, 4.63)	-0.90 (-3.47, 1.66)	1.39 (-1.13, 3.92)

b(4)

Table 2. Summary of the in vitro dissolution test method used to compare the Asacol 800 mg tablet formulations to the Asacol 400 mg tablet formulation (USP 27 procedure for mesalamine delayed-release tablets)

Phase	Time (h)	Apparatus	Media	Speed (rpm)	Media Temperature (°C)	Specification
I	2	USP Paddle	0.1 N Hydrochloric Acid, 900 mL	100	37 ± 0.5	Level 1: No tablet exceeds — dissolved
II	1	USP Paddle	pH 6.0 Phosphate Buffer, 1000 mL	100	37 ± 0.5	Level 1: No tablet exceeds — dissolved
III	1.5	USP Paddle	pH 7.2 Phosphate Buffer, 1000 mL	50	37 ± 0.5	A minimum of — (Q) is released. Level 1: Each unit must be — minimum.

b(4)



b(4)

[1]

Fig. 1. Comparative dissolution profiles of Asacol 800 mg and 400 mg tablet formulations

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[1] The similarity factor (f2) for the —— 800 mg tablet formulation and the 400 mg tablet formulation was 53.5.

b(4)

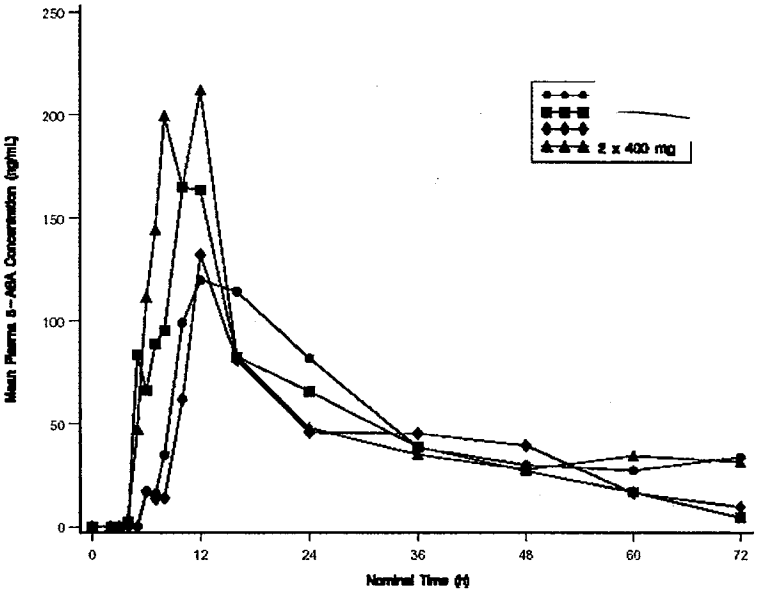

Fig. 2. Mean 5-ASA plasma conc.-time profiles following administration of a single 800 mg dose of the various Asacol formulations

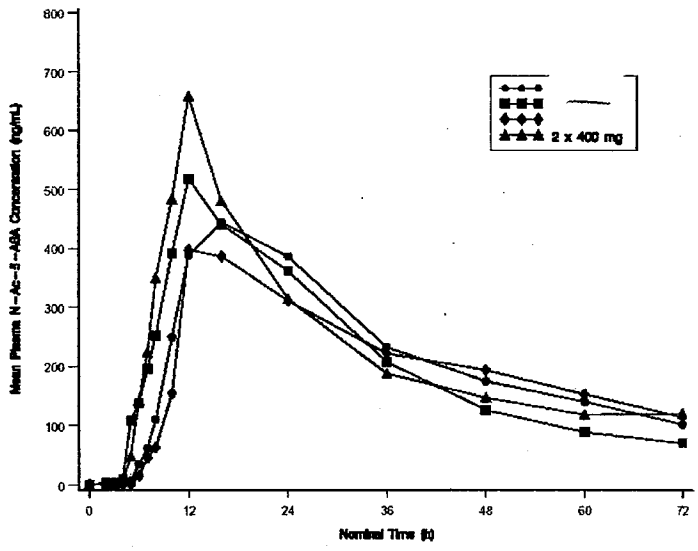

Fig. 3. Mean N-Ac-5-ASA plasma conc.-time profiles following administration of a single 800 mg dose of the various Asacol formulations

2.2.2. What are the multiple dose PK characteristics of the Asacol 800 mg Delayed-Release Tablet?

The mean Cmax and AUC values of 5-ASA and N-Ac-5-ASA increased significantly with multiple dose administration of the 800 mg tablet indicating that significant accumulation of 5-ASA and N-Ac-5-ASA takes place at the studied TID regimen.

