CLINICAL REVIEW

Application Type	NDA
Submission Number	20-610
Submission Code	SE5-016
Letter Date	19Jun06
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PDUFA Goal Date	20Dec06
Reviewer Name	Keith B. St. Amand, MD
Review Completion Date	15Nov06
Established Name	balsalazide disodium
Trade Name	Colazal
Therapeutic Class	5-Aminosalicylate
Applicant	Salix Pharmaceuticals, Inc.
Priority Designation	Priority
Formulation	Capsule
Dosing Regimen	3 capsules taken 3 times per day for 8 weeks OR 1 capsule taken 3 times per day for 8 weeks
Indication	Treatment of mildly to moderately active ulcerative colitis
Intended Population	Patients 5 to 17 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The reviewer recommends **approval** of NDA 20-610/ SE5-016: Colazal for the treatment of mildly to moderately active UC for patients 5-17 years of age (in addition to the adult population already approved) at **a dose of 3 capsules three times per day (6.75 grams/ day)** for up to 8 weeks. This approval is contingent on the sponsor's acceptance of the reviewer's important labeling changes as detailed below.

The reviewer also recommends **approval** for the lower proposed dose of **1 capsule three times per day (2.25 grams/ day)** in patients 5-17 years of age for up to 8 weeks since this dose showed comparable efficacy to the higher dose (no statistically significant difference) and a comparable, although slightly worse safety profile than the higher dose (possibly due to its lower efficacy.)

The reviewer recommends approval of both doses so that prescribing clinicians have a choice of regimens. Since the weight range and severity of disease for the intended patient population (ages 5-17 years) will be quite variable, some clinicians will prefer to start with the lower recommended regimen to see if effective treatment can be accomplished at that dose, while others may decide to start with the higher dose (particularly when treating older children of adult size since the adult studies show a significantly better response for the high-dose regimen.)

In addition, having two dosage regimens available will allow clinicians to taper patients to the lower dose if desired once improvement in symptoms has been shown at the higher dose.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Risk management activities are not required.

1.2.2 Required Phase 4 Commitments

The reviewer does not recommend any additional Phase 4 commitments.

1.2.3 Other Phase 4 Requests

The reviewer does not recommend any additional Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Colazal was approved for the adult population under NDA 20-610 in July of 2000. The sponsor submitted this efficacy supplement to NDA 20-610 on June 19, 2006, to support a labeling change for Colazal (balsalazide disodium) from its original indication of "the treatment of mildly to moderately active ulcerative colitis in adults" to the new proposed indication of "the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older." The proposed dosage regimen in patients 5 years and older is 3 750-mg Colazal capsules to be taken 3 times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. The sponsor also proposes labeling to allow for an alternate lower total daily dose of 2.25 grams for the duration of 8 weeks in pediatric patients.

The sponsor submitted one study (BZUC3001) to support its proposed labeling changes. This study was performed in accordance with the FDA's Written Request (WR) which was last amended December 15, 2005. Of the 68 patients enrolled in the study, 33 (49%) received the high-dose regimen and 35 (51%) received the low-dose regimen. The entire safety database had a total population of 68 patients, and the pharmacokinetic population consisted of 12 patients.

1.3.2 Efficacy

This was a multi-center, randomized, double-blind, parallel-group study of 2 dosage regimens of Colazal in 68 subjects who were 5 to 17 years of age with a diagnosis of mild-to-moderate active UC. Patients were randomized to receive 1 of 2 oral doses of Colazal (6.75 g/day or 2.25 g/day). Daily doses were administered 3 times a day (TID), approximately 8 hours apart, for a total of 8 weeks of treatment. The pre-specified primary efficacy endpoint for this study was the proportion of subjects with clinical improvement, defined as a reduction from baseline to Week 8 of the Modified Sutherland Ulcerative Colitis index (MUCAI) total score by at least 3 points.

Primary Efficacy Endpoint Results: Table 1 displays the results of the primary efficacy endpoint. For the ITT group, 15 subjects (45%) in the Colazal 6.75 g/day group and 13 subjects (37%) in the Colazal 2.25 g/day group showed clinical improvement, with a difference in proportions of 8% and the p-value for this difference was 0.6227. This difference in response for the high-dose group, while higher than the low-dose group, was thus *not statistically significant*.

Table 1. Proportion of Subjects with Clinical Improvement (ITT Population)

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68	Differences in Proportions	p-value[a]
Proportion of subjects with Clinical Improvement	15 (45%)	13 (37%)	28 (41%)	8%	0.6227
95% CI[b]	28.1%, 63.6%	21.5%, 55.1%	29.4%, 53.8%	-15.0%, 31.7%	

[a] From 2-sided Fisher's Exact test with a significance level of 0.05.

[b] Exact (Clopper-Pearson) 2-sided 95% confidence interval.

Table from Module 5, Vol. 16.1, 11.4.1, Table 10.

The data above show a reasonable response rate for both low (2.25 g/day) and high (6.75 g/day) Colazal doses for the primary endpoint. When compared to the adult efficacy data from the original Colazal adult trial of 103 patients, the rates of response in children are similar to that of adults on the high-dose (approved) regimen as summarized in the table below.

Table 2 . Comparison of High- and Low-dose Colazal in adults and children (All numbers are % patients improved @ 8 weeks for the endpoint listed)

Endpoint analyzed	Low-dose (2.25 g/day) Colazal	High-dose (6.75 g/day) Colazal	p-value
Adults—Stool blood	**35%**	**55%**	**0.045**
Adults—Stool frequency	**25%**	**49%**	**0.013**
Adults—Sigmoidoscopy	**52%**	**74%**	**0.031**
Children—MUCAI decrease by at least 3 points (ITT)	**37%**	**45%**	**0.6227**
Children—MUCAI decrease by at least 3 points (PP)	**50%**	**53%**	**1.0000**
Children—MUCAI decrease by at least 3 points (ITT completed study)	**52%**	**54%**	**1.0000**

Table adapted from PI for Colazal-Figure 1 and Module 5, V. 16.1, 11.4.1, Table 10

Although not as robust, the clinical response rate for the primary endpoint in children thus seems to correlate reasonably well with the response rate seen in adults (where the primary endpoint was reduction of rectal bleeding and improvement of at least one other assessed symptom) and would indicate that Colazal is similarly effective in improving symptoms in children and in adults.
The study indicated that the high-dose population had consistently better numerical scores than the low-dose population for rectal bleeding (64% vs. 54%) and mucosal appearance (61% vs. 46%); overall, both doses showed reasonable improvement for all secondary endpoints.

In summary, this reviewer feels that the current study demonstrated reasonably comparable efficacy to that of the adult high-dose group to support the proposed indication for Colazal 750 mg capsules—1 capsule three times daily OR 3 capsules three times daily for the treatment of mildly to moderately active ulcerative colitis in children 5-17 years of age.

1.3.3 Safety

Of the 68 patients enrolled in the study, all were considered part of the safety population. No deaths occurred in this study. Four serious adverse events (SAEs) were reported, but none of these were considered drug-related. These events were as follows:

1) A 17-yo male started Colazal 6.75 grams/ day on 20 Jul 05 and completed the course on 12 Sep 05. On (b) (6) he was hospitalized for a **UC flare** which resolved on (b) (6)

2) A 17-yo female with a history of depression since 2004 started Colazal 6.75 grams/ day on 5 Jan 06 and completed the course on 28 Feb 06. On (b) (6) the subject reported increased **depression**. The study medication was interrupted and she was hospitalized for depression. The event was considered resolved on (b) (6)

3) A 5-yo female started Colazal 2.25 grams/ day on 10 May 05 and completed the course on 16 May 05. On 13 May 05 the subject had a **UC flare** and the study medication was permanently stopped. The event resolved by 16 May 05. On (b) (6) the subject had **pyrexia, abdominal pain, hematochezia, decreased albumin at 2.0 g/dL (normal= 4-5.3 g/dL), and decreased Hct at 27.7% (normal= 31.6-40.4%).** Hospitalization was required and these SAEs were considered unresolved at the time of the subject's withdrawal from the study on (b) (6)

4) 14-yo female started Colazal on 9 Nov 05 and completed the course on 27 Dec 05. On 7 Dec 05 the subject was diagnosed with a **clostridial infection**. She was hospitalized and the event was considered resolved on 9 Dec 05.

Four dropouts due to adverse events occurred (one in the high-dose group and three in the low-dose group), with two of these cases related to the study drug. These two cases were:

1) An 11-yo female developed **abdominal pain** and **urticaria (hives)** after receiving Colazal 6.75 grams/ day. The medication was discontinued and the symptoms resolved in 4 days.

2) A 12-yo female developed **frequent bowel movements** while on Colazal 2.25 grams/ day. After 14 days the medication was permanently stopped.

The other non-drug-related dropouts due to adverse events were:

3) An 11-yo female began treatment with Colazal 2.25 grams/ day on 18 Oct 05, with the last dose given on 23 Oct 05. On 22 Oct 05 the subject experienced a **rectal hemorrhage**, and the study medication was permanently stopped.

4) This subject is the same patient from the third SAE presented above.

The most common adverse events associated with Colazal administration were headache (15% of patients in the study), upper abdominal pain (13%), abdominal pain (12%), vomiting (10%), and diarrhea (9%). With the exception of abdominal pain and headache, these adverse events occurred to a **greater** extent in the low-dose group.

When investigator-determined **drug-related** adverse events were analyzed, the percentages for the most common events are as follows (low-dose group listed first): vomiting (11% vs. 0%), headache (9% vs. 3%), abdominal pain upper (9% vs. 3%), abdominal pain (3% vs. 6%), and nausea (6% vs. 0%). The overall rate of drug-related adverse events was higher in the low-dose group (26% of subjects) than in the high-dose group (21% of subjects).

Laboratory testing at screening and at Week 8 showed no concerning changes in median values, shifts from normal to abnormal, or "panic values" that indicate any safety signals for the study drug. Likewise, there were no clinically meaningful changes seen in vital signs, height, or weight of the study subjects between baseline and Week 8.

In summary, both doses showed a reasonable safety profile, but the high-dose group's profile was slightly better in that it showed **less overall dropouts due to adverse events** and **less drug-related adverse events** than the lower-dose group. The magnitude of this difference, however, is small and should not preclude approval of the lower dose.

1.3.4 Dosing Regimen and Administration

The reviewer recommends the following dose regimens be approved for patients aged 5-17 years:

> THREE 750-mg capsules to be taken three times a day for a total daily dose of 6.75 grams for up to 8 weeks.
>
> OR
>
> ONE 750-mg capsule to be taken three times a day for a total daily dose of 2.25 grams for up to 8 weeks.

Please see the sections above for the rationale behind this dual recommendation.

1.3.5 Drug-Drug Interactions

The current study did not reveal any evidence of unequivocal drug-drug interactions. One postmarketing report of a possible interaction with Colazal, Bactrim and 6-mercaptopurine was reported with a patient taking this combination experiencing thrombocytopenia (low platelet count.) The postmarketing report does not present sufficient concern to effect a change in the labeling, however, since a causal relationship could not be determined definitively.

1.3.6 Special Populations

This supplement is a pediatric study of patients 5-17 years old.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trade name: Colazal (balsalazide disodium) 750 mg capsule.

Proposed Indication: "Colazal is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older."

Proposed Age Group: 5 years of age and older

Pharmacologic Class: 5-aminosalicylate

Route of Administration, Description, and Formulation: Colazal is a beige capsule to be swallowed whole or sprinkled on applesauce (b) (4) The contents of the capsule may be chewed since the contents of Colazal are not coated beads or granules.

Proposed Treatment Regimen: The sponsor has proposed two treatment regimens for the age group studied in this supplement (ages 5-17 years.) These regimens are as follows:

1) 1 capsule three times daily (total daily dose of 2.25 grams/ day)
2) 3 capsules three times daily (total daily dose of 6.75 grams/ day)

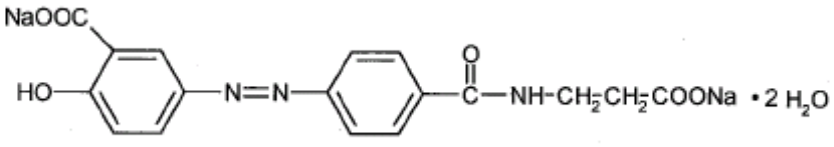
These regimens are to be used for up to 8 weeks in this pediatric population.

Chemical name of the main ingredient in Colazal:

(E)-5-[[-4[[(2-carboxyethyl)amino]carbonyl]phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate.

The molecular formula is $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$

The structural formula is:



2.2 Currently Available Treatment for Indications

The current list of FDA-approved products available for the treatment of ulcerative colitis in children is very limited, which was the impetus behind the FDA's issuance of a Written Request to the sponsor for this "orphan population." In fact, the reviewer was only able to find one product which has received approval for this indication, Azulfidine-EN™ (NDA 7073 approved June 20, 1950). Multiple generic versions of sulfasalazine have been approved as well, but concerns with the side effect profile of this drug have often forced physicians to prescribe other non-approved aminosalicylates off-label, including mesalamine (Asacol™, Canasa™, Pentasa™, and Rowasa™) and olsalazine (Dipentum™) products.

Various corticosteroids and other immunosuppressants have also been used extensively in the treatment of UC in children, but none of these drugs have been FDA-approved for this indication. Newer biologic products such as the TNF-α blocker infliximab (Remicade™) have been approved in adults, but have yet to be studied in children.

2.3 Availability of Proposed Active Ingredient in the United States

Colazal is currently approved in the U.S. for the treatment of mildly to moderately active ulcerative colitis in adult patients. It is the only form of balsalazide disodium (the active ingredient in Colazal) available in the U.S. It should be noted, however, that balsalazide is a prodrug which is metabolized to mesalamine in the colon, and there are many mesalamine products available as mentioned above.

2.4 Important Issues With Pharmacologically Related Products

Postmarketing events of hepatotoxicity have been reported with other mesalamine products, including elevated liver function tests (AST, ALT, GGT, LDH, alkaline phosphatase, bilirubin), jaundice, cholestatic jaundice, cirrhosis, hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal; however, no causal relationship with mesalamine and liver failure has been established. In the current supplement, there were no deaths seen and no significant changes in any monitored liver function tests.

2.5 Presubmission Regulatory Activity

The highlights of the regulatory activity pertaining to this supplement are as follows:

- 7/18/00 NDA 20-610 approved
- 11/8/00 Sponsor submits Pediatric Development Plan and Proposed Pediatric Study Request (PPSR)
- 12/17/01 FDA issues original pediatric Written Request letter (WR)
- 12/18/02 FDA issues amended WR

- 3/2/04 Sponsor submits Study BZUC3001 (this supplement's study) protocol for review
- 12/21/04 FDA provides comments concerning BZUC3001
- 4/14/05 Type A Meeting held to discuss WR
- 12/15/05 FDA issues Final Amended WR
- 6/19/06 Sponsor submits Supplement 16 to NDA 20-610 (efficacy supplement for pediatric population)

2.6 Other Relevant Background Information

In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100,000 and an estimated prevalence of approximately 70 to 150 per 100,000.[1] Many cases are diagnosed between the ages of 10-19, but exact prevalence estimates in children were not available despite an extensive online search for this information. In any case, UC in children was deemed rare enough that Colazal was granted orphan drug designation in August 2005 by the Office of Orphan Drugs.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There was no new data submitted to CMC with this supplement.

