iii. Reviewer Comments.

1. *Overall, the efficacy shown in these two supportive studies, confirm the findings of the large, multi center USA trial. In that large multi center trial, the results showed comparability in primary efficacy between balsalazide and an approved mesalamine formulation.* The results reported by the sponsor in these two supportive studies revealed comparable efficacy between oral balsalazide 6.75 g/d and an oral sulfasalazine formulation, similarly approved for treatment of acute ulcerative colitis. Administration of balsalzide and sulfasalazine in therapeutic doses, during an acute ulcerative colitis episode of mild, moderate to severe intensity, resulted in improvement of relevant ulcerative colitis patient symptomatology, i.e., stool blood, bowel frequency, and in improvement in endoscopically assessed features of mucosal inflammation. *This statement specially applies to the supportive study 0028/011, in which the lack of corticosteroid use eliminated an important confounding therapeutic variable.*

It should be noted the rather relevant and detailed information on ulcerative colitis symptoms, such as stool blood, provided in the report of these two trials, which made it easer to this reviewer to assess the reported efficacy results.

2. This reviewer does not concur that the efficacy data presented in these small supportive trials allows the sponsor to claim "remission" induced by balsalazide administration. My reasons for disagreement are basically the same as those included in my comments on the second pivotal trial 57-3001. *They relate to definition of remission*, complete resolution of symptoms, endoscopic and histologic inflammation, and, *particularly, to the described concomitant use in trial 0028/017 of a corticosteroid, an approved antiinflammatory medication known to induce remission in a large proportion of acute ulcerative colitis episodes.*

3. Placebo-Controlled Trial.

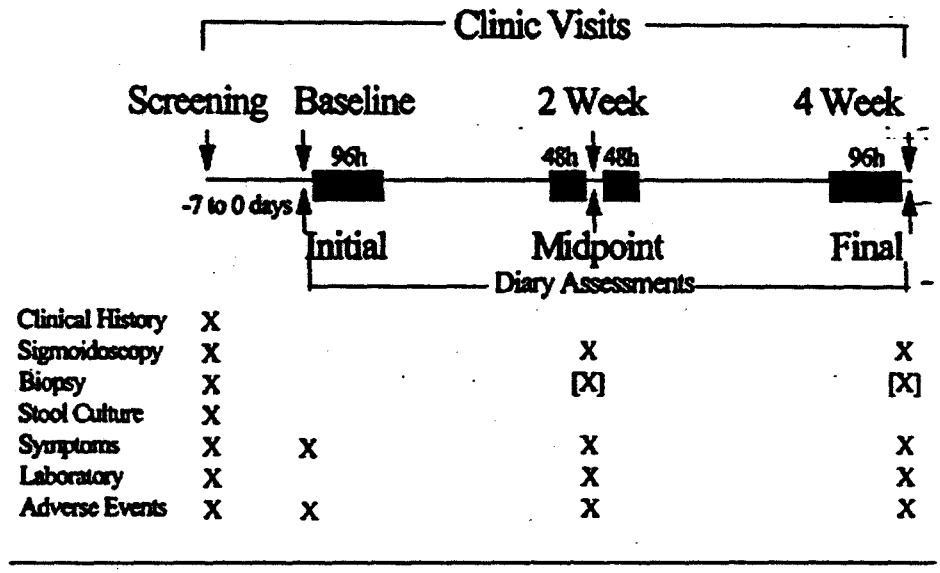
i. Protocol. The protocol design for this multi center trial, conducted in the USA, was essentially the same as the study protocol presented in Pivotal Trial CP099301. Hence, I will only include in this section the protocol's SYNOPSIS and schematic Study Design:

SYNOPSIS

This is a randomized, **placebo** controlled, double-blind, **dose response** comparison trial of Colazide™ (balsalazide sodium), 4.5 g/day or 6.75 g/day, in patients with active mild or moderate ulcerative colitis. **Primary endpoints include the improvement of symptoms as documented by individual symptom scores, Physician's Global Assessment, overall symptom a ssessment and flexible sigmoidoscopy.** The cumulative proportion of patients achieving remission will also be assessed, supported by histologic findings. Safety will be assessed by laboratory findings, incidence of adverse events and volunteered complaints. A pharmacokinetic study will also be performed at up to three study sites. **Two hundred and**

thirty patients, at fifteen to twenty clinical sites, will participate in the four week trial, with two hundred and ten expected to complete the treatment phase.

Figure I. Overall Study Design



ii. Descriptive.

The following are summaries of the ITT Placebo, Colazide 4.5 g/d and 6.75 g/d population, the disposition of patients, and, the demographics of enrolled patients.

*Number of Subjects: Intent-to-Treat
Treated: 180
Colazide 6.75 g/d: 72 (F=26, M=46; mean age 40.6 years; range 20–73)
Colazide 4.5 g/d: 73 (F=38, M=35; mean age 36.7 years; range 18–75)
Placebo: 35 (F=16, M=19; mean age 39.8 years; range 22–70)

At entry: No significant demographic differences. 14.4% UC newly diagnosed. Symptoms in Colazide 6.75 g/d group; mean 62.6 months history vs. 66.6 months, Colazide 4.5 g/d and 79.6 months, Placebo (NS). Duration of current relapse similar; mean 4.7 weeks for Colazide 6.75 g/d, 4.8 weeks for Colazide 4.5 g/d, and 5.1 weeks for Placebo (NS). Smokers in Placebo group slightly more frequent (11.4% vs. 6.9% for Colazide 6.75 g/d, and 2.7% for Colazide 4.5 g/d, NS). Characteristics of UC similar between groups: Disease extent: <60 cm, 68.0% Colazide 6.75 g/d, 69.9% Colazide 4.5 g/d, 71.5% Placebo (NS); Sigmoidoscopy: grade 1, 2.8% Colazide 6.75 g/d, 1.4% Colazide 4.5 g/d, 5.7% Placebo; grade 2, 72.2% Colazide 6.75 g/d, 76.7% Colazide 4.5 g/d, 71.4% Placebo; grade 3, 25% Colazide 6.75 g/d, 21.9% Colazide 4.5 g/d, 22.9% Placebo (NS).

