CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022205Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	February 3, 2012
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 022205
Applicant Name	Salix Pharmaceuticals, Inc.
Date of Submission	August 3, 2011 [Original submission July 16, 2007]
PDUFA Goal Date	February 3, 2012
Proprietary Name / Established (USAN) Name	Giazo Balsalazide disodium
Dosage Forms / Strength	Tablet for oral administration Each tablet contains 1.1g balsalazide disodium
Proposed Indication	Treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older
Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Previous reviews: Christopher Leptak, MD, PhD/John Hyde, Ph.D., MD
Statistical Review	Shahla Farr, MS/Mike Welch, PhD
CDTL Review	Robert Fiorentino, MD Previous reviews: John Hyde, Ph.D., MD
Clinical Pharmacology	Insook Kim, PhD/ Sue-Chih Lee, PhD
CMC	Marie Kowblansky, PhD/Moo-Jhong Rhee, PhD

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This is the third resubmission of NDA 022205. The NDA was not approved in its original July 17, 2007, submission because the Clinical and Statistical reviewers determined that the Applicant had not established the efficacy of the product. An Approvable letter was issued on May 16, 2008. The first resubmission, on June 30, 2008, resulted in a CR letter, dated December 22, 2008, after FDA's Clinical and Statistical reviewers again determined that the Applicant had not adequately established efficacy. The Applicant submitted a third time on October 26, 2009. Although the reviewers recommended approval in that review cycle, the NDA wasn't approved, due to the Office of Compliance's "Withhold Approval" recommendation. This recommendation was prompted by manufacturing issues at the finished dosage manufacturer (Nexgen Pharma Inc.).

The original NDA submission included a single placebo-controlled clinical study (BZUC3002) to support the proposed indication "treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older." The Applicant submitted an additional clinical study during the course of the first review cycle, but the study was not reviewed in that cycle. The NDA was not approved because the reviewers determined that the single study submitted in the original NDA submission (Study BZU3002) did not provide adequate evidence of efficacy. The Division cited both the lack of a statistically persuasive finding of treatment effect and the lack of consistency in treatment effect between the subsets of men and women within the single study as deficiencies that precluded approval.

In the first resubmission, Dr. Hyde, the Cross Disciplinary Team Leader (CDTL), noted that the Division's guidance in its meetings and letters regarding this NDA, which emphasized the requirements of a single study for evidence of effectiveness delineated in section II.C.3 of the "Evidence Document" (*Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* 1998), demanding that the study be statistically very persuasive with a "very low p-value" (conventionally viewed as being a p-value that provides a strength of evidence comparable to two studies with $p < 0.05$), was arguably too stringent. His position was based on the fact that the product is an oral balsalazide product, and oral balsalazide has previously been shown to be efficacious for the indication proposed in this NDA. He did not agree that a statistically highly persuasive p-value should be required for an application that seeks marketing approval for a new dosing format for balsalazide (tablets administered twice a day) when the product is already marketed as capsules (three times a day dosing), and is a pro-drug for a drug, mesalamine, which has been shown to be effective for the same indication in multiple other marketing applications. He supported this conclusion with section II.C.2.a of the Evidence Document, which allows taking into account related study data when considering the strength of evidence provided by the single trial.

Dr. Hyde concluded in his review of the first resubmission that the large and unexplained difference in treatment effect observed between genders in that single trial was an important

deficiency that rendered the trial inadequate as a stand alone trial to support marketing approval of Giazo, as proposed by the Applicant. The female subset represented half the study population. The Statistical and Clinical reviewers concluded that the noninferiority trial BZUC3003 submitted for review in the second cycle did not establish the efficacy of Giazo and could not resolve the issue of the inconsistent treatment effects observed between genders in BZUC3002. The FDA issued a CR letter at the completion of the review.

In the third submission, the Applicant presented arguments to support their conclusion that Giazo is effective in both men and women with mildly to moderately active ulcerative colitis, based on data from the previously submitted trials BZUC3002 and BZUC3003. The reviewers ultimately were persuaded that this balsalazide product can be marketed if the indication is narrowed to treatment of men:

"GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older; effectiveness in female patients was not demonstrated in clinical studies. Safety and effectiveness of GIAZO therapy beyond 8 weeks have not been established."

The Office of Compliance issued a "Withhold Approval" recommendation that ultimately precluded approval at completion of the last review cycle.