3.2 Animal Pharmacology/Toxicology

There were no new animal studies submitted with this supplement.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

One sponsor-conducted trial (Study BZUC3001) was evaluated by the reviewer. In addition, the reviewer examined the following documents to assist in the review:

1-Current Package Insert for Colazal
2-Amended Written Request (December 15, 2005)
3-Package Inserts for other 5-ASA products
4-Literature Review for Ulcerative Colitis and for 5-ASA products including balsalazide disodium (Colazal)

4.2 Tables of Clinical Studies

Table 3. Listing of Clinical Study Submitted for Colazal Pediatric Supplement

Study	Design	Treatment Groups	N
BZUC3001	Randomized, double-blind, parallel group	Colazal 750 mg TID (2.25 g/day) **OR** Colazal 3 X 750 mg TID (6.75 g/day) All subjects 5-17 yrs of age	68 enrolled (ITT); 53 completed study; 29 per protocol; 68 in safety population; 12 in PK population

Table adapted from Module 5, Vol. 16.1, 5.2, Table 5.2.1

4.3 Review Strategy

This reviewer is responsible for the entire safety and efficacy review of this supplement seeking expansion of the indication to treat UC in patients ages 5-17 years. Please see Sections 4.1 and 4.2 above for materials reviewed.

4.4 Data Quality and Integrity

No sites were selected for Division of Scientific Investigations (DSI) inspection.

4.5 Compliance with Good Clinical Practices

The sponsor states that the protocol submitted and the informed consent and authorization form were approved by an appropriate institutional review board (IRB) which complied with current International Conference on Harmonization (ICH) Good Clinical Practices (GCP). Furthermore, the Principal Investigator and the study staff were responsible for conducting the study in accordance with the principles that have their origins in the Declaration of Helsinki, ICH GCP, and all other applicable laws and regulations.

4.6 Financial Disclosures

According to the sponsor, none of the investigators or sub-investigators involved in the study submitted in this supplement are employed by the sponsor, nor do they have any financial interest or arrangement to disclose pursuant to 21 CFR 54.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Please see the Clinical Pharmacology review completed by Dr. Suliman Al-Fayoumi for a comprehensive analysis of the data submitted for this section. This reviewer will present a

synopsis of the information presented both in this PK supplement (Study BZUC3001) and, for the purposes of background, that information presented in Supplement 14 to NDA 20-610 (Study BZPK1001 and Protocol SA/028) submitted for approval on March 23, 2006.

In Study BZPK1001, a single oral dose of Colazal 2.25 grams was given to healthy volunteers as intact capsules under fasting conditions, as intact capsules after a high-fat meal, and unencapsulated as sprinkles on applesauce in a 3-way crossover design.

When comparing the fed and fasting populations for **balsalazide** itself, no significant differences were seen in critical PK parameters (C_{max}, AUC_{last}, and T_{max}). Significant differences were observed in these parameters for **metabolites**, however, which were lower in the fed group. The sponsor believes that this finding thus supports the safety of administering the product with meals.

Medical Officer Comments: **The reviewer agrees with the sponsor that the study does not raise any new safety concerns with regard to administering the product with meals.**

Significant differences were observed in 2 critical parameters (AUC_{last} & C_{max}) between **sprinkled** balsalazide and **intact** balsalazide in fasting subjects (these parameters were lower in the subjects receiving the sprinkles). Despite this finding, however, the active **metabolite** levels between the groups were neither bioequivalent nor statistically significantly different.

The sponsor states that, "this suggests that dosing balsalazide disodium as a sprinkle or as a capsule provides highly variable, but relatively similar pharmacokinetics."

The sponsor goes on to state that "Clinical efficacy after balsalazide administration is presumably due to the local effects of 5-ASA on the colonic mucosa. Consequently, there can be no inference made as to how the systemic exposure differences of balsalazide and its metabolites in this study might predict the clinical efficacy under different dosing conditions (i.e., fasting, fed with high-fat meal, or sprinkled on applesauce."

Medical Officer Comments: **The primary purpose of this study was to demonstrate bioequivalence between the sprinkled and intact forms of balsalazide since many pediatric patients will need to use the sprinkles. (Approximately 16% of patients in Study BZUC3001 used the sprinkles.) Although bioequivalence was not demonstrated, neither were there significant differences observed for the critical parameters for the metabolites of balsalazide, so it appears that the sprinkled form shows no added safety concerns.**

Regarding efficacy, the sponsor is likely correct in that the mechanism of action of this product occurs at the level of the colonic mucosa, and variance between the PK parameters does not necessarily imply any difference in clinical efficacy between the sprinkled and intact forms. Since no controlled study comparing the efficacy of sprinkled and intact balsalazide has been accomplished, however, the reviewer cannot definitively state whether these methods of administration will differ in their efficacy. A statement to this effect should be added to the labeling under the CLINICAL PHARMACOLOGY section.

Protocol SA/028 (lab report SA/032-1) was also submitted March 23, 2006, as part of Supplement 14. This study showed that balsalazide did not convert to 5-ASA when mixed with applesauce and chocolate pudding, and thus demonstrated that opening the capsule and sprinkling the drug on food is an acceptable dosage form.

Medical Officer Comments: **The sprinkled form of balsalazide appears to be an acceptable method of administration based on this study. For a complete review please see the Clinical Pharmacology review for Protocol SA/028.**

In the current supplement, the sponsor performed PK testing in a subset of patients as per the WR issued by the FDA. Very large inter-subject variability was seen both for balsalazide and its metabolites, similar to that seen in adult PK studies.

The pro-drug moiety, **balsalazide**, showed a dose-proportional increase in critical exposure parameters between the low- and high-dose groups, with an absolute magnitude for those parameters **greater** than that seen in adults.

When the critical exposure parameters were analyzed for the **active metabolites**, however, the magnitude of these parameters was **lower** relative to the adult population, and the parameters increased at a rate which was less than the dose-proportional increase seen for the prodrug.

Medical Officer Comments: **These studies show that the levels of active metabolites are lower in children relative to adults, and this may explain why children on the higher dose regimen had a better response when compared to those on the lower dose. If the metabolism of the pediatric population is more efficient for this drug's active metabolites, higher doses than expected would be required to be effective. This may also explain why the safety profile is not appreciably worse than that seen in the adult population even though the pediatric patients received the same dose as the adults.**

5.2 Pharmacodynamics

There were no pharmacodynamic studies conducted for this supplement.

5.3 Exposure-Response Relationships

Please see Section 5.1 for this information.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication of this New Drug Application supplement is for Colazal 750 mg capsules—1 capsule three times daily OR 3 capsules three times daily for the treatment of mild to moderate active ulcerative colitis in **children** 5-17 years of age.

6.1.1 Methods

The efficacy evaluation for this NDA supplement was based upon a single clinical trial, which was a multi-center, double-blind study that evaluated the safety, efficacy, and pharmacokinetics of 8 weeks of use of the product.

6.1.2 General Discussion of Endpoints

The **primary efficacy endpoint** for this study was the proportion of subjects with clinical improvement, defined as a reduction from baseline to Week 8 of the Modified Sutherland Ulcerative Colitis index (MUCAI) total score by at least 3 points.

In correspondence dated June 27, 2002, FDA agreed that it was acceptable to replace the Sutherland Disease Activity Index with the Modified Sutherland Disease Activity Index (MUCAI). The MUCAI outlined below was used to assess the overall disease activity of each subject during the Screening and Week 8/Final Visit. At the Screening Visit, the MUCAI was graded by the Investigator based on historical recollection of the preceding 7 days by the subject and parent or legal guardian. At the Week 8/Final Visit, the calculation of stool frequency and rectal bleeding was based on the subject's diary card from the preceding 7 days.

Table 4. Modified Sutherland Ulcerative Colitis Activity Index

1. Stool frequency

0 = $\leq$3 stools/day
1 = 4 - 5 stools/day
2 = 6 - 7 stools/day
3 = $\geq$8 stools/day

2. Rectal bleeding

0= None
1 = Streaks of blood
2 = Obvious blood
3 = Mostly blood

3. Mucosal appearance

0 = Intact mucosa with preserved or distorted vessels
1 = Edematous mucosa with granularity and mild friability without ulceration
2 = Pinpoint ulceration and moderate friability
3 = Gross ulceration and spontaneous hemorrhage

4. Physician's rating of disease activity

0 = Normal
1 = Mild
2 = Moderate
3 = Severe

Minimum Score = 0; Maximum Score = 12

Table from Module 5, Vol. 16.1, 9.5.4.1, Table 3

Medical Officer Comments:

This primary endpoint utilizes the MUCAI, which is a modification of the Sutherland Disease Activity index, one of many indices used in the literature to assess more objectively a patient's symptoms of inflammatory bowel disease (IBD), which includes ulcerative colitis. The FDA agreed to this modification in June 2002 during discussions with the sponsor. The MUCAI is thus similar but not identical to the primary endpoints for efficacy used in the adult study performed in support of the original NDA for Colazal.

The selection of endpoints is difficult when evaluating potential therapies for IBD in children. Adults can typically provide good descriptions of their symptoms and can categorize easily (i.e., choose a degree of relief—complete, moderate, mild, or minimal). This is much more difficult for a child to do, particularly before they enter their teenage years and begin to think more abstractly. A child's characterization of his symptoms can be vague and often will vary considerably from day to day (i.e., he may complain of "tummy ache" one day and "cramps" the next, or he may freely interchange pain with nausea). This variability in describing symptoms is also present between different children, and this makes developing a standardized scale for rating disease to which each child can conform more difficult than doing so in an adult study population.

The MUCAI partially obviates this problem by picking very concrete signs (rather than symptoms) that the parent or the child can observe. Rather than using "diarrhea," which is often ill-defined by patients, the scale uses "number of stools per day," an easily quantifiable variable. The other patient-reported sign assessed by the MUCAI is rectal bleeding, which has some potential for variable reporting but is generally easily identified by a patient or parent.

Since it combines these two signs which can be reasonably assessed by the patient or his parent with a physician's objective assessment that includes mucosal appearance and a global rating of disease activity, the MUCAI appears to be a good choice to provide a good overall assessment of the product's efficacy, and thus is an acceptable primary endpoint.

The secondary efficacy endpoints included the following 9 measures:

> 1-The proportion of subjects achieving remission as evidenced by a score of 0 or 1 (where a score of 1 was only allowed on the stool frequency subscale) on the MUCAI at Week 8 (This can be categorized as a physician/patient-based endpoint, since it requires input from both sources).
>
> 2-Change from baseline to Week 8 in the total score of the MUCAI (also physician/patient-based)
>
> 3-Change from baseline to Week 8 in stool frequency (patient-based endpoint)
>
> 4-Change from baseline to Week 8 in rectal bleeding (patient-based endpoint)

5-Change from baseline to Week 8 in endoscopic mucosal appearance (physician-based endpoint)

6-Change from baseline to Week 8 in physician's rating of disease activity (physician-based endpoint)

7-Change from baseline to Week 8 in the histology index (physician-based endpoint), which is graded as depicted in Table 5 below

8-Number of days of fever (patient-assessed) in the 7 days prior to the Week 4 and Week 8 visits (patient-based endpoint)

9-Number of days of abdominal cramps (patient-assessed) in the 7 days prior to the Week 4 and Week 8 visits (patient-based endpoint)

Table 5. Pathology Classification for histology index for Colazal Study BZUC3001

Grade	Corresponds to	Criteria
0	Normal colon/rectum OR inactive chronic colitis/proctitis	No cryptitis or crypt abscesses, +/- evidence of chronicity
1	Mildly active chronic colitis/proctitis	Cryptitis or crypt abscesses involving <50% of sampled crypts
2	Moderately active chronic colitis/proctitis	Cryptitis or crypt abscesses involving 50% or more of sampled crypts
3	Severely active chronic colitis/proctitis	Active chronic colitis/proctitis, grade 1 or 2, plus erosions or ulcerations

Table Source: Module 5, Vol. 16.1, 9.5.4.2, Table 4.

Medical Officer Comments:

These endpoints are largely a breakdown of the MUCAI score into its components, and analysis of these may help to determine which signs of disease activity are ameliorated most by Colazal. In addition to the individual components of the index, the total change in score is assessed, as is the number of patients who achieve complete remission of their disease. These endpoints again incorporate both patient- and physician-based reporting of concrete signs, and this reduces the concerns discussed above that are inherent in self-reporting by pediatric populations, so these first 7 endpoints are acceptable.

The last two endpoints, however, which are number of days of fever and number of days of abdominal cramps, are less useful. These endpoints are quite susceptible to improper reporting by patients and parents, particularly fever. The sponsor defines fever as $\geq 100^{o}$ F or $\geq 37.8^{o}$ C, but most medical authorities consider fever to be a

temperature ≥ 100.4° F or ≥ 38° C. [2] The protocol also does not specify the method of temperature measurement that should be employed. The most reliable methods for taking a child's temperature are either rectal or oral. Other methods which may include axillary, tympanic, or skin temperature assessment are not reliable because they do not indicate body core temperature and they also show great variability in temperature even from one minute to the next in the same patient. Alternatively, many parents will simply feel a child's skin and estimate the temperature based on their subjective sensation of heat, even to the point of giving a numerical figure for the temperature. Fever can also result from many causes unrelated to IBD, which could confuse assessment of the product's efficacy. Because of all of these reasons, the undersigned medical officer does not believe this endpoint should be used as an indicator of efficacy.

Likewise, the final endpoint which assesses the presence of abdominal cramps is unlikely to yield any useful efficacy data. This question asks if any cramps were experienced, but the causes of abdominal cramps (generally defined as intermittent abdominal pain) are numerous in children. This could easily lead to confounding of any efficacy assessment for this endpoint, since children with ulcerative colitis can have other causes of abdominal pain besides their disease, and it would be impossible to exclude all patients with any history of abdominal pain from the study. Because of this concern, this medical officer does not believe this endpoint should be used as an indicator of efficacy.

6.1.3 Study Design

Study BZUC3001

Title: A Multi-Center, Double-Blind Study of COLAZAL in the Treatment of 5- to 17-Year-Old Pediatric Patients with Mild to Moderate Active Ulcerative Colitis

Study Objective: To evaluate the efficacy, safety, and pharmacokinetics (PK) of 2 dosage regimens of Colazal (balsalazide disodium) in pediatric subjects with mildly to moderately active ulcerative colitis (UC)

Study Design: This was a multi-center, randomized, double-blind, parallel-group study of 2 dosage regimens of Colazal in 68 subjects who were 5 to 17 years of age with a diagnosis of mild-to-moderate active UC. Blood samples were drawn from 12 subjects (6 subjects per dose group) to assess the multiple-dose PK of Colazal. Subjects who had PK blood samples drawn were between the ages of 9 and 17 years, inclusive. Only subjects who were assigned to have PK blood samples drawn and who withdrew early from the study (prior to the Week 2 Visit) were replaced.