Table 1. Number of Patients Evaluated at Each Study Week [1]

Overall Study Period	Colazide 6.75 g/day	Placebo	Colazide 4.5 g/day	Total
Screened:	72	35	73	211*
Randomized/Enrolled:	72	35	73	180
Not treated	1	0	0	1
Treated	71	35	73	179
Week 2:	68	34	72	174
Week 4:	57	31	57	145

*Contains 31 patients not categorized into a treatment group. These were due to sigmoidoscopic findings of 'mild' or to abnormal laboratory evaluations which excluded eligibility.

The following table summarizes the primary and relevant secondary efficacy results.

2. Primary Efficacy

24-Hour Diary Data	Patients Improved (%)			Between-Group P-Value	
Symptom/Sign	Colazide 6.75 g/d	Placebo	4.5 g/d	6.75 vs. Placebo CMH	4.5 vs. Placebo CMH
Rectal Blooding:	23/63 (36.5%)	12/30 (40.0%)	19/61 (31.1%)	0.718	0.456
Stool Frequency:	19/63 (30.2%)	9/30 (30.0%)	31/63 (49.2%)	0.952	0.074
Patient Functional Assessment:	25/63 (39.7%)	13/29 (44.8%)	33/61 (54.1%)	0.663	0.401
Abdominal Pain:	18/63 (28.6%)	14/28 (50.0%)	30/61 (49.2%)	0.061	0.941
Sigmoidoscopy:	31/66 (47.0%)	15/33 (45.5%)	27/66 (40.9%)	0.907	0.658
Physician's Global Assessment:	26/69 (37.7%)	16/33 (48.5%)	32/69 (46.4%)	0.303	0.811
Overall Assessment:	19/63 (30.2%)	12/31 (38.7%)	28/63 (44.4%)	0.424	0.597

3. Secondary Efficacy

Remission:	2 (2.9%)	2 (6.7%)	2 (2.9%)	0.456 C	0.456 C

Based on the above results, Salix concluded the following:

"Colazide treatment did not result in a significant difference in symptom improvement relative to placebo. It is concluded that this outcome was due to a greater than predicted placebo response and to a modest treatment response, both of which may be related to the characteristics of the patient population available for enrollment in a placebo-controlled study"..

iii. Reviewer Comments.

This randomized, placebo-controlled study revealed that **balsalazide treatment is ineffective if administered for a period shorther than 8 weeks**, i.e., 4 week period. Hence, and based on the results of this large muticenter study, we may conclude that an **appropriate length of therapy is a relevant factor for an effective balsalazide treatment of mild to moderately active ulcerative colitis.**

F. SAFETY.

i. Descriptive.

The brief information included in this safety section on demographics of patient exposure, overall list of adverse reactions and deaths was obtained from the INTEGRATED SUMMARY OF SAFETY, Vol. 1.082.

1. Demographics. Salix states the following:

"A total of 1034 patients were treated one or more times with Colazide. Of these, 502 patients were exposed to Colazide in more than one trial. In addition, 100 patients were exposed to mesalamine, 53 to sulfasalazine, and 35 to placebo in the acute controlled trials. An additional 38 patients were exposed to sulfasalazine and 15 to placebo in the controlled maintenance trials, while 12 patients each received Colazide plus mesalamine or Colazide plus sulfasalazine (SASP) in the PK/Pharmacology studies. One non-UC patient received placebo.
For the controlled, acute studies, the majority of patients enrolled were adults aged 18-64 years, no pediatric patients, and 44 elderly. When all studies were considered, there were 13 pediatric patients and elderly (≥65 years) accounted for about 10% of the patients. For the controlled acute studies and overall, 56% of patients were male. The majority of patients were Caucasian where race was indicated and were likely to be Caucasian in the European studies where race was not indicated.

For the controlled, acute studies, 68% of the Colazide patients completed the studies and only 23 patients (7%) discontinued because of adverse events. In the controlled maintenance trials, 51% completed and 12% discontinued for adverse events. The largest reason for discontinuation of Colazide was lack of efficacy".

Table 6: Patient Accounting in Colazide Studies

	Control Acute	Control Maint	PK & Placement	Uterot Acute	Uterot Acute & Maint	Uterot Maint	Total
Colazide							
Entered	366 [4]	288 [9a]	125 [1]	38 [1]	36 [19a]	175 [20a]	1034 (44a)
Assessed for Safety	352	264	125	39	284	383	1054 (44a)
Discontinued							
Lack of Efficacy	49 (14%)	117 (32%)	1 (3%)	12 (31%)	83 (29%)	12 (3%)	274 (18%)
Adverse Event	25 (7%)	42 (12%)	0	2 (5%)	8 (4%)	20 (13%)	125 (8%)
Intercurrent Illness	4 (1%)	0	0	0	3 (1%)	2 (1%)	9 (1%)
Other	35 (10%)	21 (6%)	3 (2%)	2 (5%)	44 (21%)	137 (91%)	262 (18%)
Completed Study	241 (69%)	184 (51%)	119 (97%)	23 (59%)	76 (36%)	97 (27%)	747 (50%)
Other Treatments[b]							
Entered	188	35	25	-	-	-	348
Assessed for Safety	188	33	23	-	-	-	344
Discontinued							
Lack of Efficacy	26 (13%)	80 (19%)	0	-	-	-	34 (13%)
Adverse Event	28 (15%)	5 (9%)	0	-	-	-	33 (12%)
Intercurrent Illness	2 (1%)	0	0	-	-	-	2 (1%)
Other	26 (13%)	2 (4%)	1 (4%)	-	-	-	27 (10%)
Completed Study	110 (59%)	26 (48%)	24 (96%)	-	-	-	120 (44%)

a: For 48 patients, study completion was not applicable (named experience).
b: Other treatment includes mesalamine, sulfasalazine, and placebo.

2. *Adverse Events.* The following Table 7 lists the overall incidence of adverse events (ADE) in acute studies of Colazide. The most common ADEs were headache, abdominal pain, and fatigue.