The multiple dose PK of the 800 mg Asacol tablet were characterized in study 2001025, an open label study in healthy subjects (n = 16) where two Asacol 800 mg tablets were administered TID for 7 days. Plasma samples were collected up to 48 hrs post-dose on day 7 of dosing, while urine samples were collected up to 8 hrs post-dose on day 7 of dosing. The study results indicate that Cmax and AUC of 5-ASA and N-Ac-5-ASA increase significantly with multiple dose administration suggesting in turn that significant accumulation of 5-ASA and N-Ac-5-ASA takes place at the studied TID regimen (Table 3). The Cmax and AUC values for 5-ASA following multiple-dosing in this study were around 10-fold and 5-fold, respectively, higher than what would be projected based on the single dose data from study 2000027.

In addition, the combined urinary excretion of 5-ASA and N-Ac-5-ASA (median of 24.5%) was similar to reported systemic absorption of 5-ASA and N-Ac-5-ASA for the 400 mg Asacol tablets (28%).

Table 3. Summary of the PK parameters of 5-ASA following administration of two 800 mg tablets TID

5-ASA Pharmacokinetics									
	AUC_τ (ng•h/mL)	C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	$t_{1/2,Z}$ (h)	$\%A_e$ (%)	CL_R (L/h)	CL_O (L/h)	V_Z/F (L)
N	16	16	16	16	15	16	16	16	15
Mean	20282.03	4972.08	2.6250	1254.08	11.8882	9.279	5.87734	187.462	1753.31
SD	13568.07	4048.39	2.7538	873.00	11.5409	9.132	2.93890	249.726	2279.11
CV(%)	66.9	81.4	104.9	69.6	97.1	98.4	50.0	133.2	130.0
Median	20131.85	5031.00	2.5000	1065.55	8.1340	6.880	5.92575	79.475	916.90
Max.	44270.8	14481.0	8.000	3248.0	39.539	35.23	12.7337	1000.08	9236.2
Min.	1599.9	270.3	0.000	143.3	1.403	0.12	1.1692	36.14	202.6

The steady state pre-dose plasma concentrations of 5-ASA and N-Ac-5-ASA were evaluated in patients with moderately active ulcerative colitis following administration of 2.4 g/d (2 X 400 mg tablet TID) and 4.8 g/d (2 X 800 mg tablet TID) for 6 weeks in a population PK analysis of study 2000082 (n = 386), which was a randomized, double-blind, parallel group, safety and efficacy study. Plasma samples were collected to determine 5-ASA and N-Ac-5-ASA steady state pre-dose levels at baseline and on weeks 3 and 6. However, it is not clear if this pre-dose blood sample collection time is identical in all patients with respect to time after dosing of the current dose. The coefficient of variation for 5-ASA ranged from 467% and 419% at baseline to 130% and 115% during steady state for the 4.8 mg/day and 2.4 mg/day doses, respectively.

The study results indicate that the steady state pre-dose plasma concentrations of 5-ASA and N-Ac-5-ASA in patients with moderately active ulcerative colitis increased with dose

with the ratio of pre-dose Css (4.8 g/d relative to 2.4 g/d) for 5-ASA ranging from 1.36 at baseline {2.01 (week 3)} to 2.25 (week 6) and from 1.44 at baseline {1.52 (week 3)} to 1.74 (week 6) for N-Ac-5-ASA (Table 4). Due to flaws in the sampling scheme and the observed high variability in the PK data, the sponsor's conclusion of similar plasma concentrations of 5-ASA and N-Ac-5-ASA in mildly and moderately active ulcerative colitis patients may not be accurate (Table 5).