Subjects were to be treated for up to 8 weeks. Eligible subjects were treated with Colazal 6.75 g/day in 3 divided doses or 2.25 g/day in 3 divided doses with matching doses of placebo.

Each subject's legally acceptable representative(s) signed an ICAF at the Initial Screening Visit.

Each subject was seen in the clinic 6 times. These visits occurred at screening, baseline, at 2, 4 and 8 weeks following the first dose of study medication, and 1 week after the last dose of study medication. Subjects participating in the PK portion of the study had 1 additional visit the day prior to the Week 2 visit.

Adverse events (AEs) and changes in clinical laboratory assessments (hematology, serum chemistry, and urinalysis) were used to evaluate the safety of the balsalazide disodium treatments.

In order to reduce any possible bias, subjects were randomly assigned to receive 1 of 2 oral treatment regimens of Colazal (6.75 g/day or 2.25 g/day) as double-blind treatment. The design of the current study evolved from the FDA's original Written Request dated December 17, 2001 for pediatric studies and subsequent correspondence between Salix and the FDA that culminated in the final December 15, 2005 Written Request-Amendment.

Inclusion Criteria:

A subject was eligible for inclusion in the study if he/she met all of the following criteria:

1. The parent or legal guardian signed and dated a written ICAF prior to any study-related activities, including discontinuation of any prohibited medications. Documentation that ICAF was obtained prior to the conduct of any study-related procedures was provided in each subject's source documentation.

2. If required by the IRB/IEC, the subject provided assent prior to any study-related activities, including discontinuation of any prohibited medications. Each IRB/IEC determined if assent was required at an individual study site and, if so, if it was to be written or verbal assent.

3. The subject was 5 - 17 years of age.

4. For PK blood sampling, the subject was 9 - 17 years of age.

5. Only subjects with confirmed or suspected UC at the time of study enrollment were considered as potential study subjects. Eligible subjects were diagnosed, via an endoscopic procedure performed within 1 month of screening, with mildly to moderately active (or suspected) UC based on the Investigator's use of the Modified Sutherland UC activity index (MUCAI) defined by:

   · A total score between 4 and 10, inclusive, and
   · A score of at least 1 on the rectal bleeding scale, and
   · A score of at least 1 on the mucosal appearance scale, and
   · A score of at least 1 on the physician's rating of disease activity scale.

6. The subject had documented proctitis, proctosigmoiditis, pancolitis, or indeterminate colitis by endoscopic procedure within 1 month before the initiation of therapy.

Note: subjects who had an endoscopic procedure with biopsy within 1 month of the Screening Visit were not required to have an endoscopic procedure at study entry as long as adequate documentation of UC diagnosis was on file in the study chart prior to randomization.

7. Subject was male or female. Female subjects met the following criteria:

· Non-childbearing potential (i.e., physiologically incapable of becoming pregnant, including any female who was premenarchal or had undergone a hysterectomy); or,

· Child bearing potential, had a negative urine pregnancy test at screening, and agreed to 1 of the following:
  · complete abstinence from intercourse for 2 weeks prior to the study drug administration, throughout the 8-week Treatment Phase, and during the 1-week Follow-up Phase;
  · double-barrier method of contraception for 2 weeks prior to the study drug administration, throughout the 8-week Treatment Phase, and during the 1-week Follow-up Phase;
  · oral birth control pills or transdermal contraceptive patch (for those women who weighed less than 198 lbs/90 kg) administered for at least 2 monthly cycles prior to study drug administration, throughout the 8-week Treatment Phase, and during the 1-week Follow-up Phase;
  · progesterone implanted rods (NORPLANT) inserted for at least 1 month prior to the study drug administration but not beyond the third successive year following insertion;

Medical Officer Comments: **The inclusion criteria were reasonable**.

Exclusion Criteria:

A subject was not eligible for inclusion in the study if he/she met any of the following criteria:

1. The subject was known to be intolerant of or allergic to salicylates.
2. The subject was known to have previous intolerance to balsalazide disodium or was known to be a treatment failure on balsalazide disodium.
3. The subject had severe UC (MUCAI> 10).
4. The subject had significant bowel distention or tenderness associated with guarding or rebound.
5. Anticholinergic or antidiarrheal drugs were not permitted once randomized and throughout the study through the Follow-up Visit (provided there was no potential risk associated with the subject not receiving these drugs).
6. Any additional 5-ASA products were not permitted once randomized and throughout the study through the Follow-up Visit (provided there was no potential risk associated with the subject not receiving these products).

7. The subject had other infectious, ischemic, or immunologic diseases with gastrointestinal involvement.
8. The subject had clinically significant hepatic disease manifested by twice the upper limit of normal (2 x ULN) for any of the following liver function tests (LFTs): alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, or total bilirubin (except an isolated
elevation of unconjugated bilirubin).
9. The subject had clinically significant renal disease manifested by 1.5 x ULN of serum creatinine or blood urea nitrogen (BUN) levels.
10. The subject had unstable cardiovascular or pulmonary disease.
11. The subject had any condition or circumstance that would prevent completion of the study or interfere with analysis of study results, including history of drug or alcohol abuse, history of mental illness, or history of noncompliance with treatments or visits.
12. The subject was pregnant or breastfeeding.
13. The subject had previous treatment under this protocol.
14. The subject had participated in an investigational drug or device study within the 30 days prior to study screening.
15. The subject had active malignancy within the last 5 years, except basal cell carcinoma of the skin or, if female, *in situ* cervical carcinoma that had been surgically excised.

Medical Officer Comments:

The exclusion criteria were reasonable. Patients with severe UC would not be candidates for non-steroidal anti-inflammatory treatment such as Colazal; thus it was ethically necessary to exclude these patients. The sponsor uses a MUCAI score > 10 as the criteria for "severe UC." A literature search reveals a recent article that summarizes the American College of Gastroenterology (ACG) grading of severity of UC as follows:

Table 6. ACG Grading of UC Severity

Classification	Features
Mild	< 4 stools/ day ± blood, normal ESR, no signs of toxicity
Moderate	≥ 4 stools/ day ± blood, minimal signs of toxicity
Severe	> 6 stools/ day + blood, evidence of toxicity (fever, tachycardia, anemia, or elevated ESR)
Fulminant	> 10 stools/ day, continuous bleeding, toxicity, abdominal tenderness and distension, transfusion requirement, colonic dilation on X-ray

ESR= erythrocyte sedimentation rate

Table adapted from Table 1 from Sands et al.[3]

This table is meant to serve as a reference for physician assessment of UC which is part of the MUCAI. This table classifies severe UC as > 6 stools/ day + blood, plus evidence of toxicity. Patients who presented this way to their physician would no doubt receive a score

of "severe" on the "Physician's rating of disease activity" portion of the MUCAI. When combined with the other 3 elements of the MUCAI, it is improbable that any patient presenting with toxicity would score less than an 11 and not be excluded from this study. Since the study exclusion criteria for severe UC thus appear to correlate with the ACG recommendations for assessment of severity, this cutoff point was appropriate.

Treatments: Patients were randomized to receive 1 of 2 oral doses of Colazal (6.75 g/day or 2.25 g/day). Daily doses were administered 3 times a day (TID), approximately 8 hours apart, for a total of 8 weeks of treatment.

Colazal is approved for treating mildly to moderately active UC in adults at a dose of 6.75 g/day. The present study tested 2 different doses of Colazal- 2.25 g/day (1 active capsule and 2 placebo capsules administered TID) and 6.75 g/day (3 active capsules administered TID)- in pediatric subjects. The dose levels selected were based on the minimal systemic absorption and the local therapeutic action of balsalazide. Olsalazine (a pro-drug consisting of two 5-ASA molecules linked by an azo bond) at 2 g/day, a dose that is twice the approved adult dose for maintaining remission of mild-to-moderate UC, was shown to have suboptimal efficacy in pediatric subjects with mild-to-moderate UC.

The sponsor conducted a survey of 10 pediatric gastroenterologists in the US and the majority reported that they routinely treat pediatric patients with mildly to moderately active UC using the FDA-approved adult dose of Colazal at 6.75 g/day, then taper the dose for maintenance. The lower dose in this study (2.25 g/day) was selected because, although not FDA approved, this dose was associated with improved sigmoidoscopic scores and physician's global assessments of disease when administered to adults with mildly to moderately active UC. Lastly, it was hypothesized that a three-fold difference in daily dose may provide adequate dose separation for pharmacokinetic and dose-response analysis.

The dosing regimen for pediatric subjects of 3 divided doses was justified as being the same regimen used for the marketed formulation in adults, 3 times daily administration.

It has been reported that children from approximately 9 years of age and older are capable of swallowing capsules intact, with plenty of water, without difficulty. For subjects who were unable to swallow the capsules intact, each capsule could have been opened and the granules sprinkled on food and immediately consumed. Subjects were encouraged to ingest the study drug capsules intact and underwent an optional swallow test (at the Investigator's discretion), using empty/blank capsules (not containing either Colazal or placebo).

For subjects requiring the capsules to be opened and sprinkled on food, there may have been temporary staining of the subject's teeth or tongue. Verbal reports from pediatricians indicate that the staining may be minimized when the granules are sprinkled on chocolate pudding. Other means of minimizing the staining include flushing with copious amounts of water and sufficient toothbrushing following each dose.

Medical Officer Comments:

This rationale for selection of dose and timing appears to be sound. The survey of 10 pediatric gastroenterologists assayed the medical community to determine typical off-label dosing of the drug in children and establish what should be a reasonably safe regimen for clinical trials. In addition, 2.25 g/day was the lowest dose considered to have any potential therapeutic effect; any lower would be equivalent to placebo and thus unethical.

The use of capsules in children 9 years and older is generally feasible; however, there are usually outliers who will not or cannot swallow capsules even as teenagers. The sponsor has submitted data comparing the use of sprinkles to intact capsules under Study BZPK1001 which showed no significant differences in the metabolites of balsalazide (specifically 5-ASA which is the clinically active molecule) between the two groups. (Further details are discussed in the Clinical Pharmacology section of this review.)

Furthermore, the sponsor's Protocol SA/028 demonstrated the stability of balsalazide in applesauce and chocolate pudding (i.e., it did not convert to 5-ASA when sprinkled on food) so this method of administration appears to be an acceptable one. These separate studies are important in relation to BZUC3001 since 11 of 68 patients enrolled sprinkled their doses at some point (4 over the entire 8-week course of treatment, and 7 over a 1- to 3-week period.)

The sponsor notes that some subjects experience staining of the teeth or tongue when using the sprinkles on food, and that "verbal reports from pediatricians indicate that the staining may be minimized when the granules are sprinkled on chocolate pudding. Other means of minimizing the staining include flushing with copious amounts of water and sufficient toothbrushing following each dose." This side effect will need to be noted on the final (b) (4) **label.**

Schedule of Procedures & Evaluations:

Table 7. Schedule of Assessments & Procedures

Procedure	Screening Period (-17 days to Time 0)		Randomization (Day 1)	Week 2 (Day 14±3)	Week 4 (Day 28±3)	Week 8/ Final[2] (Day 56±3)	Follow-up (PT Day 7±3)
	Initial Screening Visit[1] (-17 days to Time 0)	Screening [1]					
Informed Consent and Authorization	X						
Medical History	X						
Physical Examination	X					X	
Vital Signs	X		X	X	X	X	X
Urine Pregnancy Test (fecund females only)	X[3]			X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X
Blood Chemistry	X					X	
Serum Creatinine				X	X		
Hematology	X					X	
Urinalysis	X					X	
Calculated Creatinine Clearance Test	X[4]					X	
PK Samples (in a subset of subjects)				X[5,6]			
Endoscopy w/ Biopsies		X[1]				X[9]	
Assign Subject ID Number	X						
Assign Treatment ID Number			X				
Dispense CTM			X[7]	X	X		
Dispense Diary Cards[8]			X	X	X		
Collect CTM				X	X	X	
Collect/ Review Diary Cards[8]				X	X	X	
Administer MUCAI	X					X	
Record Adverse Events[8]	X		X	X	X	X	X
Schedule Next Visit	X		X	X	X	X	

CTM = clinical trial material; ID = identification; MUCAI = Modified Sutherland Ulcerative Colitis Activity Index; PT = posttreatment.

1 The screening endoscopy with biopsies was performed any time during the 17-day screening window. Subjects who had an endoscopy and biopsy within 1 month of the Screening Visit did not have the procedure repeated at study entry provided adequate documentation diagnosing ulcerative colitis (UC) was on file in the study chart at randomization.

2 Visit 8/Final procedures were completed for subjects that were terminated prematurely.

3 Urine pregnancy test was only performed once prior to randomization/initiation of study medication.

4 Calculated creatinine clearance test was performed at any time during the Screening Period.

5 For the day prior to the Week 2 Visit, a single pre dose morning blood sample was collected. Morning dose of study drug was administered in the clinic.

6 For the day of the Week 2 visit, blood samples were collected at pre dose and approximately 1, 2, 3, 4, 6, and 8 hours after the first dose of the day. Morning dose of study medication was administered in the clinic.

7 Optional swallow test was performed (at Investigator's discretion) using empty/blank capsules. Subjects were encouraged to ingest study mediation capsules intact. If subjects were unable to ingest the empty/blank capsules, they opened the study medication capsules and sprinkled the contents on food.

8 Weekly telephone contacts were made with subject/parent/guardian between study visits to assess subject symptoms and encourage study compliance.

9 Endoscopic procedures were performed and 3-4 colonic biopsies were obtained from the same region that was originally biopsied.

Table from Module 5, Vol. 16.1, 9.5.1, Table 2.

Screening Phase: Patients were screened within 17 days of their randomization at Day 1. Initial screening included history and physical (exam of heart and lungs), concomitant medications and vital signs (height, weight, pulse, respiration, temperature, and sitting blood pressure), urine pregnancy test (if female and of childbearing age), and lab evaluation for blood chemistry, hematologic indices (CBC), urinalysis, and calculated creatinine clearance test. Patient symptoms were assessed with the MUCAI and endoscopy/biopsies were performed as part of this assessment. Patients who had endoscopy/ biopsy within 1 month of the screening visit did not have the test repeated, as long as documentation of UC was on file.

Treatment Period: Patients began treatment and then were contacted weekly by telephone to assess compliance and symptoms. Subjects returned at Week 2 and Week 4 for vital signs, pregnancy testing if applicable, serum creatinine, and recording of adverse events. At Week 8 patients returned for physical exam, vital signs, pregnancy test, lab work identical to that of the screening phase, and reassessment of the MUCAI, including repeat endoscopy with biopsy. Adverse events were also detailed at this visit. The final follow-up visit occurred post-treatment day 7, and included vital signs, pregnancy test, and adverse events.