Table 7: Incidence of Common Adverse Events in Acute Studies of Colazide (in Patients Aged 18-64 Years)
N (%)

Adverse Event	Colazide N = 369	Mesalamine N = 89	Sulfasalazine N = 47	Placebo N = 32
Body as a Whole				
Asthenia	4 (1%)	1 (1%)	2 (4%)	0
Back Pain	10 (3%)	4 (4%)	5 (11%)	0
Fatigue	67 (18%)	15 (17%)	7 (15%)	6 (19%)
Fever	8 (2%)	3 (3%)	1 (2%)	0
Flu-like Disorder	11 (3%)	3 (3%)	1 (2%)	1 (3%)
Malaise	4 (1%)	0	1 (2%)	0
Pain	15 (4%)	3 (3%)	2 (4%)	1 (3%)
Gastrointestinal				
Abdominal Pain	77 (21%)	20 (22%)	15 (32%)	4 (13%)
Colitis Ulcerative Aggrav.	7 (2%)	3 (3%)	0	0
Constipation	6 (2%)	3 (3%)	1 (2%)	0
Diarrhea	48 (13%)	14 (16%)	2 (4%)	2 (6%)
Dyspepsia	40 (11%)	8 (9%)	14 (30%)	3 (9%)
Flatulence	49 (13%)	14 (16%)	4 (9%)	7 (22%)
Hemorrhoids Rectum	4 (1%)	3 (3%)	0	3 (9%)
Melena	9 (2%)	1 (1%)	0	0
Mouth Dry	6 (2%)	0	1 (2%)	0
Nausea	47 (13%)	10 (11%)	20 (43%)	5 (16%)
Stools Frequent	5 (1%)	0	0	2 (6%)
Tenesmus	8 (2%)	5 (6%)	0	1 (3%)
Vomiting	16 (4%)	4 (4%)	6 (13%)	2 (6%)
Musculoskeletal				
Arthralgia	8 (2%)	2 (2%)	0	0
Cramps	11 (3%)	1 (1%)	1 (2%)	0
Myalgia	5 (1%)	0	0	1 (3%)
Nervous System				
Anorexia	8 (2%)	0	2 (4%)	0
Depression	4 (1%)	2 (2%)	2 (4%)	0
Dizziness	19 (5%)	3 (3%)	5 (11%)	2 (6%)
Headache	87 (24%)	28 (31%)	28 (60%)	10 (31%)
Insomnia	9 (1%)	2 (2%)	2 (4%)	0
Respiratory				
Pharyngitis	9 (1%)	4 (4%)	2 (4%)	0
Respiratory Infection	17 (5%)	7 (8%)	3 (6%)	5 (16%)
Rhinitis	5 (1%)	5 (6%)	0	0
Skin and Appendages				
Pruritus	4 (1%)	0	1 (2%)	1 (3%)
Rash	10 (3%)	3 (3%)	4 (9%)	0
Other				
Ear Infection NOS	4 (1%)	0	0	0
Infection Viral	9 (1%)	2 (2%)	4 (9%)	0
Taste Perversion	4 (1%)	0	1 (2%)	1 (3%)

Table 12 compares the incidence of ADEs by gender in acute clinical studies of Colazide. As observed, there were some differences, with a higher incidence of ADEs reported in women.

Table 12: Most Common Adverse Events by Gender in Acute Clinical Studies of Colazide

Adverse Event	Females N = 168 N (%)	Males N = 223 N (%)
Headache	46 (27%)	49 (22%)
Abdominal Pain	45 (27%)	38 (17%)
Fatigue	34 (20%)	28 (13%)
Flatulence	26 (15%)	28 (13%)
Diarrhea	25 (15%)	26 (12%)
Nausea	34 (20%)	15 (7%)
Dyspepsia	36 (10%)	27 (12%)
Dizziness	11 (7%)	12 (5%)
Respiratory Infection	7 (4%)	11 (5%)
Pain	11 (7%)	9 (5%)
Vomiting	7 (4%)	9 (4%)
Back Pain	11 (7%)	5 (3%)
Rash	8 (5%)	4 (2%)
Cramps	5 (3%)	8 (4%)
Flu-like Disorder	7 (4%)	4 (2%)
Constipation	4 (2%)	2 (1%)
Infection Viral	1 (1%)	4 (2%)

a. Patients may be counted more than once.

Serious Adverse Events. The next Table 13, depicts serious ADEs in controlled acute Colazide studies.

Table 13: Serious Adverse Events

Study	Treatment	Patient	Adverse Event
Controlled Acute Studies			
CP069101	Colazide 6.75	1209	Pericarditis
	Colazide 6.75	1314	Worsening of UC
	Colazide 6.75	1811	Worsening of UC
CP099301	Colazide 6.75	5251	Nausea and worsening of UC
	Colazide 2.25	5207	Worsening of UC
	Colazide 2.25	5557	Worsening of UC
	Colazide 2.25	5102	Colonic polyps with dysplasia
	Mesalamine	5456	Worsening of UC
	Mesalamine	5558	Worsening of UC
57-3001	Mesalamine	1145	Severe abdominal pain, possible Crohn's disease
	Mesalamine	1482	Worsening of UC
	Mesalamine	1543	Joint pain, muscle ache, lethargy
	Mesalamine	1461	Very severe worsening of UC
0028-011	Colazide 6.75	1153	Allergic reaction
	Sulfasalazine	1114	Acute pancreatitis
	Sulfasalazine	1110	Carcinoma of bronchus in smoker
0028-017	Colazide 6.75	1766	Deep vein thrombosis
	Colazide 6.75	1764	Renal colic

4. Deaths. There was only 1 death on Colazide. Patient 2388, Study 57-3001Ext, died of a cardiac arrest,

4 week placebo-controlled trial, and in the lack of 4 week efficacy of the 6.75 g dose over the low 2.25 g dose, shown in the large USA multi center trial.

5. In the Clinical Studies section, information of the first USA multi center trial should include results of the ITT-2, all-treated patients. It should state that the 6.75 g/d dose was significantly superior to the low 2.25 g/d dose in improving stool blood, stool frequency and sigmoidoscopic score, but **not** in Physician Global Assessment.