In the current resubmission the CMC reviewers noted that the Office of Compliance has issued an overall recommendation of ACCEPTABLE for all facilities involved in the manufacture of this product, which addressed the CR issue from the previous review cycle. However, the CMC reviewer noted a manufacturing change (updated specifications) had been made to one of the 3 drug substance DMFs (b) (4) a change the reviewers concluded would improve manufacturing quality. In a teleconference with the applicant regarding this DMF issue on November 22, 2011, the applicant decided to withdraw the other two manufacturers (which had not updated the specifications) from the submission and rely solely on the manufacturer with the updated DMF. As a result, two of the three drug substance manufacturing sites identified in previous submissions were withdrawn, leaving (b) (4) as sole supplier.

From the ONDQA perspective this NDA may now be approved. There were no new issues identified by the other review disciplines. The pediatric development plan evaluated in the previous review cycle was reassessed during this review cycle (see Section 10 Pediatrics of this review). Final labeling from the previous review cycle was reassessed and changes that were primarily editorial in nature were incorporated.

2. Background

This is an application for a new oral formulation of balsalazide disodium, a tablet containing 1.1 g balsalazide disodium that the Applicant proposes will be dosed twice daily – three tablets twice daily, for a total dose of 6.6g – for up to 8 weeks. The original proposed indication was:

> GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. Safety and effectiveness of GIAZO beyond 8 weeks in adults have not been established.

After prior review cycles, the applicant agreed to limit the indication to male patients 18 years of age and older.

There are currently other balsalazide formulations on the market, but this would be the first product dosed twice daily. The other approved products include one marketed by the Applicant, Colazal (a capsule formulation dosed three times a day, for total dose of 6.75 g). Balsalazide is a prodrug of mesalamine (5-amino salicylic acid, 5-ASA), and there are multiple mesalamine products marketed for treatment of mild to moderately severe ulcerative colitis, including products that are dosed once a day, three times a day and four times a day, in mesalamine total doses that range 2.4 g – 4.8 grams per day.

The Applicant was told in response to a question about providing a single induction study to support approval at their August 8, 2005 End of Phase 2 meeting that two studies were recommended "unless results from a single study are robust (or adequate justification is provided as to why two are not necessary)." Similarly at the April 27, 2007 Pre-NDA Meeting the Division stated that "approvability of your new dosage form will ultimately be based on the robustness of the data and the consistency of effect seen in the primary and secondary endpoints" in response to the Applicant's proposal to submit the single study, BZUC3002, to support efficacy in their NDA. The Division further clarified that, "Also, since study BZUC3002 is intended to be a single principle [sic] study for efficacy, results are expected to be internally consistent and robust, demonstrating substantial efficacy with a p-value considerably smaller than .05."

In the original NDA submission, the Applicant submitted the single trial BZUC3002, which demonstrated inconsistency in treatment effect between males and females. Females treated with placebo and Giazo had a similar outcome. In fact, the primary efficacy outcome in females was numerically better in the placebo arm. The original Approvable letter stated the following:

> "Your placebo controlled study is not adequate as a single study to support the effectiveness of balsalazide tablets for treatment of mildly to moderately active ulcerative colitis because it did not demonstrate a statistically persuasive finding of treatment effect and because there was a lack of consistency of treatment effect between men and women, subsets that were equally represented in this study.
>
> The issuance of an approval is dependent upon the review of an additional adequate and well controlled study that demonstrates that balsalazide tablets are effective in treating mildly to moderately active ulcerative colitis."

After taking an Approvable action on May 16, 2008, the Division met with the Applicant in a June 9, 2008 Post-Action Meeting. In that meeting the Division told the Applicant that clinical

Study BZUC3003, which the Applicant had submitted during the initial review cycle but was not reviewed by the FDA, could constitute a response to the Approvable Letter. However, the Division qualified this, saying that the adequacy of the second study would be a review issue.

The Applicant's first resubmission, dated June 30, 2008, contained the clinical study discussed at the Post-Action Meeting (BZUC3003), additional clinical safety data, and stability data to extend the expiration date. The Division notified the Applicant in early November 2008 that deficiencies had been identified that precluded initiating labeling. The deficiencies were discussed in a teleconference with the Applicant on 11/13/08. The reviewers noted that the active controlled study comparing Giazo to Asacol was inadequate to establish the efficacy of Giazo because Giazo was not found to be superior to Asacol, and the study did not establish that Giazo is noninferior to Asacol. In addition, the Applicant had not adequately addressed the gender discrepancy in treatment effect observed in the originally reviewed study. The second study, BZUC3003, was inadequate to address that issue.