Medical Officer Comments:

The schedule appears to allow adequate assessment of the sponsor's endpoints. Three to four colonic biopsies are taken from the same region at screening and during the treatment phase, which allows for better comparison of histologic samples. Assessment of safety (consisting of physical exam, adverse events, electrolyte levels, CBC, creatinine, and concomitant medications) is consistent with the expected side effects for mesalamine products currently on the market. The reviewer feels that pre- and posttreatment erythrocyte sedimentation rate would also have been a useful test to monitor for either paradoxical exacerbation of UC (which has been reported in other mesalamine products) or for aiding in the documentation of remission. Also, the physical exam as discussed in the protocol does not include an abdominal or rectal exam, but with colonoscopy being performed twice during the study these elements of the physical are not crucial in the measurement of the endpoints.

Statistical Populations/Analysis:

The following patient populations were pre-specified in the study:

1) The primary endpoint analysis was based on an intent-to-treat (ITT) population that included all randomized subjects (N=68). All secondary endpoints were analyzed only for this population.

2) A per protocol (PP) population was also identified (N=29), which consisted of ITT subjects who did not violate the protocol in any fundamental way and who were at least 70% compliant in taking study medication. Subjects who violated eligibility criteria, did not meet baseline MUCAI requirements, did not have baseline colonoscopy within 30 days of starting treatment, used prohibited medications, or did not provide complete follow-up

MUCAI information between study days 42 and 70 were excluded from the PP population and analysis. The primary endpoint analysis performed on this population was considered a secondary analysis, and no secondary endpoints were analyzed for this population.

The PK analysis set included subjects age 9 to 17 inclusive from each treatment group.

The safety population included all subjects who were randomized and received at least 1 dose of study medication and had at least 1 postbaseline safety assessment.

A summary of these populations is provided in the table below.

Table 8. Summary of Analysis Populations

Analysis Populations	Colazal 6.75 g/d (N=33)	Colazal 2.25 g/d (N=35)	Total (N=68)
Number (%) Subjects in ITT Population	33 (100%)	35 (100%)	68 (100%)
Number (%) Subjects in ITT Subset that Completed the Study and had Colonoscopies at Screening and Week 8	28 (85%)	25 (71%)	53 (78%)
Number (%) Subjects in the PP Population	15 (46%)	14 (40%)	29 (43%)
Number (%) subjects in the Safety population	33 (100%)	35 (100%)	68 (100%)
Number (%) subjects in the PK population	6 (18%)	6 (17%)	12 (18%)

Table adapted from Module 5, Vol. 16.1, 10.1, Table 5 & 11.1, Table 6

All statistical tests were 2-tailed at the 5% level of significance. Data from all study centers was pooled for analysis. Missing data were imputed for the ITT population using the last observation carried forward (LOCF) method for primary and secondary efficacy endpoints. Baseline observations were not carried forward if all subsequent measurements were missing. The PP analysis utilized observed cases; no imputation was performed.

6.1.4 Efficacy Findings

Disposition of Patients: In this study there were two main populations as summarized above. The following table lists the number and frequency of subjects in each population and lists the reasons that subjects were excluded from the PP population. It also lists the number and frequency of subjects that completed the study and had colonoscopies both at screening and at Week 8 (i.e., completed the study), and gives reasons for those patients that withdrew early from the study.

Table 9. Summary of Analysis Populations with Reasons for Withdrawal & Protocol Violations

Analysis Populations	Colazal 6.75 g/d (N=33)	Colazal 2.25 g/d (N=35)	Total (N=68)
Number (%) Subjects in ITT Population	33 (100%)	35 (100%)	68 (100%)
Number (%) Subjects in ITT Subset that Completed the Study and had Colonoscopies at Screening and Week 8	28 (85%)	25 (71%)	53 (78%)
Number (%) Subjects Withdrawn Early from the Study	5 (15%)	10 (29%)	15 (22%)
Adverse Event	1(3%)	3 (9%)	4 (6%)

Lack of Efficacy	**2 (6%)**	**2 (6%)**	**4 (6%)**
Subject Request to Withdraw or Other[a]	**2 (6%)**	**5 (14%)**	**7 (10%)**
Number (%) Subjects in the PP Population	**15 (46%)**	**14 (40%)**	**29 (43%)**
Number (%) Subjects Excluded from the PP Population	**18 (55%)**	**21 (60%)**	**39 (57%)**
Violated Any Exclusion Criteria	**12 (36%)**	**7 (20%)**	**19 (28%)**
Immunosuppressant drugs within 90 days	3 (9%)	2 (6%)	5 (7%)
5-ASA drugs within 7 days	9 (27%)	3 (9%)	12 (18%)
A dose of oral, IV, or rectal steroids within 14 days	6 (18%)	1 (3%)	7 (10%)
Other infectious, ischemic, or immunologic diseases with gastrointestinal involvement.	0 (0%)	1 (3%)	1 (1%)
Clinically significant hepatic disease (2 X ULN for ALT, AST, GGT, alkaline phosphatase, or total bilirubin)	0 (0%)	1 (3%)	1 (1%)
< 70% Study Drug Compliant[b]	**7 (21 %)**	**12 (34%)**	**19 (28%)**
Week 8 MUCAI Data Not Collected[c]	**5 (15%)**	**10 (29%)**	**15 (22%)**
Week 8 MUCAI Data Not Complete	**4 (12%)**	**8 (23%)**	**12 (18%)**
Did not Meet Inclusion Criteria	**3 (9%)**	**7 (20%)**	**10 (15%)**
> 30 days between colonoscopy and start of study medication[d]	3 (9%)	5 (14%)	8 (12%)
Did not meet baseline MUCAI requirements	0 (0%)	2 (6%)	2 (3%)
Used Prohibited Medications[e]	2 (6%)	2 (6%)	4 (6%)
Number (%) subjects in the Safety population	**33 (100%)**	**35 (100%)**	**68 (100%)**
Number (%) subjects in the PK population	**6 (18%)**	**6 (17%)**	**12 (18%)**

a. Subjects could have discontinued from the clinical trial at any time, and in any case in which emerging effects were of such a nature that the risk/benefit ratio was unacceptable to the subject or parent/guardian.
b. Subject took less than 70% of study medication for at least 1 of the visits. Assessed by the Investigator based on the amount of returned drug (subjects were asked to return used and unused daily blistercards at the Week 2, Week 4, and Week 8/Final visits)
c. Week 8 MUCAI data not collected between days 42 and 70.
d. The screening endoscopy with biopsy must have been performed within 17 days after the initial Screening Visit. Subjects who had already had an endoscopy with biopsy within 1 month of the Screening Visit did not have to have the procedure performed at study entry as long as adequate documentation diagnosing UC was on file in the study chart prior to randomization.
e. Concomitant use of anticholinergics, antidiarrheals, and other 5-ASA drugs was prohibited.

Table adapted from Module 5, Vol. 16.1, 10.1, Table 5 & 11.1, Table 6

Primary Efficacy Endpoint: The primary measure of efficacy was the proportion of subjects with clinical improvement, defined as a reduction from baseline in the MUCAI total score by at least 3 points at Week 8.

For the ITT group, 15 subjects (45%) in the Colazal 6.75 g/day group and 13 subjects (37%) in the Colazal 2.25 g/day group showed clinical improvement, with a difference in proportions of 8% and the p-value for this difference was 0.6227. This difference in response was thus not statistically

significant, but the study was not designed with enough power to show such a difference between the groups.

Table 10. Proportion of Subjects with Clinical Improvement (ITT Population)

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68	Differences in Proportions	p-value[a]
Proportion of subjects with Clinical Improvement	15 (45%)	13 (37%)	28 (41%)	8%	0.6227
95% CI[b]	28.1%, 63.6%	21.5%, 55.1%	29.4%, 53.8%	-15.0%, 31.7%	

[a] From 2-sided Fisher's Exact test with a significance level of 0.05.

[b] Exact (Clopper-Pearson) 2-sided 95% confidence interval.

Table from Module 5, Vol. 16.1, 11.4.1, Table 10.

When the primary efficacy endpoint was analyzed using the PP population, 8 subjects (53%) in the Colazal 6.75 g/day group and 7 subjects (50%) in the Colazal 2.25 g/day group showed clinical improvement, with no statistically significant difference in response (rate difference=3%; p=1.0000).

An additional analysis of clinical improvement was performed among subjects in the ITT group who did not terminate early (N=53). Clinical improvement was demonstrated in 15 of 28 (53.6%) subjects in the Colazal 6.75 g/day group and 13 of 25 (52%) subjects in the Colazal 2.25 g/day group. Once again, this was not a statistically significant difference (rate difference=1.6%; p=1.0000).

Medical Officer Comments:

The data above show a reasonable response rate for both low (2.25 g/day) and high (6.75 g/day) Colazal doses for the primary endpoint. The study was not designed with enough power to show any statistically significant difference between the two groups, so the key measure of efficacy, albeit an indirect one, lies in comparing these results to those seen in adults. When compared to the high-dose (approved dose) efficacy data from the original Colazal adult trial of 103 patients, the rates of response in children are similar as summarized in the table below.

Table 11 . Comparison of High- and Low-dose Colazal in adults and children (All numbers are % patients improved @ 8 weeks for the endpoint listed)

Endpoint analyzed	Low-dose (2.25 g/day) Colazal	High-dose (6.75 g/day) Colazal	p-value
Adults—Stool blood	**35%**	**55%**	**0.045**
Adults—Stool frequency	**25%**	**49%**	**0.013**
Adults—Sigmoidoscopy	**52%**	**74%**	**0.031**
Children—MUCAI decrease by at least 3 points (ITT)	**37%**	**45%**	**0.6227**
Children—MUCAI decrease by at least 3 points (PP)	**50%**	**53%**	**1.0000**
Children—MUCAI decrease by at least 3 points (ITT completed study)	**52%**	**54%**	**1.0000**

Table adapted from PI for Colazal-Figure 1 and Module 5, V. 16.1, 11.4.1, Table 10

The clinical response rate for the primary endpoint in children thus seems to correlate well with the response rate seen in adults (where the primary endpoint was reduction of rectal bleeding and improvement of at least one other assessed symptom) and would indicate that Colazal is similarly effective in improving symptoms in children and in adults.

An important distinction is apparent, however, between the child and adult populations. The adult study showed a statistically significant difference in patient response to high-dose Colazal versus low-dose. In the pediatric study, the percentage of patients experiencing improvement in the high-dose group was higher than that in the low-dose group, but the difference was not statistically significant. Despite this, it is interesting to note that in each population analyzed, the absolute percentage of responders is higher for the high-dose group. Perhaps with a larger sample size a statistically significant difference would have been seen.

Dr. Milton Fan is the statistical reviewer for this NDA supplement, and he notes in his review that the low-dose group had a higher withdrawal rate (10/35 [28.6%]) than the high-dose group (5/33 [15.2%]), and that this may be why the analysis of the ITT populations shows a greater difference in efficacy than the analysis of the populations who did not terminate from the study early.

For both the ITT population and the ITT population who completed the study, the sponsor performed an analysis of factors influencing the primary efficacy measurement of clinical improvement including age, sex, treatment, and MUCAI total score at baseline. Among both populations, MUCAI total score at baseline was the only statistically significant factor in influencing clinical improvement. The odds ratio indicated that subjects with higher baseline scores were likely to experience greater improvement.

Table 12. Analysis of Factors Influencing Clinical Improvement

Model/Variables	Parameter Estimate	Standard Error	p-value	Odds Ratio
ITT Population				
Logistic Regression Model[a]				
Treatment	-0.0609	0.5814	0.9166	0.9409
MUCAI Total Score at Baseline	0.7028	0.2655	0.0081	2.0195
ITT Population Who Did Not Terminate from the Study Early				
Logistic Regression Model[a]				
Treatment	0.0169	0.6038	0.9776	1.0171
MUCAI Total Score at Baseline	0.7384	0.2759	0.0074	2.0926

[a] A logistic regression model (Wald chi-square test) was used for this statistical analysis with a two-sided significance level of 0.05.

Table from Module 5, Vol. 16.1, 11.4.1, Table 11.

Medical Officer Comments:

This observation is not surprising given that patients who have more severe symptoms of UC would be expected to respond more robustly to treatment than those with milder symptoms.

Secondary Endpoints:

The secondary measures of efficacy were:

1- the proportion of subjects achieving remission, as evidenced by a score of zero (0) or one (1) (a score of 1 was only allowed on the stool frequency index) on the MUCAI at Week 8
2- change from baseline to Week 8 in the total score of the MUCAI
3- changes from baseline to Week 8 in the individual items (stool frequency, rectal bleeding, mucosal appearance, physician's rating of disease activity) of the MUCAI
4- change from baseline in pathology classification of histologic assessments of inflammation in colonic biopsies at Week 8
5- number of days abdominal cramps were reported on the individual subject diary card assessments in the 7 days prior to the Week 4 and Week 8 visits
6- number of days fever was reported on the individual subject diary card assessments in the 7 days prior to the Week 4 and Week 8 visits

The percentage rates for attainment of the various secondary endpoints have been summarized in the composite table below:

Table 13. Comparative table for secondary endpoints in pediatric ITT population

Secondary endpoint	**Colazal 6.75 g/day (N=33)**	**Colazal 2.25 g/day (N=35)**	**Difference in Proportions/ Scores**	**p-value**
Proportion of subjects achieving remission	12%	9%	3%	0.7053
Change from baseline to Week 8 in MUCAI total score	-2.6	-2.4	0.1	0.7185
Percent improved from baseline to Week 8/ stool frequency	33%	23%	10%	0.8177
Percent improved from baseline to Week 8/ rectal bleeding	64%	54%	10%	0.8038
Percent improved from baseline to Week 8/ mucosal appearance	61%	46%	15%	0.5389
Percent improved from baseline to Week 8/ physician rating	39%	31%	8%	0.7687
Percent improved from baseline to Week 8/ pathology classification	24%	9%	15%	0.4433
Change from baseline to Week 8 in Pathology Classification	-0.3	-0.2	0.1	0.6132
Number of days of abdominal cramps @Week 4	2.6	3.2	0.6	0.5381
Number of days of abdominal cramps @ Week 8	2.6	3.1	0.5	0.4190
Number of days of fever @ Week 4	0.0	0.3	0.3	0.1538
Number of days of	0.0	0.4	0.4	0.1538

fever @ Week 8				
Number of days of fever AND abdominal cramps @ Week 4	0.0	0.3	0.3	0.1538
Number of days of fever AND abdominal cramps @ Week 8	0.0	0.4	0.4	0.1538

Table adapted from Module 5, Vol. 16.1, 11.4.2, Table 12-14, 16-17

Medical Officer Comments:

No statistically significant difference between the high-dose and low-dose populations was shown for any of the secondary endpoints. It is interesting to note, however, that each of the endpoints showed a higher rate of response, a greater decrease from baseline scores, or fewer mean days of symptoms for the high-dose group compared to the low-dose group. With a larger sample size, it is possible that a statistically significant difference in efficacy would be seen.