Table 4. Summary of the mean steady state plasma levels of 5-ASA and N-Ac-5-ASA in patients with moderately active ulcerative colitis

5-ASA

	2.4 gram/day (400 mg tablet)[a]			4.8 gram/day (800 mg tablet)[a]				
	Baseline	Week 3	Week 6	Baseline	Week 3	Week 3 Ratio[a]	Week 6	Week 6 Ratio[a]
N	190	158	153	185	167		154	
Arithmetic Mean	191.96	973.31	952.49	261.50	1953.85	2.01	2144.44	2.25
Geometric Mean	207.74	539.10	455.51	289.95	1179.33	2.19	1237.32	2.72
SD	804.03	1264.82	1408.01	1221.17	2237.15		2634.67	
Median	0.00	508.00	388.00	0.00	1300.00	2.56	1230.00	3.17
CV%	418.85	129.95	147.82	466.99	114.50		122.86	
Minimum	0.0	0.0	0.0	0.0	0.0		0.0	
Maximum	8220.0	9000.0	8680.0	12900.0	12200.0		19100.0	

N-AC-5-ASA

	2.4 gram/day (400 mg tablet)[a]			4.8 gram/day (800 mg tablet)[a]				
	Baseline	Week 3	Week 6	Baseline	Week 3	Week 3 Ratio[a]	Week 6	Week 6 Ratio[a]
N	190	159	153	185	168		154	
Arithmetic Mean	346.88	1883.02	1729.24	501.04	2854.70	1.52	3016.30	1.74
Geometric Mean	578.20	1471.19	1213.05	768.81	2147.88	1.46	2220.58	1.83
SD	923.70	1501.45	1721.79	1896.65	2197.69		2849.51	
Median	0.00	1500.00	1250.00	0.00	2355.00	1.57	2145.00	1.72
CV%	266.29	79.74	99.57	378.54	76.99		94.47	
Minimum	0.0	0.0	0.0	0.0	0.0		0.0	
Maximum	6700.0	9020.0	9820.0	18700.0	13300.0		14900.0	

Includes patients whose concentration values were available and the elapsed time since last dose for a given visit was positive and within 24 hours.

[a] 4.8 g per day with the 800 mg tablet/2.4 g per day with the 400 mg tablet.

Table 5. Exposure ratio (Mild UC/Moderate UC) of 5-ASA and N-Ac-5-ASA plasma conc. At weeks 3 and 6 visits (study 2000082)

	5-ASA			
	2.4 Ratio		4.8 Ratio	
Statistics	Week 3	Week 6	Week 3	Week 6
Arithmetic Mean	0.85	0.77	0.98	0.95
Geometric Mean	0.79	0.91	0.90	1.01
Median	0.90	0.80	0.91	0.97

	N-AC-5-ASA			
	2.4 Ratio		4.8 Ratio	
Statistics	Week 3	Week 6	Week 3	Week 6
Arithmetic Mean	0.91	0.77	1.00	1.11
Geometric Mean	0.89	0.95	0.80	1.24
Median	0.92	0.75	0.93	1.11

2.3. General Biopharmaceutics

2.3.1. What is the formulation composition of the 800 mg Asacol tablet?

The sponsor sought to utilize an 800 mg tablet formulation with in vitro dissolution characteristics and an in vivo pharmacokinetic profile that were similar to those of the 400 mg tablet formulation.

The 800 mg formulation is not exactly compositionally similar to the currently approved 400 mg tablet. In developing the 800 mg delayed-release tablet formulation, the ——— (sodium starch glycolate) content was varied along with the protective enteric coating (Eudragit S and L). Three pilot Asacol 800 mg tablet formulations were tested for similarity to the Asacol 400 mg tablet formulation based on *in vitro* dissolution and *in vivo* PK profiles. The formulation ultimately selected for further clinical development ——— involved ——— adding an additional protective enteric coating (Eudragit S and Eudragit L in a ratio ——— respectively) over the Eudragit S coating. The ratio of Eudragit S:L imparts a protective coating that begins to dissolve at approximately pH 6.5. b(4)