The Complete Response (CR) letter dated December 22, 2008, cited two major deficiencies:

1) Inadequate justification of the (b) (4) non-inferiority margin for Study BZUC3003.
2) Inability of the results of Study BZUC3003 to address the deficiencies of the May 16, 2008, Approvable letter.

The Applicant met with FDA on March 16, 2009, after receiving the CR letter. The Applicant presented additional analyses to explain the gender differences. The Applicant also proposed a (b) (4) for the noninferiority study to show (b) (4) The FDA responded that the proposed (b) (4) could not be used to establish (b) (4). The FDA advised the Applicant that additional clinical data would be best, but that the Applicant could consider submitting the additional analyses and additional external information, including comparative PK between genders, to help explain the gender difference.

In the subsequent resubmission, no new study was submitted. As stated above in Section 1 Introduction, the reviewers were persuaded that the product could be approved for treatment of male patients only, and product labeling was agreed upon; however, Compliance recommended "Withhold Approval" based on issues at a manufacturing site.

3. CMC

In the original review cycle, the CMC Reviewer found that sufficient information was provided to assure the identity, strength, purity, and quality of the drug product. The stability data supported a 24-month expiration date. In the first resubmission, additional stability data were submitted that supported a 36-month expiration.

The Office of Compliance issued an "Acceptable" overall recommendation on 3/17/08 for all the facilities involved; however, during the last review cycle, on April 12 2010, the Office of Compliance issued a new overall recommendation of Withhold, after completion of an inspection of the finished dosage manufacturer (Nexgen Pharma Inc.). The District Office

noted that the inspection revealed "widespread GMP deficiencies and the marketing of at least 20 potential unapproved drugs."

As stated in the Section 1 Introduction, the Office of Compliance has now issued an overall "Acceptable" recommendation for all facilities involved in the manufacture of this product. During this review cycle, changes in manufacturing at one of the drug substance manufacturing sites led to discussions between the Applicant and the CMC reviewers. The Applicant subsequently decided to withdraw the remaining two drug substance manufacturing sites from the NDA, leaving (b) (4) as sole supplier.

The CMC reviewers have determined that this application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the commercial drug product. In addition, they have determined that labeling is appropriate from a CMC standpoint.

4. Nonclinical Pharmacology/Toxicology

There were no new Pharmacology/Toxicology data in this resubmission. Dr. Ke Zhang recommended approval from the preclinical standpoint in his review of the original submission.

5. Clinical Pharmacology

The Clinical Pharmacology reviewers recommended approval of the original NDA submission. In the second resubmission, the Applicant submitted analyses of available pharmacokinetic data (by gender) in an effort to address the observed inconsistent treatment effect between men and women in Study BZU3002. Dr. Kim noted the Applicant's argument using comparable systemic exposure to balsalazide and its metabolites between men and women cannot address the observed inconsistency. Dr. Kim stated in her review that, "The equivalent therapeutic efficacy in different subpopulations (men vs. women) may be expected based on the equivalent systemic exposure when one can reasonably assume similar disease progression and similar response to treatment between these subpopulations. However, one can not reasonably assume similar disease progression and similar response to treatment between men and women especially in this case with the identified inconsistent placebo effect between men and women. As such, the similar systemic exposure to balsalazide and mesalamine can not be used to support similar therapeutic effect between men and women."

The Clinical Pharmacology reviewers provided a labeling review this cycle. The review included their conclusions supporting their recommendation to change the applicant's proposed product administration instructions regarding (b) (4) food. (b) (4) A food effect study has demonstrated that administration with a high fat meal results in reduction of the Cmax and AUC of balsalazide and its active metabolites, 5-ASA and N-Ac-5-ASA. The following table, reproduced from the Clinical Pharmacology review (from original review cycle), summarizes the observed food effects.