One other set of secondary endpoints analyzed was the change from baseline to Week 8 in MUCAI individual items (absolute change in score as opposed to percent improved which is listed in the table above.) These results are summarized in the table below.

Table 14. Change from Baseline to Week 8 in MUCAI Individual Items (ITT Population)

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68	p-value[a]
Stool Frequency				
Baseline Mean (SD)	0.8 (0.74)	0.8 (0.86)	0.8 (0.80)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	0.5 (0.87)	0.3 (0.47)	0.4 (0.71)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-0.2 (0.95)	-0.3 (0.66)	-0.3 (0.81)	0.8195
Rectal Bleeding				
Baseline Mean (SD)	1.6 (0.71)	1.6 (0.77)	1.6 (0.74)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	0.6 (0.69)	0.6 (0.88)	0.6 (0.78)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-1.0 (0.98)	-0.9 (0.95)	-0.9 (0.96)	0.5280
Mucosal Appearance				
Baseline Mean (SD)	1.9 (0.70)	2.0 (0.86)	2.0 (0.78)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	1.1 (0.94)	1.1 (0.72)	1.1 (0.83)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-0.9 (0.88)	-0.9 (0.91)	-0.9 (0.88)	0.9037
Physician's Rating of Disease Activity				
Baseline Mean (SD)	1.4 (0.56)	1.4 (0.61)	1.4 (0.58)	
Week 8/Final	n=29	n=27	n=56	
Mean (SD)	0.9 (0.74)	1.0 (0.73)	0.9 (0.74)	
Change from Baseline	n=29	n=27	n=56	
Mean (SD)	-0.5 (0.78)	-0.4 (0.80)	-0.5 (0.79)	0.8231

SD = standard deviation

[a] Based on a Wilcoxon rank-sum test comparing treatment groups.

Table from Module 5, Vol. 16.1, 11.4.2, Table 15.

Medical Officer Comments:

These changes from baseline are small, often less than one point. If the mean change for both groups taken together is used, the clinical significance of these changes would be as follows:

- **Stool frequency=no difference in severity (decrease of 0.4 point in severity)**
- **Rectal bleeding=decrease from streaks of blood to no blood (decrease of one point in severity)**

- **Mucosal appearance=decrease from pinpoint ulceration and moderate friability to edematous mucosa with granularity and mild friability without ulceration (decrease of 0.9 point in severity)**
- **Physician rating=decrease from mild-to-moderate to normal-to-mild (decrease of 0.5 point in severity)**

There was no significant difference between the two treatment groups for these endpoints. These clinical changes would thus be small, but noticeable by the physician and the patient.

An analysis of secondary endpoints for the ITT population who completed the study showed similar results in that no significant difference between the two groups could be demonstrated for any of the endpoints.

Medical Officer Comments:
Given the even smaller sample size for this population, it is not surprising that no statistical difference could be shown for these variables.

6.1.5 Clinical Microbiology

This section is not applicable.

6.1.6 Efficacy Conclusions

The study demonstrated efficacy in terms of response rates for the primary endpoint (clinical improvement as evidenced by a reduction of MUCAI score by at least 3 points at 8 weeks) for both low- and high-dose Colazal. Normal response rates for placebo in this class of drugs are around 20%, and both dose populations experienced a better response at 37% (low-dose) and 45% (high-dose). These efficacy rates are comparable to the adult (approved) high-dose efficacy rates seen in the original Colazal study (55% for stool blood, 49% for stool frequency, and 74% for sigmoidoscopy.)

The difference in response between the two pediatric populations was not statistically significant; however, this was a very small study and it is possible that with a larger population a statistical difference could be obtained.

The study demonstrated no significant differences between the two doses in any of the secondary endpoints; however, the high-dose population had consistently better numerical scores than the low-dose population for all variables assessed. Both doses showed reasonable improvement for all variables.

In summary, this reviewer feels that the study demonstrated sufficient efficacy for both doses to support the proposed indication for Colazal 750 mg capsules—1 capsule three times daily OR 3 capsules three times daily for the treatment of mildly to moderately active ulcerative colitis in children 5-17 years of age.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths were reported during the study.

7.1.2 Other Serious Adverse Events

Four subjects (2 in each treatment group) experienced serious adverse events (SAEs). None of the events were considered by the Investigator to be related to study drug. The four case narratives are summarized in the table below.

Table 15. Patient Narratives of Serious Adverse Events in Colazal Pediatric Trial

	Subject#	AE Preferred Term	Narrative Synopsis
Colazal 6.75 g/day group			
1	0337-0002	Colitis ulcerative	17-yo male w/ UC diagnosed 12 Apr 05. Pt started Colazal 20 Jul 05 and completed course 12 Sep 05. On (b) (6) pt was hospitalized for **UC flare** which resolved (b) (6) The investigator considered this a **moderate** SAE which was **unrelated** to therapy.
2	0576-0002	Depression	17-yo female w/ UC diagnosed 4 Jan 06. Pt had history of depression since 2004. Pt started Colazal 5 Jan 06 and completed course 28 Feb 06. On (b) (6) the subject reported increased **depression**. Study medication was interrupted and the pt was hospitalized for depression. The event was considered resolved (b) (6) The investigator considered this a **severe** SAE which was **unrelated** to therapy.

Colazal 2.25 g/day group			
3	0097-0002	-Abd. Pain -Hematochezia -Pyrexia -Blood albumin decreased -Hematocrit decreased	5-yo female w/ UC diagnosed 17 Oct 03. Pt started Colazal on 10 May 05 and completed course 16 May 05. On 13 May 05 the subject had **UC flare** and study med was permanently stopped. The event resolved by 16 May 05. On (b) (6) the subject had **pyrexia, abd. Pain, hematochezia, decreased albumin at 2.0 g/dL (normal= 4-5.3 g/dL), and decreased Hct at 27.7% (normal= 31.6-40.4%).** Hospitalization was required and these SAEs were considered unresolved at the time of the subject's withdrawal from the study on (b) (6) The investigator felt that these events were **severe** SAEs (except the pyrexia which was **moderate**) but were considered **unrelated** to therapy.
4	0433-0004	Clostridial infection	14-yo female w/ UC diagnosed 11 July 01. Pt started Colazal on 9 Nov 05 and completed course 27 Dec 05. On (b) (6) the subject was diagnosed with a clostridial infection. The pt was hospitalized and the event was considered resolved on (b) (6) The investigator felt that this SAE was **moderate** and **unrelated** to therapy.

Table adapted from Module 5, Vol. 16.1, 12.3.1, Table 32 and pages 98-101.

Medical Officer Comments:

This reviewer agrees that these serious adverse events were likely not related to the study drug. The first case presented (UC flare) was likely due to lack of efficacy of the medication or to the withdrawal of the medication. The second case (depression) occurred in a patient with a prior history of depression, and this adverse event is not listed as a common AE for other mesalamine products. The third case was similar to the first in that a flare of the patient's UC occurred while on Colazal. It is possible that this flare occurred due to lack of efficacy of the study drug, or to a lack of adequate duration of treatment. In any case, the AE does not appear to be the result of the medication. Finally, the fourth case (clostridial infection) occurred in a patient who was on several medications that could have predisposed her to the infection. The patient was being treated with prednisone, Immodium, and Levaquin. The prednisone could have weakened her immune system, the Immodium would have slowed emptying of the bowel, and the Levaquin would have caused disruption of the normal colonic flora. All of these factors could have combined to allow the clostridial infection to occur. While this cannot be definitively proven, it is far more likely that these agents contributed to the SAE than the Colazal.

In summary, out of 68 patients exposed to Colazal in the study, 4 (5.9%) suffered a serious adverse event, but none of these are believed by the reviewer to be caused by the study drug.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Of the 68 total patients in the study, 53 (78%) completed the study and had colonoscopies at screening and at Week 8. The reasons for dropouts are listed in the table below.

Table 16. Summary of Dropouts

Analysis Populations	**Colazal 6.75 g/day (N=33)**	**Colazal 2.25 g/day (N=35)**	**Total (N=68)**
Number (%) Subjects in ITT Population	33 (100%)	35 (100%)	68 (100%)
Number (%) Subjects in ITT Subset that completed the study	28 (85%)	25 (71%)	53 (78%)
Number (%) Dropouts from the study	**5 (15%)**	**10 (29%)**	**15 (22%)**
Adverse Event	**1 (3%)**	**3 (9%)**	**4 (6%)**
Lack of Efficacy	2 (6%)	2 (6%)	4 (6%)
Subject Request to Withdraw or Other	2 (6%)	5 (14%)	7 (10%)

Table adapted from Module 5, Vol. 16.1, 10.1, Table 5.

7.1.3.2 Adverse events associated with dropouts

Four subjects discontinued treatment because of adverse events. One subject in each treatment group discontinued due to adverse events that were considered by the investigator to be related to the study drug.

Table 17. Patient Narratives of Dropouts Due to Adverse events

	Subject #	**AE Preferred Term**	**Narrative Synopsis**
			Colazal 6.75 g/day group
1	0528-0001	-Abdominal pain -Urticaria	11 yo female with UC diagnosed 16 Mar 05. Colazal treatment began 9 Apr 05, and ended 12 Apr 05. The first day of treatment the patient developed **abdominal pain and urticaria**. Study medication was permanently **discontinued** and the symptoms resolved by 13 Apr 05. The investigator believed that both symptoms were **moderate** and **related** to study therapy.
			Colazal 2.25 g/day group
2	0097-0002	-Colitis ulcerative -Abd. Pain -Hematochezia -Pyrexia -Blood albumin	5-yo female w/ UC diagnosed 17 Oct 03. Pt started Colazal on 10 May 05 and completed course 16 May 05. On 13 May 05 the subject had **UC flare** and study med was permanently **stopped**. The event resolved by 16 May 05. On (b) (6) the subject had **pyrexia, abd. Pain, hematochezia, decreased albumin at 2.0 g/dL (normal= 4-5.3 g/dL), and decreased Hct at 27.7%**

		decreased -Hematocrit decreased	**(normal= 31.6-40.4%).** Hospitalization was required and these SAEs were considered unresolved at the time of the subject's withdrawal from the study. On (b) (6) The investigator felt that these events were **severe** SAEs (except the pyrexia which was **moderate**) but were considered **unrelated** to therapy.
3	0468-0001	Frequent bowel movements	12-yo female with UC diagnosed 23 Sept 05. Treatment began 4 Oct 05 and was completed 4 Nov 05. On 21 Oct 05 the pt developed **frequent bowel movements**. On 4 Nov 05 the investigator decided to discontinue the subject due to the adverse event, and study medication was permanently **discontinued**. The investigator believed the AE to be **moderate** and **related** to the therapy.
4	0508-0001	Rectal hemorrhage	11-yo female with UC diagnosed 23 August 05. Treatment began 18 Oct 05, with the last dose given 23 Oct 05. On 22 Oct 05 the subject experienced a **rectal hemorrhage**. Study medication was permanently **stopped**. The investigator felt that the hemorrhage was **moderate** and **unrelated** to study therapy.

Table adapted from Module 5, Vol. 16.1, 12.3.2, Table 33 and pages 102-103.

Medical Officer Comments:

The reviewer concurs with the investigator's findings regarding the probable etiology of these events. The first event is concerning for an allergic reaction and the medication was stopped appropriately. The second and fourth subjects appear to have had AEs which are common to those patients with UC. The first appears to be a full-fledged flare of the disease while the fourth is one symptom only (rectal hemorrhage). Neither of these AEs are common reactions to the salicylate pharmacologic class. The third patient, however, developed frequent bowel movements. Diarrhea is a known adverse reaction of Dipentum (olsalazine), another salicylate drug. In the adult Colazal study, approximately 5% of the subjects complained of diarrhea, while 9% of the pediatric subjects reported the same. While "diarrhea" is not always equivalent to "frequent bowel movements," it is reasonable to attribute the patient's symptoms to the study drug based on the side effect profile of other salicylates and the overall incidence of this adverse reaction in the study populations.

These AEs leading to dropouts were some of the common AEs in the general safety population as well, especially abdominal pain which was reported in 8 patients (12% of safety population), and diarrhea which was reported in 6 patients (9%).

In summary, the low-dose group had 3 dropouts due to AE (8.6%) and the high-dose group had 1 dropout due to AE (3%). The fact that the high-dose group had fewer AE-related dropouts than the low-dose group helps support the safety of the high-dose form in this population.

7.1.3.3 Other significant adverse events

Adverse events of special interest included any event involving renal or hepatic toxicity and the

specific events of pericarditis, myocarditis, pancreatitis, gastritis, and cholecystitis. No cardiovascular or hepatic adverse events and no cases of pancreatitis, gastritis, or cholecystitis were reported during this study. Four teenage female subjects had events of blood urine (verbatim terms "blood in urine" or "microscopic blood in urine")--2 occurred only during the pretreatment period, one occurred at pretreatment and continued throughout the subject's course of Colazal, and one occurred prior to treatment, resolved at Week 2 testing, and recurred later in the study.

The table below summarizes these adverse events.

Table 18. Patient Narratives of Adverse Events of Special Interest

	Subject #	**AE Preferred Term**	**Narrative Synopsis**
1	0281-0001	-Blood albumin decreased -Blood alkaline phosphatase decreased	13-yo male w/ UC diagnosed 14 Apr 05. Pt began Colazal 6.75 g/day on 2 Jul 05 and completed course 16 Aug 05. On 17 Aug 05 the pt experienced **decreased albumin and decreased alkaline phosphatase**. At the final visit on 22 Aug 05 the subject's albumin was 2.7 g/dL (nl=4-5.3 g/dL) and his alk phos was 79 U/L (nl=200-495 U/L). The subject's screening values for these labs were low as well (3.8 g/dL and 105 U/L, respectively.) In addition, GGT was 37 U/L at randomization, but this was considered clinically insignificant by the investigator, and decreased to normal by Week 8. The events (low albumin and alk phos) were considered not resolved at study completion. The investigator felt that these changes were **mild** and **unrelated** to study therapy.
2	0281-0002	Blood urine present	17-yo female w/ UC diagnosed Aug 02. Pt started Colazal 2.25 g/day on 1 Jul 05 and completed course 16 Aug 05. On 17 Aug 05 the subject had **blood in urine**. Final visit (24 Aug 05) UA showed 2+ blood in urine. Baseline UA had also showed 2+ blood in urine but Week 2 UA was negative for blood. The event was considered not resolved at study completion. The investigator felt that this change was **mild** and **unrelated** to study therapy.
3	0429-0001	Blood urine present	15-yo female with UC diagnosed 22 Nov 05. Pt started Colazal 2.25 g/day 19 Dec 05 and completed course 18 Jan 06. The pt was withdrawn from the study on this date due to lack of efficacy. On 12 Dec 05 (Study day -7), the subject had **blood in urine.** (2+ on Randomization UA). The subject had **not** yet taken any Colazal. Additional UA's were not performed, and the event was considered not resolved at study withdrawal. The investigator deemed the severity **not applicable** and the AE **unrelated** to any study therapy.