Table 5. Composition of the 400 mg and 800 mg Asacol tablets

Component	400 mg	800 mg	800 mg	800 mg
5-Aminosalicylic acid	400	800	800	800
Lactose, monohydrate				
Sodium starch glycolate				
Talc				
Povidone				
Magnesium stearate				
Colloidal silicon dioxide				
Methacrylic acid copolymer type B (Eudragit S				
Methacrylic acid copolymer type A (Eudragit L				
Talc				
Red ferric oxide				
Dibutyl phthalate				
Yellow ferric oxide				
Polyethylene glycol				

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2.3.2. Is there a significant effect of food requiring the timing of administration of Asacol 800 tablet be adjusted relative to meals?

There is a significant food-effect on the rate of absorption of 5-ASA following administration of the 800 mg tablet. However, the 800 mg Asacol Delayed Release Tablet should was administered in the pivotal clinical trials without regard to food.

In study 2001095, the effect of a standard FDA high-fat breakfast on the bioavailability of the 800 mg Asacol tablet formulation was assessed in an open label, randomized, single dose, two-period crossover study (n = 18 [9 males and 9 females], age = 18-45 years). A washout period of 2 weeks separated the treatment periods. The results indicate that was a significant food-effect on the Cmax value of the 800 mg Asacol tablet. Cmax of 5-ASA decreased by 47% under fed conditions and wide 90% confidence intervals for Cmax and AUC were observed indicating that there was large variability in the systemic absorption of 5-ASA (Table 6). A marked delay in tmax was observed under fed conditions with tmax increasing by 14 hours relative to fasting conditions (geometric mean of 24 hours under fed conditions compared to 10 hours under fasting conditions). The mean tlag under fed conditions is 15 hours compared to 6 hours under fasting conditions. With respect to AUC, there was a decrease of about 7% for AUC_{tlast}. The percent excreted unchanged amount of 5-ASA and N-Ac-5-ASA was about 5% to 6% lower in fed conditions compared to fasting conditions. Since the plasma sampling was not adequate in many subjects to capture the full PK profile of 5-ASA under fed conditions, estimates of $AUC_{(0-\infty)}$ were highly unreliable.

It should be noted that in the approved package insert for Asacol 400 mg delayed release tablets, the food-effect is described as "absorption of mesalamine is similar in fasted and fed subjects". The mean Cmax, tmax, and AUC values under fed and fasting conditions for the 400 strength were 0.72 and 0.39 μg/mL, 12 and 10 hr, and 3.5 and 2.9 μg/mL·hr, respectively. Thus, administration under fed conditions resulted in a higher bioavailability for the 400 mg strength. However, it appears that plasma AUC values and urinary drug recoveries of 5-ASA and N-Ac-5-ASA were combined and evaluated for the effect of food. As a result, it appears that an overall conclusion was made that the extent of absorption was similar in fed and fasting conditions.

In conclusion, while there is a marked food-effect on tmax and Cmax of 5-ASA following administration of the 800 mg tablet, the clinical relevance of such an observation is not known. Moreover, the 800 mg tablet was administered in the pivotal clinical trials without regard to food. Therefore, the 800 mg tablet can be labeled for administration without regard for food.

Table 6. Summary of the PK parameters for 5-ASA and N-Ac-5-ASA following administration of the 800 mg Asacol tablet under fed and fasted conditions

	Geometric Mean[a]/Median[b]		Ratio Point Estimate	
Analyte Parameter	Fed	Fasted	Ratio Fed/Fasted	90% Confidence Interval
5-ASA				
AUC_{tlast} (ng•h/mL)[b]	3651.7	3913.6	92.9	(63.8, 142.6)
AUC (ng•h/mL)[b]	5786.4	4105.0	139.3	(2.8, 226.6)
C_{max} (ng/mL)[b]	175.7	294.0	53.3	(25.9, 130.7)
$\%A_e$ (%)[a]	0.20	0.21	94.71	(38.45, 233.28)
N-Ac-5-ASA				
AUC_{tlast} (ng•h/mL)[b]	19350.1	21850.1	91.1	(73.5, 116.1)
AUC (ng•h/mL)[a]	21547.2	22034.2	97.8	(87.4, 109.4)
C_{max} (ng/mL)[a]	837.43	1028.68	81.41	(49.18, 134.75)
	Least-squares Mean (Untransformed)		Ratio Fed/Fasted	90% Confidence Interval[c]
N-Ac-5-ASA				
$\%A_e$ (%)	11.29	12.04	93.72	(67.71, 130.62)

2.4. Analytical Section

1. Have the analytical methods been adequately validated?

Validated HPLC/MS analytical assay methods were developed and used to quantify 5-ASA and N-acetyl-5-ASA in biological fluids during the clinical development program.