6. The Clinical Studies section, the reference of Colazide efficacy on Asacol in the second pivotal study, should **omit** the use of *"remission"* from the sentence. It should just state that Colazide was more effective than Asacol in overall symptomatic improvement. This paragraph should also make reference to the fact that in this second study, topical hydrocortisone acetate 10% was used as rescue medication throughout the trial.

7. This Clinical Studies section would be greatly improved by the inclusion of the results reported in the Supportive Study 0028/011.

8. The ADVERSE REACTIONS section should make reference that there was gender difference in some ADRs, i.e., abdominal pain, fatigue and nausea, and that these ADRs were more frequently reported in women.

This recommendation for approval is based on my review of the reported clinical data. Final approval would require concomitant approval of the requested chemistry information. which is presently pending.

/S/

Robert Prizont, M.D.

cc:
NDA 20,610
HFD-180
HFD-180/LTalarico
HFD-180/RPrizont
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 5/18/98 jgw
MED\N\20610805.1RP

5-20-98

APPENDIX 1 - Intention-To-Treat Analysis of All Treated Subjects

Table 23: Intent to Treat 2 Patient Population, Improved Patient Functional Assessment (96 Hours)

PFA Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=50	N=50	N=49		
Improved	21 (42 %)	16 (32 %)	18 (36.7%)	0.336 CMH	0.581 CMH
Not Improved	29 (58 %)	34 (68 %)	31 (63.3%)		
Missing	0	3	2		
Total	50	53	51		
Interim 2 Assessment	N=50	N=50	N=49		
Improved	23 (46 %)	23 (46 %)	22 (44.9%)	0.954 CMH	0.936 CMH
Not Improved	27 (54 %)	27 (54 %)	27 (55.1%)		
Missing	0	3	2		
Total	50	53	51		
Final Assessment	N=50	N=50	N=49		
Improved	25 (50 %)	31 (62 %)	24 (49 %)	0.229 CMH	0.212 CMH
Not Improved	25 (50 %)	19 (38 %)	25 (51 %)		
Missing	0	3	2		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

Source: n:\testsas\fda\itt2tab.sas submitted by ILH 27JAN98 08:20 SAS 6.11

Table 24: Intent to Treat 2 Patient Population, Improved Abdominal Pain (96 Hours)

Abdominal Pain Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=50	N=50	N=49		
Improved	11 (22 %)	14 (28 %)	13 (26.5%)	0.552 CMH	0.934 CMH
Not Improved	39 (78 %)	36 (72 %)	36 (73.5%)		
Missing	0	3	2		
Total	50	53	51		
Interim 2 Assessment	N=50	N=50	N=49		
Improved	12 (24 %)	18 (36 %)	19 (38.8%)	0.167 CMH	0.737 CMH
Not Improved	38 (76 %)	32 (64 %)	30 (61.2%)		
Missing	0	3	2		
Total	50	53	51		
Final Assessment	N=50	N=50	N=49		
Improved	14 (28 %)	18 (36 %)	18 (36.7%)	0.416 CMH	0.896 CMH
Not Improved	36 (72 %)	32 (64 %)	31 (63.3%)		
Missing	0	3	2		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

Source: n:\testsas\fda\itt2tab.sas submitted by ILH 27JAN98 08:20 SAS 6.11

Table 25: Intent to Treat 2 Patient Population, Improved Physician Global Assessment

PGA Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=49	N=52	N=49		
Improved	18 (36.7%)	22 (42.3%)	16 (32.7%)	0.42 CMH	0.238 CMH
Not Improved	31 (63.3%)	30 (57.7%)	33 (67.3%)		
Missing	1	1	2		
Total	50	53	51		
Interim 2 Assessment	N=49	N=52	N=49		
Improved	27 (55.1%)	31 (59.6%)	25 (51 %)	0.541 CMH	0.321 CMH
Not Improved	22 (44.9%)	21 (40.4%)	24 (49 %)		
Missing	1	1	2		
Total	50	53	51		
Final Assessment	N=49	N=52	N=49		
Improved	26 (53.1%)	35 (67.3%)	28 (57.1%)	0.13 CMH	0.276 CMH
Not Improved	23 (46.9%)	17 (32.7%)	21 (42.9%)		
Missing	1	1	2		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

Source: n:\testsas\fda\itt2tab.sas submitted by ILH 27JAN98 08:20 SAS 6.11

Table 26: Intent to Treat 2 Patient Population, Improved Overall Assessment

OSA Change At	Colazide 2.25 g/d	Colazide 6.75 g/d	Asacol 2.4 g/d	Between-Group P-value 6.75 vs. 2.25	Between-Group P-value 6.75 vs. Asacol
Interim 1 Assessment	N=49	N=49	N=48		
Improved	10 (20.4%)	18 (36.7%)	12 (25 %)	0.039 CMH	0.151 CMH
Not Improved	39 (79.6%)	31 (63.3%)	36 (75 %)		
Missing	1	4	3		
Total	50	53	51		
Interim 2 Assessment	N=49	N=49	N=48		
Improved	22 (44.9%)	26 (53.1%)	22 (45.8%)	0.339 CMH	0.426 CMH
Not Improved	27 (55.1%)	23 (46.9%)	26 (54.2%)		
Missing	1	4	3		
Total	50	53	51		
Final Assessment	N=49	N=49	N=48		
Improved	22 (44.9%)	29 (59.2%)	26 (54.2%)	0.148 CMH	0.626 CMH
Not Improved	27 (55.1%)	20 (40.8%)	22 (45.8%)		
Missing	1	4	3		
Total	50	53	51		

Statistical abbreviations:
CMH = Cochran-Mantel-Haenszel Test, controlling for entry PGA