4	0433-0004	Blood urine present	14-yo female with UC diagnosed 11 Jul 01. Pt started Colazal 2.25 g/day on 9 Nov 05 and completed course 27 Dec 05. On 28 Oct 05 (Study day -12) the subject had **blood in urine** (2+ on Randomization UA). The subject had **not** yet taken any Colazal. UA was repeated on 2 Nov 05 and was negative; the event was thus considered resolved. The investigator deemed the severity **mild** and the AE **unrelated** to any study therapy.
5	0576-0002	Hematuria	17-yo female with UC diagnosed 4 Jan 06. Pt started Colazal 6.75 g/day 5 Jan 06 and completed course 28 Feb 06. At the randomization visit on 22 Dec 05 (Study day -14), the subject experienced **hematuria**. UA obtained at that visit indicated 2+ blood in urine. The subject had **not** yet taken any Colazal. UA results at Week 2 showed 1+ blood and at Week 8 showed 2+ blood; the event was considered not resolved at study completion. The investigator deemed the hematuria **moderate** and **unrelated** to study therapy.

Table adapted from Module 5, Vol. 16.1, 12.3.3, 104-107

Medical Officer Comments:

The reviewer concurs with the investigator's opinion that none of the above AEs were likely related to the study drug. The first case was a worsening of lab values that were already abnormal at the beginning of the study, which seems to indicate a pre-existing process such as the patient's UC causing the abnormal lab values. It is theoretically possible that the study drug had a role in worsening the values, but if this is the case then it seems to be clinically insignificant given that the values changed only mildly with 8 weeks of drug treatment.

The second case was hematuria which was intermittent throughout the study, including at baseline. Since no worsening of the hematuria occurred with treatment, it appears that this condition was pre-existing as well.

The third and fourth cases were similar in that both patients experienced hematuria prior to taking any Colazal. It does not appear, therefore, that the study drug contributed to this AE in either of these patients.

The final case was similar to the second in that the subject had hematuria at baseline which continued throughout the study. This case again appears to be a pre-existing condition and it is unlikely that the study drug had any effect on this AE.

The most likely cause of this hematuria, given the timing of the hematuria and the sex and ages of the patients, is menstrual bleeding, but of course this can not be definitively proven by the data that is present here.

7.1.4 Other Search Strategies

Investigators were instructed to monitor each subject for specific safety concerns including renal toxicity, hepatic toxicity, pericarditis, myocarditis, pancreatitis, gastritis, and cholecystitis. No cases of any of these entities were detected during the safety evaluation for this study.

Medical Officer Comments:
These events were specifically mentioned in the written request (WR) issued to the sponsor as events that should be monitored for closely during the study. These are AEs of concern to the agency because of their occurrence in other mesalamine products. The fact that none of these AEs occurred in the pediatric study supports the safety of the product.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

AEs were recorded throughout the study for all patients in the safety population (N=68).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor categorized events appropriately and used the Medical Dictionary for Regulatory Activities (MEDRA) to classify preferred AE terms.

7.1.5.3 Incidence of common adverse events

One or more treatment-emergent adverse events were reported by 42 (62%) subjects [23(70%) of subjects in the 6.75 g/day group and 19(54%) of subjects in the 2.25 g/day group.] The table below shows the frequencies of the AEs reported by 2 or more subjects in either group.

Table 19. Treatment-Emergent AEs Reported by 2 or More Subjects in Either Treatment Group

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68
	N (%)	N (%)	N (%)
Subjects with ≥ 1 Adverse Event	**23 (70%)**	**19 (54%)**	**42 (62%)**
Gastrointestinal Disorders	13 (39%)	17 (49%)	30 (44%)
Abdominal pain upper	3 (9%)	6 (17%)	9 (13%)
Abdominal pain	4 (12%)	4 (11%)	8 (12%)
Vomiting	1 (3%)	6 (17%)	7 (10%)
Diarrhea	2 (6%)	4 (11%)	6 (9%)
Colitis ulcerative	2 (6%)	2 (6%)	4 (6%)
Hematochezia	0 (0%)	3 (9%)	3 (4%)
Nausea	0 (0%)	3 (9%)	3 (4%)
Stomatitis	0 (0%)	2 (6%)	2 (3%)
General Disorders and Administration Site Conditions	2 (6%)	6 (17%)	8 (12%)
Pyrexia	0 (0%)	4 (11%)	4 (6%)
Fatigue	2 (6%)	1 (3%)	3 (4%)
Infections and Infestations	7 (21%)	6 (17%)	13 (19%)
Nasopharyngitis	3 (9%)	1 (3%)	4 (6%)
Influenza	1 (3%)	2 (6%)	3 (4%)
Nervous System Disorders	6 (18%)	6 (17%)	12 (18%)
Headache	5 (15%)	5 (14%)	10 (15%)
Reproductive System and Breast Disorders	2 (6%)	0 (0%)	2 (3%)
Dysmenorrhea	2 (6%)	0 (0%)	2 (3%)
Respiratory, Thoracic and Mediastinal Disorders	4 (12%)	3 (9%)	7 (10%)
Cough	0 (0%)	2 (6%)	2 (3%)
Pharyngolaryngeal pain	2 (6%)	0 (0%)	2 (3%)

Table from Module 5, Vol. 16.1, 12.2.3, Table 31.

Medical Officer Comments:

These AEs are similar to those experienced by the adult study population for Colazal. In addition, they are similar to those listed for the other mesalamine products already approved for the treatment of UC. This reviewer compared the frequency of these adverse events for the pediatric and adult populations in the following table.

Table 20. Comparison of Adult and Pediatric Adverse Events for Colazal

Adverse Events (treatment-emergent)	**# of Adults (%) @ 6.75 g/day**	**# of Children (%) @ 6.75 g/ day**	**# of Children (%) @ 2.25 g/ day**
Headache	22 (8)	5 (15)	5 (14)
Upper abdominal pain	0 (0)	3 (9)	6 (17)
Abdominal pain	16 (6)	4 (12)	4 (11)
Vomiting	11 (4)	1 (3)	6 (17)
Diarrhea	14 (5)	2 (6)	4 (11)
UC	0 (0)	2 (6)	2 (6)
Nasopharyngitis	0 (0)	3 (9)	1 (3)
Pyrexia	0 (0)	0 (0)	4 (11)
Nausea	14 (5)	0 (0)	3 (9)
Respiratory infection	9 (4)	0 (0)	0 (0)
Arthralgia	9 (4)	0 (0)	0 (0)

Table adapted from Module 5, Vol. 16.1, 12.3.3, Table 31 and PI for Colazal, Table 1.

The percentages of cases in children are higher for many of these AEs, specifically headache, upper abdominal pain, abdominal pain, vomiting, and diarrhea. The reason for this is not entirely clear. It is possible that the children or their parents were more forthcoming in reporting symptoms to the investigator, or that these symptoms simply occur more frequently in this population (especially diarrhea, vomiting, and abdominal pain). Whatever the cause, it does not appear that the incidence of these AEs is high enough to raise any serious safety concerns at this time.

It is also interesting to note that many of the AEs were reported more frequently in the low-dose population, especially upper abdominal pain, vomiting and pyrexia (17% vs. 9%, 17% vs. 3%, and 11% vs. 0%, respectively). This would seem to indicate a low likelihood of relationship with the study drug for these AEs, since a higher dose would be expected to induce a greater frequency of these events if they were drug-related. In fact, many of these AEs that are higher for the low-dose group could be a sign of decreased efficacy with the lower dose, such as upper abdominal pain, diarrhea, and pyrexia. These are all symptoms of ulcerative colitis flares, which would likely be more frequent with a less efficacious dose. In any case, this finding is supportive of the relative safety of the 6.75 g/day dose; however, the difference seen in these AEs between the two groups is not of great significance given the small size of the study populations.

7.1.5.4 Common adverse event tables

Please see the tables above in the prior section.

7.1.5.5 Identifying common and drug-related adverse events

The most common adverse events were headache (5 subjects) and abdominal pain (4 subjects) in the 6.75 g/day group and abdominal pain upper (6 subjects), vomiting (6 subjects), headache (5 subjects), abdominal pain (4 subjects), diarrhea (4 subjects), and pyrexia (4 subjects) in the 2.25 g/day group. All other adverse events were reported by 3 or fewer subjects in either treatment group. Please see Section 7.1.5.3 for a discussion of these events and their relationship to the adult study population.

The following table summarizes the AEs in each treatment group that were considered by the investigator to be related to Colazal treatment.

Table 21. DRUG-RELATED Adverse Events for Pediatric Study Groups

Adverse Event	**Colazal 6.75 g/ day**	**Colazal 2.25 g/ day**
Abdominal pain	2 (6%)	1 (3%)
Abdominal pain upper	1 (3%)	3 (9%)
Fecal incontinence	1 (3%)	0
Flatulence	1 (3%)	0
Loose stools	1 (3%)	0
Headache	1 (3%)	3 (9%)
Urticaria	1 (3%)	0
Vomiting	0	4 (11%)
Nausea	0	2 (6%)
Ulcerative colitis	0	1 (3%)
Constipation	0	1 (3%)
Diarrhea	0	1 (3%)
Frequent bowel movt.	0	1 (3%)
Hematochezia	0	1 (3%)
Influenza	0	1 (3%)

Table adapted from Module 5, Vol. 16.1, 12.2.3, page 97.

Medical Officer Comments:

The symptoms and signs which comprise these AEs are seen quite frequently in patients with UC, so it is difficult to definitively link the events with the study drug. Nevertheless, the investigator felt that each of these events were linked to the study drug's use. Even if all of these events are drug-related, however, the incidence of each event is acceptably small, and all treatment-related AEs were mild or moderate in severity (i.e., no serious adverse events were believed to have been caused by the study drug.)

7.1.6 Less Common Adverse Events

Less common adverse events are listed in Table 19 above. In summary, the least common events (≤3% of the total safety population) included stomatitis, dysmenorrhea, cough, and pharyngolaryngeal pain.

Medical Officer Comments:
Given the relatively low incidence of these events and the fact that all of them occur frequently in the general pediatric population, they are unlikely to be related to the study drug.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine laboratory tests (blood chemistry, hematology, urinalysis, and creatinine clearance) were collected at screening and at Week 8. Minor increases and decreases from baseline to Week 8/ Final visit in mean values for lab parameters were observed in both treatment groups, none of which were considered by the sponsor's medical monitor to be clinically meaningful. Further analysis is provided below.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Routine laboratory tests (blood chemistry, hematology, and urinalysis) were collected at screening and at Week 8. Minor increases and decreases from baseline to Week 8/Final visit in median values for laboratory parameters were observed in both treatment groups, none of which were considered by the Salix Medical Monitor to be clinically meaningful.

Medical Officer Comments:
Based on this information, the study drug did not appear to affect median lab values in any clinically meaningful way.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Shifts in individual lab values from **normal** at baseline to **abnormal** at Week 8 for chemistry, hematology, and urinalysis were compiled and are presented in the table below. All shifts were minimally out of range, and none were considered by the sponsor's medical monitor to be clinically meaningful.

Table 22. Shifts in Laboratory Parameters from Normal at Baseline to Abnormal at Week 8

Shifts from normal at baseline	Colazal 6.75 g/day Group	Colazal 2.25 g/day Group
To low serum albumin	0297-0004: from 4.2 g/dL to 3.7 g/dL 0461-0003: from 4.7 g/dL to 3.3 g/dL 0552-0002: from 4.2 g/dL to 3.9 g/dL	0281-0002: from 4.6 g/dL to 3.9 g/dL; 0433-0001: from 4.0 g/dL to 3.5 g/dL
To high alkaline phosphatase	0337-0003: from 86 U/L to 166 U/L	0461-0005: from 371 U/L to 525 U/L 0097-0003: from 521 U/L to 496 U/L[a]
To high AST	0337-0003: from 43 U/L to 46 U/L	
To high GGT	--	0001-0001: from 22 U/L to 26 U/L; 0097-0006: from 24 U/L to 32 U/L; 0281-0002: from 22 U/L to 31 U/L; 0433-0004: from 23 U/L to 35 U/L
To low hemoglobin	0461-0003: from 13.0 g/dL to 10.5 g/dL	--
To low platelets	0461-0003: from 320 x10^9/L to 182 x10^9/L	0576-0001: 235 x10^9/L to 200 x10^9/L
To low RBCs	0528-0002: from 4.01 x10^{12}/L to 3.88 x10^{12}/L	--

[a] Subject's unflagged baseline value was higher than the Visit 8 flagged value; subject had a birthday between baseline and Visit 8 and moved into a different normal range age group (see normal ranges in Listing 16.4.2, Appendix 16.2.6).

Table from Module 5, Vol. 16.1, 12.4.2.2, Table 34.

Medical Officer Comments:

All subjects had normal urine pH and specific gravity at baseline and Week 8, and the above changes for the lab parameters are not concerning to this reviewer. Some of the changes, such as albumin decrease and hemoglobin/ RBC decrease would be fairly common in patients with UC.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Marked outliers are listed in the table below. These patients had lab values that were flagged by the central laboratory as "high panic" or "low panic."

Table 23. Subjects with One or More Panic-Range Laboratory Values

Treatment Group, Subject Number/ Age/Gender	Test	Visit	Date of Specimen	Result		Normal Range
6.75 g/day						
0281-001/ 13 years/male	Random serum glucose	Randomization	28 Jun 2005	38 mg/dL	LP	70 to 141 mg/dL
		Week 8/Final	17 Aug 2005	53 mg/dL	L	
2.25 g/day						
0311-0001/ 12 years/male	Platelets	Randomization	18 Aug 2005	537 x 10^9/L	H	179 to 360 x 10^9/L
		Week 8/Final	06 Sep 2005	829 x 10^9/L	HP	
0410-0001/ 12 years/female	Hemoglobin	Randomization	28 Sep 2004	7.2 g/dL	LP	10.9 to 14.6 g/dL
		Week 8/Final	29 Nov 2004	10.9 g/dL	NR	
0433-0001/ 16 years/female	Hemoglobin	Randomization	11 Nov 2004	7.8 g/dL	LP	10.9 to 14.6 g/dL
		Week 8/Final	06 Dec 2004	6.5 g/dL	LP	
0549-0002/ 16 years/male	WBC	Randomization	11 Jan 2006	21.58 x 10^9/L	HP	4.4 to 10.5 x 10^9/L
		Week 8/Final	09 Mar 2006	9.39 x 10^9/L	NR	

H = high; HP = high panic; L = low; LP = low panic; NR = normal range; WBC = white blood cell

Table from Module 5, Vol. 16.1, 12.4.2.3, Table 35.

Subject 0433-0001 (2.25 g/day group) had a hemoglobin of 7.8 g/dL at randomization and a hemoglobin of 6.5 g/dL on Day 26 (normal range: 10.9 to 14.6 g d/L). The investigator considered these values clinically significant, related to the patient's chronic anemia, and not reportable as an adverse event. Subject 0433-0001 withdrew voluntarily after taking 6 days of study medication.