The methods for analysis of 5-ASA and N-Ac-5-ASA in human plasma and urine were validated at P&GP and ——— a contract analytical laboratory. b(4)

5-ASA and N-Ac-5-ASA in human plasma and urine, along with the added isotopically-labeled internal standards, are derivatized with propionic anhydride. The derivatized analytes are then subjected to HPLC analysis on a 3 µ C-18 column. The analytes and internal standards are detected by mass spectrometry operating under multiple reaction monitoring (MRM) MS/MS conditions.

The HPLC/MS methods developed to measure ——— were accurate, precise, and sensitive. The lower limit of quantitation (LLOQ) for 5-ASA was established at 10 ng/mL in plasma and 50 ng/mL in urine. The lower limit of quantitation (LLOQ) for N-Ac-5-ASA was established at 20 ng/mL in plasma and 150 ng/mL in urine. b(4)

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Table 7. Validation summary of the bioanalytical assay methods used to determine

5-ASA and N-Ac-5-ASA in plasma and urine

Matrix	Analytical Site	Sample Preparation	Analyte	Nominal Linear Range	CV (%)	Relative Error (%)
Plasma	P&GP	Protein Precipitation-Derivatization	5-ASA	10 - 1500 ng/mL	3.7 to 8.4	-4.3 to 0.6
			N-Ac-5-ASA	20 - 2500 ng/mL	3.7 to 6.6	-2.2 to 4.6
	—	Protein Precipitation-Derivatization	5-ASA	10 - 1500 ng/mL	1.76 to 11.6	2.50 to 8.32
			N-Ac-5-ASA	20 - 2500 ng/mL	1.33 to 11.0	-0.493 to 2.36
Urine	P&GP	Dilution-Derivatization	5-ASA	0.05 – 10 µg/mL	3.0 to 12.3	-2.0 to 8.8
			N-Ac-5-ASA	0.15 150 µg/mL	3.8 to 14.0	5.1 to 10.4
	—	Dilution-Derivatization	5-ASA	0.05 – 10 µg/mL	2.89 to 8.13	-1.80 to 8.00
			N-Ac-5-ASA	0.15 – 150 µg/mL	2.34 to 8.25	0.00 to 6.67

b(4)

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3. Detailed Labeling Recommendations

The key CPB labeling recommendations are summarized as follows:

- Under **General** subsection of the **PRECAUTIONS** section, the following statement was inserted:

b(4)

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4. Appendices

4.1 Proposed labeling (original and Agency proposed)

4.2 OCPB Filing and Review Form

Appendix 4.1

Proposed Package Insert

14 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio-_____

Appendix 4.2

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-830	Proposed Brand Name	Asacol 800
OCPB Division (I, II, III)	II	Generic Name	Mesalamine (5-ASA)
Medical Division	GI & Coagulation	Drug Class	Anti-inflammatory
OCPB Reviewer	Suliman Al-Fayoumi	Indication(s)	Treatment of Ulcerative Colitis
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Delayed Release tablet
		Dosing Regimen	2 X 800 mg TID
Date of Submission	7/1/04	Route of Administration	Oral
Estimated Due Date of OCPB Review	12/20/04	Sponsor	Proctor and Gamble
PDUFA Due Date	2/1/05	Priority Classification	Standard
Estimated Division Due Date	11/20/04		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	1	1	
Patients-				
single dose:				
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	1	1	
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	X	5	5	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)	**Is there a food-effect on the PK of Asacol 800?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suliman Alfayoumi
7/28/05 02:00:03 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
8/1/05 07:33:33 AM
BIOPHARMACEUTICS