Source: n:\testsas\fda\itt2tab.sas submitted by ILH 27JAN98 08:20 SAS 6.11

APPENDIX 2 - Histology Results (Appendix F), Pivotal USA Study

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
BERRY								
2.25	5404	Female	49	Caucasian	Entry:	Severe	9/30/94	
					Exit:	Moderate	11/30/94	61
	5405	Female	39	Caucasian	Entry:	Severe	10/26/94	
					Exit:	Inactive	12/29/94	64
6.75	5402	Male	31	Caucasian	Entry:	Inactive	8/9/94	
					Exit:	Severe	10/14/94	66
	5403	Male	38	Caucasian	Entry:	Moderate	8/31/94	
					Exit:	Inactive	10/27/94	57
ASACOL	5401	Female	28	Caucasian	Entry:	Moderate	2/17/95	
					Exit:	Inactive	4/21/95	63
	5406	Male	50	Caucasian	Entry:	Severe with erosion	8/31/94	
					Exit:	Inactive	11/2/94	63
	5410	Female	64	Caucasian	Entry:	Mild	11/12/94	
					Exit:	Inactive	1/9/95	58
KOGUT								
2.25	5651	Male	27	Caucasian	Entry:	Inactive	8/17/94	
					Exit:	Inactive	10/13/94	57
	5652	Male	49	Caucasian	Entry:	Severe	8/7/95	
					Exit:			
6.75	5654	Male	46	Caucasian	Entry:	Inactive	8/30/94	
					Exit:	Inactive	10/25/94	56
ASACOL	5006	Male	48	Caucasian	Entry:		1/5/96	
					Exit:		3/11/96	66
	5653	Male	67	Caucasian	Entry:	Severe	6/28/94	
					Exit:	Inactive	8/31/94	64
	5656	Male	47	Caucasian	Entry:	Moderate	7/28/94	
					Exit:			
KOVAL								
2.25	5351	Female	26	Caucasian	Entry:	Moderate	8/3/94	
					Exit:	Severe	10/4/94	62
	5356	Male	40	Caucasian	Entry:	Severe	3/14/95	
					Exit:	Severe with erosion	5/16/95	63

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race	BiopsyScore		Draw Date	Elapsed Time (days)
2.25	5357	Male		Asian	Entry:			
					Exit:	Inactive	11/3/95	
	5362	Male		Caucasian	Entry:			
					Exit:	Severe with erosion	10/26/95	
6.75	5106	Female	49	Caucasian	Entry:	Inactive	10/3/95	
					Exit:			
	5311	Male	42	Caucasian	Entry:	Severe	11/7/95	
					Exit:			
	5352	Male	38	Caucasian	Entry:	Severe	8/25/94	
					Exit:	Inactive	10/27/94	63
	5353	Female	39	Caucasian	Entry:	Moderate	9/14/94	
					Exit:	Mild	11/16/94	63
	5359	Male	38	Caucasian	Entry:	Severe	11/7/94	
					Exit:			
	5360	Male	40	Caucasian	Entry:	Moderate	12/22/94	
					Exit:	Severe	2/24/95	64
	5658	Female	38	Caucasian	Entry:	Moderate	7/6/95	
					Exit:	Severe	9/15/95	71
ASACOL	5308	Female	25	Caucasian	Entry:	Severe	11/15/95	
					Exit:		2/13/96	90
	5354	Male	23	Caucasian	Entry:	Inactive	1/18/95	
					Exit:	Inactive	3/28/95	69
	5355	Male		Caucasian	Entry:			
					Exit:	Severe with erosion	5/25/95	
	5358	Male	42	Caucasian	Entry:	Inactive	5/22/95	
					Exit:	Inactive	6/8/95	17
	5361	Female		Caucasian	Entry:			
					Exit:	Mild	10/24/95	
	5659	Female	37	Caucasian	Entry:	Severe with erosion	8/24/95	
					Exit:	Severe	11/3/95	71
LEVINE								
2.25	5151	Male	38	Caucasian	Entry:	Mild	11/28/94	
					Exit:			

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
2.25	5153	Male	36	Caucasian	Entry:	Severe	2/13/95	
					Exit:			
	5158	Male	43	Caucasian	Entry:	Severe with erosion	6/2/95	
					Exit:	Severe with erosion	6/16/95	14
6.75	5154	Male	32	Caucasian	Entry:	Severe with erosion	3/27/95	
					Exit:	Moderate	5/22/95	56
	5156	Male	66	Caucasian	Entry:	Severe	4/14/95	
					Exit:	Moderate	6/9/95	56
	5157	Female	35	Caucasian	Entry:	Mild	5/22/95	
					Exit:	Severe	6/19/95	28
	5160	Female	39	Caucasian	Entry:	Moderate	6/2/95	
					Exit:	Inactive	6/23/95	21
	5312	Male	29	Caucasian	Entry:	Inactive	11/14/95	
					Exit:		1/16/96	63
	5462	Male	46	Caucasian	Entry:	Severe with erosion	9/8/95	
					Exit:	Mild	11/9/95	62
ASACOL	5152	Male	39	Black	Entry:	Moderate	11/21/94	
					Exit:	Inactive	1/17/95	57
	5155	Female	39	Caucasian	Entry:	Moderate	2/3/95	
					Exit:			
	5159	Male	35	Caucasian	Entry:	Severe	2/17/95	
					Exit:	Mild	4/14/95	56
MERRELL								
2.25	5305	Female	37	Caucasian	Entry:	Severe	1/10/95	
					Exit:	Severe		
6.75	5302	Female	35	Caucasian	Entry:	Severe with erosion	7/28/94	
					Exit:	Severe with erosion	9/27/94	61
	5303	Female	33	Caucasian	Entry:	Moderate	12/15/94	
					Exit:	Severe	2/23/95	70
ASACOL	5301	Male	45	Other	Entry:	Mild	6/30/94	
					Exit:	Inactive	9/7/94	69
	5304	Male	21	Caucasian	Entry:	Severe	1/6/95	
					Exit:	Severe with erosion		
PRUIT								