Subject 0311-0001 (2.25 g/day group) had a high platelet count of 537 x 10^9/L at randomization and a high platelet count of 829 x 10^9/L on Day 20. The investigator considered these high platelet counts to be clinically significant and due to the underlying ulcerative colitis. Subject 0311-0001 withdrew due to lack of efficacy after taking 4 days of study medication.

Subject 0410-0001 (2.25 g/day group) had a hemoglobin of 7.2g/dL at randomization that the investigator deemed clinically significant, but did not consider to be an adverse event. The value rose to 10.9 g/dL at Week 8.

Subject 0549-0002 (2.25 g/day group) had a white blood cell count of 21.58 x 10^9/L at randomization that the investigator did not consider clinically significant. This value decreased to 9.39 x 10^9/L at Week 8.

Subject 0281-0001 had a "low panic" value for glucose of 38 mg/dL at baseline, which the investigator considered possibly due to lab error. This value was prior to beginning the study medication, and the value rose to 53 mg/dL by Week 8.

Medical Officer Comments:
These "panic" values do not appear to represent a significant safety signal for the study drug. The low blood sugar was pre-treatment, the high platelet counts are not generally clinically meaningful, the low hemoglobin resolved in one case, and the high white blood cell count resolved as well. The only value which worsened that is clinically meaningful is the hemoglobin for Subject 0433-0001, which declined from 7.8 g/dL to 6.5 g/dL. The reviewer concurs with the investigator's belief that the shift was likely due to the patient's chronic anemia, a condition which is not unusual in patients with UC. Also, the patient withdrew from the study after only 6 days of study medication, so it is unlikely that the study medication contributed directly to the patient's worsening hemoglobin.

One patient who dropped out of the study had known lab abnormalities. Pt 0097-0002 had low serum albumin and low hematocrit. Please see Section 7.1.3.1 for more information.

7.1.7.4 Additional analyses and explorations

Subject 0281-0001 (6.75 g/day group) had adverse events of decreases in blood albumin and blood alkaline phosphatase not considered related to study drug. This subject also had a blood sugar of 38 mg/dL at randomization (Table 23), which the investigator considered as possibly due to a lab error. In addition, GGT was 37 U/L at randomization, which the investigator considered clinically significant, and decreased to normal by Week 8. AST, ALT, and bilirubin levels were normal at randomization and at the Week 8 visit.

7.1.7.5 Special assessments

There were no special assessments performed.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Physical exams (including vital signs) were recorded at screening and at each visit (where available). These measurements included heart rate, blood pressure, respiratory rate, temperature, height, and weight.

Medical Officer Comments:
The vital signs chosen for measurement were appropriate for the pediatric population.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

N/A

7.1.8.3 Standard analyses and explorations of vital signs data

No clinically meaningful changes occurred in blood pressure, heart rate, or respiratory rate for either treatment group. Three 2.25 g/day subjects experienced adverse events of pyrexia, and 1 2.25 g/day subject experienced a serious adverse event of pyrexia. One 6.75 g/day subject experienced an adverse event of increased body temperature.

There were no clinically meaningful shifts in height or weight for subjects in either treatment group. (One subject's weight increased from 41.5 lbs at Randomization to 90.2 lbs at Week 8. It was later confirmed that the weight at Randomization was incorrectly noted on the CRF and that the correct weight was 91.3 lbs.)

Medical Officer Comments:

The patient who experienced the SAE is Subject 0097-0002 whose case is discussed above under Section 7.1.2. The investigator classified her pyrexia as moderate despite the fact that the event was classified as severe. As mentioned above, the most likely cause of the pyrexia was the patient's UC flare.

The remainder of the changes in vital signs are not concerning to this reviewer. It is not clear why the subject on high-dose Colazal was classified as having "increased body temperature" while the other subjects were categorized as having "pyrexia." It is likely that the high-dose patient's temperature was increased above baseline but was not high enough to be called "pyrexia," which typically is defined as a core temperature (rectal or oral) of 100.5 ^{0}F. Interestingly, the incidence of pyrexia was 6% in the low-dose group, but was 0% in the high-dose group. One possible explanation for this observation is that those patients receiving the high-dose Colazal had better control of their disease and thus were less likely to experience fever and other signs of UC.

The timeframe for this study was too short to demonstrate any effect on height. Also, the sponsor did not provide detailed information on the methods used to standardize the measurement of heights and weights (i.e., whether replication of measurements occurred, whether weights were obtained in unclothed subjects on calibrated scales, and whether heights were measured via stadiometry). The sponsor does state, however, that "all measurements of efficacy, PK, and safety (which included the heights and weights) used in this study were considered standard."

7.1.8.4 Additional analyses and explorations

N/A

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No ECG's were obtained for this study population.

Medical Officer Comments:
This is acceptable not to monitor ECGs since the mesalamine products do not typically cause electrolyte disturbances which could predispose to arrythmias.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

N/A

7.1.9.3 Standard analyses and explorations of ECG data

N/A

7.1.9.4 Additional analyses and explorations

N/A

7.1.10 Immunogenicity

Colazal is not a protein and does not demonstrate evidence for immunogenicity.

7.1.11 Human Carcinogenicity

Non-clinical carcinogenicity studies were carried out in the development phase of Colazal prior to adult trials being undertaken. In a 24-month rat (Sprague Dawley) carcinogenicity study, oral (dietary) balsalazide disodium at doses up to 2 grams/kg/day was not tumorigenic. For a 50-kg person of average height this dose represents 2.4 times the recommended human dose on a body surface area basis.

7.1.12 Special Safety Studies

There were no other safety studies performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The mesalamine products have very low potential for abuse and/or withdrawal phenomena.

7.1.14 Human Reproduction and Pregnancy Data

No studies were carried out with Colazal in pregnant women. Urine pregnancy screenings were carried out for all females of childbearing age prior to administration of study drug.

7.1.15 Assessment of Effect on Growth

Please see Section 7.1.8.3 above.

7.1.16 Overdose Experience

No case of overdose has occurred with COLAZAL. A 3-year-old boy is reported to have ingested 2 grams of another mesalamine product. He was treated with ipecac and activated charcoal with no adverse reactions.

If an overdose occurs with COLAZAL, treatment should be supportive, with particular attention to correction of electrolyte abnormalities.

A single oral dose of balsalazide disodium at 5 grams/kg or 4-aminobenzoyl-ß-alanine, a metabolite of balsalazide disodium, at 1 gram/kg was non-lethal in mice and rats. No symptoms of acute toxicity were seen at these doses.

Medical Officer Comments:
It is unclear why the sponsor recommends correction of electrolyte abnormalities in potential cases of overdosage of this product, since the mesalamine products do not typically cause electrolyte disturbances. As with any overdose, however, the patient would need to be monitored carefully and treated symptomatically for any complications.

7.1.17 Postmarketing Experience

Since Colazal's marketing approval in the United States in July of 2000, thirteen quarterly Periodic Adverse Drug Experience (ADE) Reports and two Annual Periodic ADE Reports have been filed. The last Annual Periodic ADE Report covered the period from July 19, 2004 through July 18, 2005. The Colazal safety database was examined through June 9, 2006, for cases where the patient's age was able to be determined as less than 18 years, or the patient was referred to as the child of the reporter.

Nineteen (19) pediatric post-marketing reports were found, 6 of which were submitted as 15-day alerts and 13 as periodic reports. Two of the six 15-day alerts (SP00078 and SP00478) were reports from a foreign source.

In the group of adverse events of specific interest to FDA in the BZUC3001 study, there were spontaneous reports of pericarditis in 1 patient (SP00096) and pancreatitis in 2 patients (SP00028 and SP00273). There were no pediatric post-marketing adverse events reported as renal toxicity, hepatic toxicity, myocarditis, gastritis or cholecystitis.

Three cases of tooth discoloration were reported. One patient (SP00343) who was taking ferrous sulfate solution as well as Colazal was noted to have "blackish staining along the margins between the teeth." Two twin sisters (SP00426 and SP00427) were observed to have new teeth erupting with a yellowish color. One child had been on Colazal for 2 months and the other for 7 months.

A case of thrombocytopenia (SP00350) the physician felt could have been related to Colazal having a potential drug interaction resolved when the co-suspect medications (Bactrim solution and 6-mercaptopurine) were discontinued while Colazal was continued.

Two 15-day alerts (SP00383 and SP00078) reported the diagnosis of hypothyroidism by routine newborn screening in infants whose mothers were receiving Colazal during pregnancy.

Other pediatric post-marketing adverse events reported included headache, diarrhea, abdominal pain, vomiting, pain, pruritis, arthralgia, and alopecia. Several of these events were also reported in the pediatric clinical trial BZUC3001, and all of these adverse events are listed in the current labeling for Colazal.

The few cases of pediatric post-marketing adverse events reported with Colazal since product approval do not allow for a meaningful comparison with reports in the adult population.

Medical Officer Comments:
The postmarketing safety reports do not appear to contain any signals of concern. The tooth discoloration appears to be unrelated to the study drug since different types of discoloration were seen in the cases cited. The case of the "blackish staining" was most likely due to the ferrous sulfate solution which is known to cause such a reaction.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Please see Section 6.1.3 of this review for this information. The safety population analyzed included all subjects who were randomized and received at least 1 dose of study medication and had at least 1 postbaseline safety assessment.

7.2.1.2 Demographics

The following table displays the demographics in the pediatric Colazal trial.

Table 24. Subject Demographics (ITT Population)

Characteristic	Colazal 6.75 g/day (N=33)	Colazal 2.25 g/day (N=35)	Total (N=68)
Age (years)			
Mean (SD)	12.8 (3.56)	13.2 (3.35)	13.0 (3.43)
Gender (N, %)			
Male	13 (39%)	10 (29%)	23 (34%)
Female	20 (61%)	25 (71%)	45 (66%)
Race (N, %)			
Asian	2 (6%)	1 (3%)	3 (4%)
Black or African-American	2 (6%)	3 (9%)	5 (7%)
White	29 (88%)	31 (89%)	60 (88%)
Ethnicity (N, %)			
Hispanic or Latino	1 (3%)	4 (11%)	5 (7%)
Not Hispanic or Latino	32 (97%)	31 (89%)	63 (93%)
Urine Pregnancy Test (N, %)			
Negative	10 (50%)	15 (60%)	25 (56%)
Positive	0 (0%)	0 (0%)	0 (0%)
N/A	10 (50%)	10 (40%)	20 (44%)

N/A = not applicable; SD = standard deviation.

Table from Module 5, Vol. 16.1, 11.2.1, Table 7.

The following table displays demographics by specific age group.

Table 25. Subject Demographics by Age Group (ITT Population)

	Subjects 5 to 8 years of Age		Subjects 9 to 17 years of Age	
Characteristic	**6.75 g/day (N=5)**	**2.25 g/day (N=4)**	**6.75 g/day (N=28)**	**2.25 g/day (N=31)**
Age (years)				
Mean (SD)	6.4 (1.14)	6.8 (1.50)	14.0 (2.41)	14.0 (2.50)
Gender (N, %)				
Male	1 (20%)	1 (25%)	12 (43%)	9 (29%)
Female	4 (80%)	3 (75%)	16 (57%)	22 (71%)
Race (N, %)				
Asian	1 (20%)	0 (0%)	1 (4%)	1 (3%)
Black or African-American	1 (20%)	0 (0%)	1 (4%)	3 (10%)
White	3 (60%)	4 (100%)	26 (93%)	27 (87%)

SD = standard deviation.

Table adapted from Module 5, Vol. 16.1, 11.2.1, Table 8.

Medical Officer Comments:

The demographics for the age groupings were similar to the entire ITT population. The majority of patients were female in each age group (78% and 64% in the younger and older groups, respectively) and in the entire ITT population (66%). Also, the majority of patients were white in each age group (78% and 90% in the younger and older groups, respectively) and in the entire ITT population (88%). This is consistent with the demographics for UC as a disease entity in the general populace as well.

7.2.1.3 Extent of exposure (dose/duration)

The mean and median number of days on study drug was 50.9 and 55.0 (minimum = 4, maximum = 67), respectively, in the Colazal 6.75 g/day group and 43.3 and 54.0 (minimum = 2, maximum = 65), respectively, in the Colazal 2.25 g/day group (Table !). The majority of subjects were on study drug between 29 and 56 days.

Table 26. Summary of Study Drug Exposure

	Colazal 6.75 g/day N=33	Colazal 2.25 g/day N=35	Total N=68
Number of Days on Drug			
N	32[a]	35	67
Mean (SD)	50.9 (14.00)	43.3 (21.44)	46.9 (18.53)
Median	55.0	54.0	55.0
Minimum - maximum	4 - 67	2 - 65	2 - 67
Number (%) of Subjects on Drug			
≥1 day to ≤14 days	2 (6%)	8 (23%)	10 (15%)
>14 days to ≤28 days	2 (6%)	0 (0%)	2 (3%)
>28 days to ≤56 days	20 (61%)	17 (49%)	37 (54%)
>56 days	8 (24%)	10 (29%)	18 (26%)

[a] Subject 0001-0006 had incomplete date noted for last dose of study medication, and study drug exposure was therefore not calculated for this subject.

Table from Module 5, Vol. 16.1, 12.1, Table 29.

Medical Officer Comments:

It is evident from this table that for both the high- and low-dose Colazal groups, the mean number of days on drug is less than the 56 days that would be expected if a subject completed the 8-week study. It is likely that this mean is decreased by those patients who withdrew early from the study (5 from the high-dose group and 10 from the low-dose group), and by those patients that were <70% study drug compliant (7 from the high-dose group and 12 from the low-dose group).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Medical Officer Comments:

A review of the package inserts for the other aminosalicylates does not reveal any other studies performed specifically in children for either safety or efficacy documentation.

7.2.2.2 Postmarketing experience

Please see Section 7.1.17 above.

7.2.2.3 Literature

Medical Officer Comments:
A brief review of the literature for all aminosalicylates reveals no particular outstanding safety concerns, particularly for the sulfa-free products including Colazal. The only other 5-ASA product with any dosing recommendations for treatment of pediatric UC is sulfasalazine, the use of which has typically been limited by its dose-dependent side effects, including intolerance, thought to be due to the sulfa moiety, which is not present in Colazal. In fact, 80 to 90% of those patients allergic to, or intolerant of, sulfasalazine are tolerant to the 5-ASA moiety. [4]

7.2.3 Adequacy of Overall Clinical Experience

Medical Officer Comments:
The reviewer believes that the overall safety database is acceptable for this product. Although the sample size is small, the design of the trial is consistent with that specified in the Written Request. The dose was equivalent to that used in adults (for the high-dose group), and the duration of exposure (mean of 46.9 days for the total sample of 68 patients) is adequate to derive short-term safety data for a product that treats this disease entity. The exclusion criteria were reasonable and should not have limited the value of the safety assessments.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal or in vitro testing was undertaken for this supplement. Please see the Pharm/Tox review for more details.