Table 1. The geometric mean ratios (GMR) and 90% Confidence Intervals for PK parameters of balsalazide and key metabolites after a single dose – Fed and Fasted State

Compound/ Parameter	Treatment	Geometric LS Mean	GMR (Fed/Fasted)	90% CI for GMR	
				Lower	Upper
Balsalazide					
C_{max} (ng/mL)	Fed	188	56.42	49.70	64.05
	Fasted	334			
AUC_T (ng·h/mL)	Fed	1200	91.27	81.89	101.72
	Fasted	1320			
$AUC_{0-\infty}$ (ng·h/mL)	Fed	1210	91.28	81.88	101.75
	Fasted	1330			
5-ASA					
C_{max} (ng/mL)	Fed	157	34.33	29.16	40.42
	Fasted	456			
AUC_T (ng·h/mL)	Fed	4110	52.37	46.51	58.96
	Fasted	7850			
$AUC_{0-\infty}$ (ng·h/mL)	Fed	4340	54.45	48.48	61.16
	Fasted	7980			
N-Ac-5-ASA					
C_{max} (ng/mL)	Fed	665	52.46	47.29	58.19
	Fasted	1270			
AUC_T (ng·h/mL)	Fed	23600	80.55	74.96	86.56
	Fasted	29200			
$AUC_{0-\infty}$ (ng·h/mL)	Fed	25100	83.41	76.27	91.22
	Fasted	30100			

The Clinical Pharmacology reviewers have recommended that the Dosage and Administration section of the label state that the product can be taken *without* regard to food, because 1) the product was taken without regard to food in phase 3 trials, which established both the safety and efficacy of the product and, 2) the systemic exposures are likely to be reflective of the availability of drug in the intestine. Based on the mechanism by which mesalamine is released by microflora in the colon, the lower systemic absorption may reflect lower local availability of mesalamine, the active form of the product locally (before its absorption).

The CDTL concurred with this recommendation and noted that Colazal, which contains the same active ingredient in capsular form, is also currently labeled to take "with or without food" in the Dosage and Administration instructions for both adult and pediatric patients.

I agree with the reviewers' labeling recommendations.

The Clinical Pharmacology reviewer noted in her review that the applicant had provided a response to an information request regarding whether Cetero Research in Houston, TX had conducted bioanalytical studies to support this NDA. The applicant stated that no studies were conducted by Cetero. She confirmed that Cetero Research was not involved in the conduct of the food effect study and the multiple dose PK study, by reviewing the study reports.

Dr. Kim recommended a post marketing study to characterize the pharmacokinetics of balsalazide, mesalamine and N-acetyl aminosalicylic acid in pediatric patients. She also recommended a post marketing study of the in vivo effect of concomitant antibiotics on conversion of balsalazide to mesalamine by gut-flora.

I have concurred with her recommendations. See Section 7 Clinical/Statistical-Efficacy and Section 10 Pediatrics for further discussion of the PMC trials.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Please refer to Dr. John Hyde's summary of the clinical and statistical review findings in his CDTL review from the previous review cycle. There were no new efficacy data submitted for review in this resubmission.

The primary endpoint of the clinical trials Study BZUC3002 and Study BZUC3003 was based on the Modified Mayo Disease Activity Index, MMDAI. This index is comprised of 4 subscores (bowel frequency, rectal bleeding, endoscopic appearance and physician's global assessment), which range from 0-3 (higher score representing more severe disease). Totaling the subscores yields a score that can range from 0-12. The primary endpoint, clinical improvement at the end of the treatment period, was defined by at least a 3 point improvement in MMDAI, associated with an improvement in rectal bleeding score of at least 1 point.

The single clinical study BZUC3002, which was submitted and reviewed in the original review cycle, was a randomized, double-blind, placebo-controlled study of Giazo that enrolled 250 patients with mildly to moderately active UC from 55 U.S. centers. The primary endpoint was assessed at 8 weeks. Primary efficacy endpoint results are summarized in the table below, which includes the subgroup analysis by gender.

Table 2. Proportion of Patients with Clinical Improvement at Week 8 in Study BZUC3002

	Giazo 6.6 g/day % (# response/N)	Placebo % (# response/N)	Difference (Giazo – Asacol)	P-value
Total Population	**55%** (b) (4)	**40%** (b) (4)	**15%**	0.024
Males	**57%** (b) (4)	**20%** (b) (4)	**37%**	<0.001
Females	**54%** (b) (4)	**58%** (b) (4)	**-4%**	(b) (4)

Despite the statistically significant difference favoring Giazo in the overall study population, the outcome was not consistent between genders. In fact, in females there was a numerically higher response rate on the placebo arm. A nominally statistically significant difference between treatment effects by gender (37% vs. -4%, nominal $p < 0.003$ by M-H Chi-square test for homogeneity) was noted.