57 Sixth pts. with incomplete or absent biopsies.

CLINICAL STUDY REPORT
PROTOCOL CP099301

APPENDIX F.2.3

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
2.25	5051	Female	40	Caucasian	Entry:	Severe	7/25/94	
					Exit:	Severe with erosion	9/18/94	55
	5053	Female	50	Caucasian	Entry:		8/5/94	
					Exit:			
	5058	Female	31	Caucasian	Entry:	Mild	11/11/94	
					Exit:	Mild	1/11/95	61
	5060	Female	37	Caucasian	Entry:	Severe	4/4/95	
					Exit:	Inactive	6/2/95	59
	5108	Male	23	Black	Entry:	Mild	5/10/95	
					Exit:	Moderate	7/14/95	65
	5111	Male	41	Caucasian	Entry:	Moderate	6/21/95	
					Exit:	Inactive	7/31/95	40
6.75	5012	Male	43	Caucasian	Entry:	Severe with erosion	9/25/95	
					Exit:	Moderate	10/3/95	8
	5052	Male	50	Caucasian	Entry:	Severe with erosion	6/24/94	
					Exit:	Inactive	8/30/94	67
	5054	Female	43	Caucasian	Entry:	Inactive	7/1/94	
					Exit:	Inactive	8/12/94	42
	5057	Male	36	Caucasian	Entry:	Inactive	11/29/94	
					Exit:	Inactive	1/27/95	59
	5059	Female	32	Caucasian	Entry:	Severe	2/28/95	
					Exit:	Inactive	4/3/95	34
	5107	Male	60	Caucasian	Entry:	Severe with erosion	3/14/95	
					Exit:	Severe with erosion	5/16/95	63
ASACOL	5055	Male	28	Caucasian	Entry:	Moderate	7/15/94	
					Exit:			
	5056	Male	43	Caucasian	Entry:		8/23/94	
					Exit:	Moderate	10/25/94	63
	5061	Female	49	Caucasian	Entry:	Severe	12/2/94	
					Exit:	Inactive	2/8/95	68
	5062	Female	55	Caucasian	Entry:	Severe	2/6/95	
					Exit:	Inactive	4/5/95	58
	5110	Female	22	Caucasian	Entry:	Severe	3/29/95	
					Exit:	Severe	5/31/95	63

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
ASACOL	5112	Female	38	Caucasian	Entry:	Severe	4/20/95	
					Exit:	Severe with erosion	6/1/95	42
REX								
2.25	5003	Female	33	Caucasian	Entry:	Inactive	12/6/94	
					Exit:	Inactive	2/28/95	84
	5005	Female	24	Caucasian	Entry:	Severe with erosion	1/25/95	
					Exit:	Mild	3/15/95	49
6.75	5001	Male		Black	Entry:			
					Exit:	Severe with erosion	3/3/95	
	5002	Female	49	Caucasian	Entry:	Severe with erosion	7/12/95	
					Exit:	Severe with erosion	9/20/95	70
	5009	Female	23	Caucasian	Entry:	Mild	11/16/95	
					Exit:			
ASACOL	5004	Female	43	Caucasian	Entry:	Inactive	12/16/94	
					Exit:			
RIFF								
2.25	5011	Male		Caucasian	Entry:			
					Exit:	Severe with erosion	11/6/95	
	5307	Female	38	Asian	Entry:		1/15/96	
					Exit:		3/15/96	60
	5409	Male	74	Caucasian	Entry:		12/5/95	
					Exit:		2/2/96	59
	5458	Male	50	Caucasian	Entry:		12/18/95	
					Exit:		2/22/96	66
	5461	Male	60	Caucasian	Entry:	Severe with erosion	11/13/95	
					Exit:		1/19/96	67
	5610	Male	55	Caucasian	Entry:	Severe	4/4/95	
					Exit:			
	5612	Female	21	Caucasian	Entry:	Severe	2/13/95	
					Exit:			
	5662	Female	28	Caucasian	Entry:	Moderate	4/20/95	
					Exit:	Mild	7/6/95	77
	5701	Male	54	Caucasian	Entry:	Inactive	10/27/94	
					Exit:	Inactive	12/21/94	55

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
2.25	5706	Male	59	Caucasian	Entry:	Moderate	11/30/94	
					Exit:	Inactive	12/19/94	19
	5707	Female	25	Caucasian	Entry:	Severe	12/14/94	
					Exit:	Severe with erosion	2/7/95	55
	5711	Female	36	Caucasian	Entry:	Severe with erosion	1/17/95	
					Exit:			
6.75	5109	Male	26	Hispanic	Entry:	Severe	11/16/95	
					Exit:		1/25/96	70
	5262	Male	74	Other	Entry:	Severe	9/20/95	
					Exit:		11/27/95	68
	5603	Female	42	Caucasian	Entry:	Severe with erosion	3/27/95	
					Exit:	Severe	5/22/95	56
	5606	Male	26	Caucasian	Entry:		1/9/96	
					Exit:			
	5608	Female	58	Caucasian	Entry:	Moderate	3/9/95	
					Exit:	Inactive	5/4/95	56
	5611	Female	20	Hispanic	Entry:	Moderate	2/8/95	
					Exit:			
	5704	Male	33	Hispanic	Entry:	Severe	11/3/94	
					Exit:			
	5705	Female	49	Caucasian	Entry:	Severe with erosion	11/30/94	
					Exit:	Severe with erosion	1/25/95	56
	5708	Female	51	Hispanic	Entry:	Mild	2/1/95	
					Exit:			
	5710	Female		Caucasian	Entry:			
					Exit:	Inactive	1/23/95	
ASACOL	5007	Male	70	Caucasian	Entry:	Severe with erosion	10/18/95	
					Exit:		12/21/95	64
	5206	Female	28	Caucasian	Entry:	Moderate	9/25/95	
					Exit:		11/27/95	63
	5412	Male	77	Caucasian	Entry:	Mild	2/27/95	
					Exit:	Inactive	4/24/95	56
	5604	Female	38	Caucasian	Entry:		1/10/96	
					Exit:			