7.2.5 Adequacy of Routine Clinical Testing

Medical Officer Comments:
In general, routine clinical testing was adequate for this study. Appropriate parameters were assessed for both laboratory values and vital signs both at baseline and at the end of treatment. In addition, adverse events were carefully followed and documented throughout the duration of the study.

The addition of an erythrocyte sedimentation rate (sed rate) to the battery of lab tests may have been helpful in detecting those patients who were relapsing at the end of the study treatment, but this was not stipulated in the written request.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The PK study population was quite small (12 patients total) but met the terms of the written request. For more details, please see the Clinical Pharmacology review by Dr. Suliman Al-Fayoumi.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation for potential adverse events was adequate. The common adverse events that are known to occur in this class of drugs (aminosalicylates) would all be elicited by the measures undertaken with this protocol. In addition, special attention was given to those items that were delineated in the WR, such as cardiovascular and hepatic adverse events.

Medical Officer Comments:
One item notably absent in the safety evaluation which is standard in adult safety studies is the measurement of ECGs before and after treatment, but arrhythmias are not listed as common adverse events for any of the other aminosalicylates, so this reviewer does not feel that this compromised the safety assessment for this study drug.

7.2.8 Assessment of Quality and Completeness of Data

The sponsor provided sufficient information in this submission for a complete review. It was determined that the sponsor fairly met the terms of the WR.

7.2.9 Additional Submissions, Including Safety Update

No further submissions have been received since the original submission for this NDA supplement.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Table 27. Summary of Important Drug-Related Adverse Events

	Subject #	AE Preferred Term	Narrative Synopsis
Colazal 6.75 g/day group			
1	0528-0001	-Abdominal pain -Urticaria	11 yo female with UC diagnosed 16 Mar 05. Colazal treatment began 9 Apr 05, and ended 12 Apr 05. The first day of treatment the patient developed **abdominal pain and urticaria**. Study medication was permanently **discontinued** and the symptoms resolved by 13 Apr 05. The investigator believed that both symptoms were **moderate** and **related** to study therapy.
Colazal 2.25 g/day group			
2	0468-0001	Frequent bowel movements	12-yo female with UC diagnosed 23 Sept 05. Treatment began 4 Oct 05 and was completed 4 Nov 05. On 21 Oct 05 the pt developed **frequent bowel movements**. On 4 Nov 05 the investigator decided to discontinue the subject due to the adverse event, and study medication was permanently **discontinued**. The investigator believed the AE to be **moderate** and **related** to the therapy.

Table adapted from Module 5, Vol. 16.1, 12.3.2, Table 33 and pages 102-103.

For further information regarding these events, please see Section 7.1.3.2 of this review.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Since only one study was performed for this application, no pooling of data was possible.

7.4.1.1 Pooled data vs. individual study data

N/A

7.4.1.2 Combining data

N/A

7.4.2 Explorations for Predictive Factors

Medical Officer Comments:

Sixteen subjects experienced AEs that were believed to be caused by the study drug, and of these only 2 resulted in the discontinuation of the study drug. (These cases are listed in Table above.) None of these cases shows any dose-dependency findings, time-dependency findings, drug-demographic, drug-disease, or drug-drug interactions that allow establishment of any predictive factors for which patients will suffer adverse events when taking Colazal.

7.4.2.1 Explorations for dose dependency for adverse findings

Table 28. Overview of Treatment-Emergent Adverse Events

	Colazal 6.75 g/day N=33 N (%)	Colazal 2.25 g/day N=35 N (%)	Total N=68 N (%)
Subjects with ≥ 1 Adverse Event	**23 (70%)**	**19 (54%)**	**42 (62%)**
Deaths	0 (0%)	0 (0%)	0 (0%)
Serious Adverse Events	2 (6%)	2 (6%)	4 (6%)
Discontinuations Due to Adverse Events	1 (3%)	3 (9%)	4 (6%)
Severity[a]			
Mild	10 (30%)	5 (14%)	15 (22%)
Moderate	11 (33%)	13 (37%)	24 (35%)
Severe	2 (6%)	1 (3%)	3 (4%)
Relationship to Study Drug[b]			
Related	7 (21%)	9 (26%)	16 (24%)
Unrelated	16 (49%)	10 (29%)	26 (38%)

[a] Number (%) subjects by maximum severity.
[b] Number (%) subjects by maximum relationship.

Table from Module 5, Vol. 16.1, 2.7.4.2.1, Table 2.7.4.5

Medical Officer Comments:

Two doses were used in this study, but the higher dose showed a lower incidence of patients who dropped out due to AE (3% of high-dose group vs. 9% of low-dose group) and a lower incidence of patients with drug-related AEs when compared to the lower dose (21% of high-dose group vs. 26% of low-dose group). The incidence of patients experiencing a SAE was equal between the two groups (6%). With this in mind, the reviewer does not feel that any dose-dependent predictive factors are evident at this time. Please see Section 7.1.5.3 for additional discussion of the difference in AEs between the two dose groups.

7.4.2.2 Explorations for time dependency for adverse findings

None of the drug-related AEs appears to show any time-dependent predictive factors since a large variability in duration of drug exposure was seen in the safety population.

7.4.2.3 Explorations for drug-demographic interactions

No particular drug-demographic interactions are evident.

7.4.2.4 Explorations for drug-disease interactions

No particular drug-disease interactions are evident.

7.4.2.5 Explorations for drug-drug interactions

No particular drug-drug interactions are evident.

7.4.3 Causality Determination

Please see Sections 7.1.3.2 and 7.3 for a discussion of those events which were believed to be caused by the study drug.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor proposes the following two Colazal dosage regimens for use in pediatric patients (ages 5-17 years):

1) Three 750-mg capsules to be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks.

2) One 750-mg capsule to be taken three times a day for a total daily dose of 2.25 grams for a duration of 8 weeks.

The sponsor also proposes labeling that "some patients required treatment for up to 12 weeks."

Medical Officer Comments:

The above dosing regimens were both studied in the adult population in the original NDA approved in 2000. Due to a marked difference in efficacy for the higher dose, only the 6.75 g/day dosing regimen was approved for use. In the current supplement, the sponsor demonstrated evidence of adequate clinical response for both doses. Although the absolute percentage of responders was higher for the high-dose group, the difference was not statistically significant. The safety profiles were also similar for both dose groups, with a lower incidence of dropouts and drug-related adverse events in the higher-dose group.

The statement regarding 12 weeks of use would apply only to the adult population since no pediatric patients underwent treatment with Colazal beyond 8 weeks in the submitted study.

8.2 Drug-Drug Interactions

The current study did not reveal any evidence of unequivocal drug-drug interactions. As mentioned above, one postmarketing report of a possible interaction with Bactrim and 6-mercaptopurine was reported (thrombocytopenia).

No drug interaction studies have been conducted for Colazal [redacted] (b) (4)

Medical Officer Comments:
The postmarketing report does not present sufficient concern to effect a change in the labeling, since the causal relationship could not be determined definitively. [redacted] (b) (4)

8.3 Special Populations

N/A

8.4 Pediatrics

This NDA supplement is for a pediatric indication, so no additional information is presented here.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was required for this supplement.

8.6 Literature Review

The pertinent findings from a literature review regarding all salicylate products for the treatment of UC are presented where appropriate in the body of this review.

8.7 Postmarketing Risk Management Plan

The reviewer does not recommend a postmarketing risk management plan.

8.8 Other Relevant Materials

N/A

9 OVERALL ASSESSMENT

9.1 Conclusions

One randomized, double-blind, parallel-group, multi-center study of 2 dosage regimens of Colazal in 68 subjects who were 5 to 17 years of age was performed in response to the WR issued by the FDA. The study demonstrated reasonable evidence of efficacy for the proposed indication of the treatment of mildly to moderately active UC at both doses, with a higher (although non-statistically significant) percentage of the high-dose group responding to treatment. In addition, the study demonstrated reasonable evidence of safety for the intended use, with the high-dose group showing a slightly more favorable safety profile over the low-dose group.

9.2 Recommendation on Regulatory Action

The reviewer recommends **approval** of Colazal for the treatment of mildly to moderately active UC for patients 5-17 years of age (in addition to the adult population already approved) at **a dose of 3 capsules three times per day (6.75 grams/ day)** for up to 8 weeks. This approval is contingent on the sponsor's acceptance of the reviewer's important labeling changes as detailed below.

The reviewer also recommends **approval** for the lower proposed dose of **1 capsule three times per day (2.25 grams/ day)** in patients 5-17 years of age for up to 8 weeks since this dose showed comparable efficacy to the higher dose (no statistically significant difference) and a comparable, although slightly worse safety profile than the higher dose (possibly due to its lower efficacy.)

The reviewer recommends approval of both doses so that prescribing clinicians have a choice of regimens. Since the weight range and severity of disease for the intended patient population (ages 5-17 years) will be quite variable, some clinicians will prefer to start with the lower recommended regimen to see if effective treatment can be accomplished at that dose, while others may decide to start with the higher dose (particularly when treating older children of adult size since the adult studies show a significantly better response for the high-dose regimen.)

In addition, having two dosage regimens available will allow clinicians to taper patients to the lower dose if desired once improvement in symptoms has been shown at the higher dose.

9.3 Recommendation on Postmarketing Actions

Standard postmarketing actions (i.e., periodic adverse event reports and annual reports) are recommended for this product.

9.3.1 Risk Management Activity

Risk management activities are not indicated at this time.

9.3.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended at this time.

9.3.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

9.4 Labeling Review

The reviewer recommends important revisions to the **INDICATIONS AND USAGE** section regarding duration of use in children. Other recommendations include providing more information regarding the lower-dose recommendation for pediatric patients in the **DOSAGE AND ADMINISTRATION** section and clarifying the efficacy findings under the **CLINICAL STUDIES** section. Please see Appendix 10.2 for the line-by-line changes recommended by the reviewer.

A portion of the labeling changes proposed by the sponsor relate to the findings in the PK population for this supplement which will be reviewed by the Clinical Pharmacology team. Please see their review of this supplement for their specific labeling recommendations.

9.5 Comments to Applicant

The reviewer does not have any comments for the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Since only one study report was submitted, the body of the review contains this information.

10.2 Line-by-Line Labeling Review

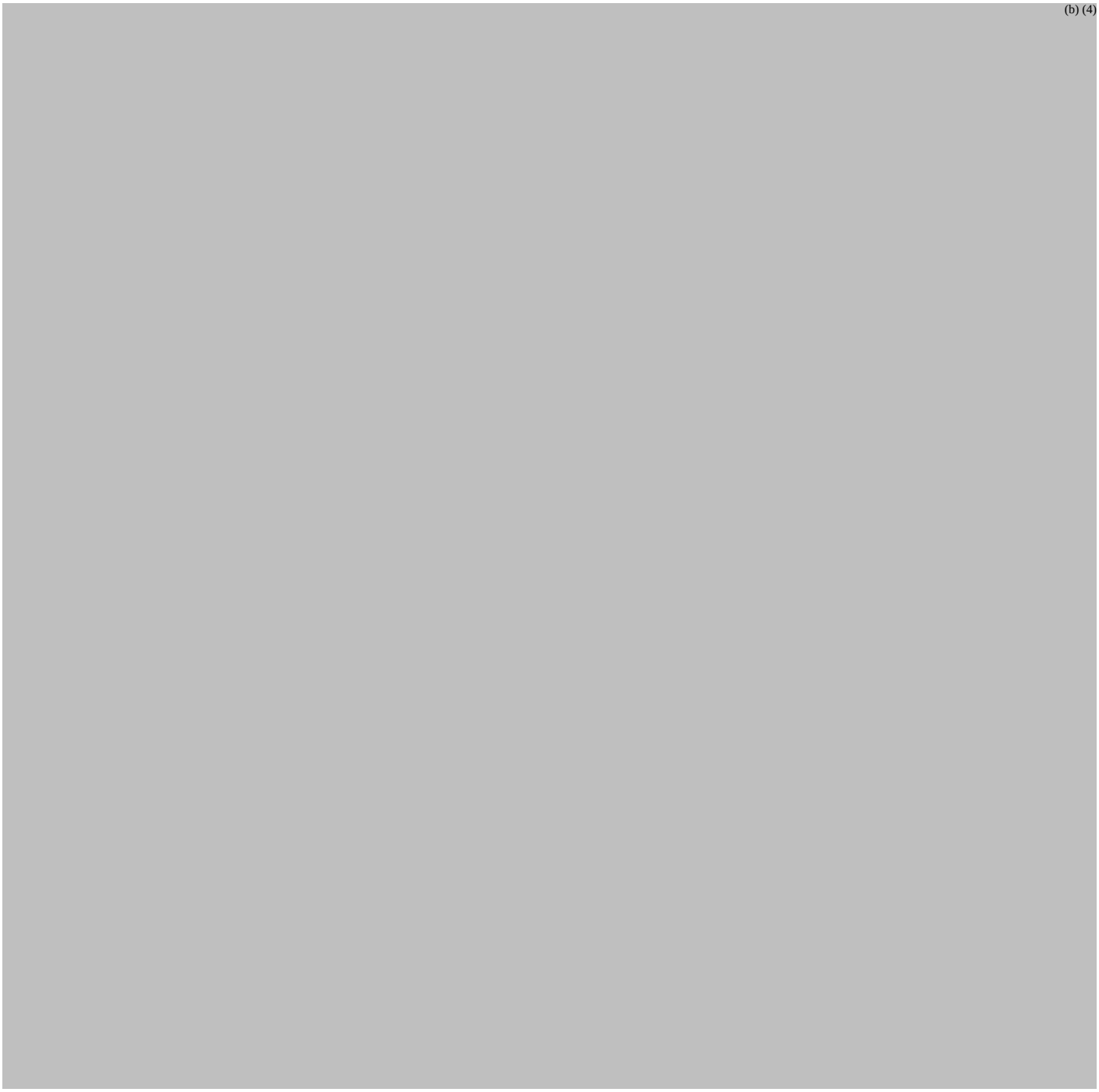
For this labeling review, words underlined and **boldfaced** represent additions and words formatted with a ~~strikethrough~~ represent deletions to the sponsor's proposed Colazal label (last updated 10/2006.) This review pertains only to those labeling changes that the sponsor has proposed as a result of its pediatric study (BZUC3001), not to any parts of the label that have remained unchanged since the original approval in July 2000.

This label was submitted in an attempt to conform to the Physician Labeling Rule (PLR), and as such multiple formatting changes have occurred when compared to the original label. The Study

Endpoints and Label Development Division (SEALD) of the Office of New Drugs was consulted for this supplemental application and provided its recommendations to the sponsor in the 74-day filing letter sent August 28, 2006. As finalization of the label will be accomplished with the assistance of the SEALD team during labeling negotiations with the sponsor, the review below will not provide any comments regarding the formatting but will address content only.

Sponsor's Proposed New Label:

(b) (4)



13 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

Keith B St.Amand
11/21/2006 02:55:05 PM
MEDICAL OFFICER

Ruyi He
11/21/2006 05:18:34 PM
MEDICAL OFFICER