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race	BiopsyScore		Draw Date	Elapsed Time (days)
ASACOL	5607	Female	47	Caucasian	Entry:	Severe	2/14/95	
					Exit:	Severe	4/13/95	58
	5702	Female	67	Caucasian	Entry:	Moderate	8/15/94	
					Exit:			
	5703	Male	31	Caucasian	Entry:	Severe with erosion	10/6/94	
					Exit:			
	5709	Female	31	Hispanic	Entry:	Mild	10/11/94	
					Exit:	Inactive	12/13/94	63
	5712	Female	75	Caucasian	Entry:	Severe	10/26/94	
					Exit:	Severe	12/27/94	62
RUBIN								
2.25	5601	Female	38	Caucasian	Entry:	Severe	7/6/94	
					Exit:		8/31/94	56
	5605	Male	58	Caucasian	Entry:	Severe	7/8/94	
					Exit:	Severe	7/18/94	10
SALESBERG								
2.25	5102	Male	58	Caucasian	Entry:	Moderate	5/31/95	
					Exit:	Severe	7/24/95	54
	5501	Male	50	Caucasian	Entry:	Severe	7/20/94	
					Exit:	Inactive	9/14/94	56
	5506	Male	66	Caucasian	Entry:	Severe	11/4/94	
					Exit:		12/28/94	54
	5507	Female	49	Caucasian	Entry:	Moderate	1/11/95	
					Exit:	Severe with erosion	3/8/95	56
	5510	Female	76	Caucasian	Entry:	Severe with erosion	6/14/95	
					Exit:	Severe with erosion	8/11/95	58
6.75	5104	Male	72	Caucasian	Entry:	Severe with erosion	2/9/95	
					Exit:	Severe with erosion	4/5/95	55
	5408	Female	32	Caucasian	Entry:		1/16/96	
					Exit:			
	5503	Male	28	Caucasian	Entry:	Inactive	10/28/94	
					Exit:	Inactive	12/23/94	56
	5504	Female	48	Caucasian	Entry:	Severe with erosion	1/4/95	
					Exit:	Moderate		

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race	BiopsyScore		Draw Date	Elapsed Time (days)
6.75	5508	Female	35	Caucasian	Entry:	Moderate	1/11/95	
					Exit:	Inactive	3/13/95	61
	5511	Male	45	Caucasian	Entry:	Severe	5/19/95	
					Exit:	Severe	6/7/95	19
ASACOL	5101	Female	31	Caucasian	Entry:	Severe	5/26/95	
					Exit:	Inactive	7/13/95	48
	5103	Male	25	Caucasian	Entry:	Moderate	8/8/95	
					Exit:	Severe	10/5/95	58
	5502	Female	37	Caucasian	Entry:	Severe with erosion	7/13/94	
					Exit:	Mild	9/13/94	62
	5505	Female	36	Caucasian	Entry:	Moderate	9/27/94	
					Exit:			
	5509	Female	39	Caucasian	Entry:	Severe	11/17/94	
					Exit:	Moderate	1/5/95	49
	5512	Female	31	Caucasian	Entry:	Severe with erosion	1/30/95	
					Exit:	Moderate	2/15/95	16
SALZB								
2.25	5255	Female	20	Caucasian	Entry:	Severe with erosion	6/17/94	
					Exit:			
	5256	Male	29	Caucasian	Entry:	Mild	7/26/94	
					Exit:			
6.75	5251	Female	27	Caucasian	Entry:	Moderate	7/6/95	
					Exit:			
ASACOL	5252	Male	32	Caucasian	Entry:	Severe	2/17/95	
					Exit:			
	5253	Female	38	Caucasian	Entry:	Mild	7/6/95	
					Exit:			
TORRES								
2.25	5452	Female	30	Hispanic	Entry:		11/3/94	
					Exit:	Mild	1/3/95	61
6.75	5451	Female	47	Hispanic	Entry:	Moderate	7/21/94	
					Exit:		9/19/94	60
	5454	Female	68	Hispanic	Entry:	Severe	11/28/94	
					Exit:	Moderate	1/31/95	64

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
ASACOL	5455	Male	23	Hispanic	Entry:	Moderate	7/14/94	
					Exit:	Inactive	9/19/94	67
	5456	Male	73	Hispanic	Entry:	Mild	8/2/94	
					Exit:	Severe with erosion	8/15/94	13
	5457	Female	51	Hispanic	Entry:	Severe with erosion	2/14/95	
					Exit:			
	5459	Female	29	Hispanic	Entry:	Moderate	3/6/95	
					Exit:	Severe	5/2/95	57
WRUBLE								
2.25	5202	Female	32	Black	Entry:	Inactive	12/21/94	
					Exit:	Inactive	2/15/95	56
	5205	Female	28	Caucasian	Entry:	Severe with erosion	1/9/95	
					Exit:	Severe with erosion	2/6/95	28
	5207	Male	32	Caucasian	Entry:	Severe with erosion	6/19/95	
					Exit:	Severe	7/10/95	21
	5551	Female	23	Caucasian	Entry:	Mild	6/27/94	
					Exit:	Mild	7/11/94	14
	5555	Male	51	Caucasian	Entry:	Moderate	7/1/94	
					Exit:	Severe	7/29/94	28
	5557	Female	77	Caucasian	Entry:	Moderate	9/8/94	
					Exit:	Inactive	9/22/94	14
	5562	Male	37	Caucasian	Entry:	Mild	10/3/94	
					Exit:	Inactive	11/30/94	58
6.75	5203	Female	52	Black	Entry:	Moderate	5/1/95	
					Exit:	Inactive	6/30/95	60
	5204	Male	48	Caucasian	Entry:	Moderate	5/12/95	
					Exit:	Inactive	7/7/95	56
	5210	Female	47	Caucasian	Entry:	Mild	7/5/95	
					Exit:		8/30/95	56
	5552	Male	31	Caucasian	Entry:	Severe	6/21/94	
					Exit:	Inactive	8/16/94	56
	5554	Female	52	Caucasian	Entry:	Mild	9/8/94	
					Exit:	Inactive	11/4/94	57

BIOPSY SCORES

Investigator Treatment	Patient	Sex	Age at Screening (years)	Race		BiopsyScore	Draw Date	Elapsed Time (days)
6.75	5559	Male	68	Caucasian	Entry:	Severe	9/19/94	
					Exit:	Inactive	11/14/94	56
	5560	Female	53	Caucasian	Entry:	Moderate	3/13/95	
					Exit:			
ASACOL	5201	Male	43	Black	Entry:	Moderate	12/14/94	
					Exit:	Moderate	1/5/95	22
	5553	Male	57	Caucasian	Entry:	Severe	7/1/94	
					Exit:	Mild	8/29/94	59
	5556	Female	32	Black	Entry:	Mild	9/14/94	
					Exit:	Moderate	10/17/94	33
	5558	Male	74	Caucasian	Entry:		3/14/95	
					Exit:			
	5561	Female	63	Caucasian	Entry:	Inactive	3/28/95	
					Exit:	Inactive	5/23/95	56

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 3 - Individual Symptomatology, Pivotal English-Irish Study

Appendix 6. Diary card daily assessments.

		Balsalazide	*Mesalazine*	*P-value*
Number of times needed to go to lavatory to pass a stool:				
Times/night	Mean ± SD	0.18 ± 0.33	0.42 ± 0.59	p=0.0558
	N	37	37	
	Min - Max			
Times/day	Mean ± SD	2.71 ± 1.98	2.45 ± 1.49	p=0.7907
	N	38	38	
	Min - Max			
Blood on stools:				
Nights/week	Mean ± SD	0.09 ± 0.38	1.18 ± 2.25	p=0.0065
	N	34	32	
	Min - Max			
Days/week	Mean ± SD	1.00 ± 2.03	2.36 ± 2.59	p=0.0053
	N	38	36	
	Min - Max			
Blood on toilet paper:				
Nights/week	Mean ± SD	0.21 ± 0.69	1.41 ± 2.44	p=0.0110
	N	34	33	
	Min - Max			
Days/week	Mean ± SD	1.47 ± 2.37	3.00 ± 2.89	p=0.0136
	N	38	37	
	Min - Max			
Passed mucus with stools:				
Nights/week	Mean ± SD	0.15 ± 0.44	1.24 ± 2.29	p=0.0326
	N	34	33	
	Min - Max			
Days/week	Mean ± SD	1.65 ± 2.22	3.00 ± 2.94	p=0.0469
	N	38	37	
	Min - Max			
Abdominal pain:				
Nights/week	Mean ± SD	0.15 ± 0.56	0.70 ± 1.67	p=0.1343
	N	34	33	
	Min - Max			
Days/week	Mean ± SD	1.77 ± 2.33	2.30 ± 2.80	p=0.5867
	N	38	37	
	Min - Max			

The March 2, 2000 Medical Officer Review covers the Safety Update submitted September 23, 1999 in response to the Agency's June 15, 1998 AE letter.

Another Safety Update will be requested in the action letter.

/S/ 3-6-2000

Alice Kacuba
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

A Safety Update will be requested in the first action letter.

/S/ 2/25/98

Melodi McNeil
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20610	**Trade Name:**	[redacted] (BALSALAZIDE DISODIUM) 750MG CAP
Supplement Number:		**Generic Name:**	BALSALAZIDE DISODIUM
Supplement Type:		**Dosage Form:**	Capsule; Oral
Regulatory Action:	AP	**Proposed Indication:**	Treatment of mildly to moderately active ulcerative colitis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_Children (25 months-12 Years)
____Infants (1-24 Months) _X_Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	Protocols are under discussion. Comment attached

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
3-20-2000: In 6-15-1998 letter, the Agency requested a Phase 4 commitment for all age groups. Negotiations continue over phase 4 commitments. 6/14/00: The applicant has requested a partial pediatric waiver for the youngest age groups. Review is pending. 7/6/00: The applicant's phase 4 commitments have been reviewed and found acceptable. Review of the waiver is still pending. There have been no discussions with the applicant re: development of age appropriate formulations.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MELODI MCNEIL

/S/ 7/6/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20610	**Trade Name:**	~~ (BALSALAZIDE DISODIUM)750MG CAP
Supplement Number:		**Generic Name:**	BALSALAZIDE DISODIUM
Supplement Type:		**Dosage Form:**	Capsule; Oral
Regulatory Action:	AE	**Proposed Indication:**	Treatment of mildly to moderately active ulcerative colitis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
____Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	
Studies Needed	STUDIES needed. Applicant in NEGOTIATIONS with FDA
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
3-20-2000: In 6-15-1998 letter, the Agency requested a Phase 4 commitment for all age groups. Negotiations continue over phase 4 commitments.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ALICE KACUBA

/S/ 3-20-2000

Signature Date

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/PLA/PMA # 20-610 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: ~~—~~ ibalsalazide) capsules Action: AP AE NA

Applicant Salix Therapeutic Class inflammatory bowel disease

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Proposed indication in this application treatment of mildly to moderately active UC

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ✓ Yes (Continue with questions) ___ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___ Neonates (Birth-1month) ✓ Infants (1month-2yrs) ___ Children (2-12yrs) ___ Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- ___ c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**

- ___ a. Pediatric studies are needed.
- ___ b. Pediatric studies may not be needed but a pediatric supplement is needed.

✓ 6. If none of the above apply, attach an explanation, as necessary. (See attached telecon)

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ project manager 5/22/98

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-610
HFD-180/Div File
NDA/PLA Action Package
HFD-006/ KRoberts

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

MEMORANDUM OF TELECON

DATE: May 20, 1998

APPLICATION NUMBER: NDA 20-610; Colazide (balsalazide disodium) Capsules

BETWEEN:

Name: Ms. Mary Ketchum, Regulatory Affairs
Phone: (650)849-5908
Representing: Salix Pharmaceuticals, Inc.

AND

Name: Melodi McNeil, Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Pediatric Development Plans

BACKGROUND: This application was submitted June 23, 1997 by Salix Pharmaceuticals, Inc. to market Colazide 750 mg Capsules, at a dose of 2.25 gm tid, for the treatment of mildly to moderately active ulcerative colitis.

TODAY'S PHONE CALL: I called the firm to inquire about their pediatric development plans. In response to my question, Ms. Ketchum said that the firm does not have any plans to develop Colazide for use in the pediatric population at this time. She indicated, however, that the firm would welcome Agency advice on this subject.

/S/ 5/20/98
Melodi McNeil
Regulatory Health Project Manager

cc: Original NDA 20-610
HFD-180/Div. File
HFD-180/MMcNeil

TELECON