Two key secondary efficacy endpoints were Clinical Remission and Mucosal Healing. Clinical Remission was defined as a score of 0 for rectal bleeding plus a combined score of ≤ 2 for bowel frequency and physician's global assessment (MMDAI); the endoscopic sub-score was not considered in this definition. This endpoint's definition differed from the primary endpoint "clinical improvement" not only in its deletion of the endoscopy component, but in its requirement of a rectal bleeding score of zero (compared to a reduction in rectal bleeding by at least one point in the primary endpoint) and a total remaining score for the two components (physician global and bowel frequency) that couldn't be exceeded. (Clinical improvement defined the total shift downward in score that was considered an improvement.) Mucosal Healing was defined as an endoscopy/sigmoidoscopy score of 0 or 1, where a score of 1 could include signs of erythema or decreased vascular pattern; by definition, the presence of friability indicated a score of 2 or 3.

The following table, reproduced and modified from Dr. Hyde's CDTL review, summarizes the outcomes by gender for the secondary endpoints Clinical Remission and Mucosal Healing. It also summarizes outcomes for the bowel frequency and rectal bleeding subscores of the MMDAI. Dr. Hyde pointed out in his review that no nominally statistically significant outcomes in females were observed in any of these additional analyses, and that there were lower rates of improvement (as defined for responder analysis) in rectal bleeding and bowel frequency with Giazo than placebo in females.

Table 3. Secondary Endpoint Results in Study 2 by Gender

Variables	Giazo n/N (%)	Placebo n/N (%)	Difference	p-value for Difference	p-value for Inhomo-geneity
Clinical Remission					(b) (4)
Males	28/81 (**35**)	5/40 (**13**)	**22%**	0.01	
Females				(b) (4)	
Mucosal Healing					
Males	42/81 (**52**)	8/40 (**20**)	**32%**	<0.001	
Females				(b) (4)	
Bowel Frequency					
Males	43/81 (**53**)	12/40 (**30**)	**23%**	0.02	
Females				(b) (4)	
Rectal Bleeding					
Males	51/81 (**63**)	13/40 (**33**)	**30%**	0.002	
Females				(b) (4)	

The second study (reviewed in the second review cycle), BZUC3003, was a randomized, double-blind, active-controlled study in patients with mildly to moderately active UC. Patients were randomized between Giazo (balsalazide) or Asacol (mesalamine). Treatment duration was six weeks. The dose of Asacol (mesalamine) was 0.8g TID (total 2.4 g/D), the approved dose. The Giazo dose was the dose proposed for marketing, 3.3g BID (total 6.6 g/D). Like Study BZU3002, the primary endpoint was defined as a reduction of at least 3 points in MMDAI and a reduction of at least 1 point in the rectal bleeding score. In BZU3003, however, the end of study assessment occurred at Week 6 instead of Week 8. The objective was to establish noninferiority of Giazo to Asacol. The Applicant's proposed noninferiority margin was (b) (4). The design features, including duration of treatment, dose, method of assessment, schedule of assessments, and eligibility criteria, were carefully evaluated by the Clinical and Statistical reviewers, in order to determine whether suitable previously conducted studies had been utilized to establish an appropriate noninferiority margin.

Although the initial BZU3003 protocol specified the primary analysis would utilize the ITT population, the first protocol amendment (approximately 3 months after initiating the study) changed the population for analysis to the per-protocol population. As part of these changes, the definition of the ITT population was modified. The ITT population became all patients who met the following criteria: 1) took at least one dose of study drug, 2) baseline MMDAI score is between 6 and 10, inclusive, 3) MMDAI bleeding score is at least 2 or greater, and 4) MMDAI endoscopy score is at least 2 or greater. This revised ITT population definition was referred to by the FDA reviewers as the modified ITT population, or mITT. The per protocol population was defined as the patients in the mITT population who had no major protocol deviation and had at least one post-baseline assessment of the primary efficacy endpoint. The changes made in the analysis population were a significant review issue for the Statistical reviewer, and prompted FDA exploratory analyses utilizing differing definitions of the primary analysis population. These analyses are described in detail in the second cycle Statistical review.

Of the total of 410 patients randomized in this study, 351 qualified for inclusion in the per protocol population. The population was nearly evenly split between males and females –

48% were males. The table below summarizes the outcome observed for the primary endpoint in the overall ITT population ("All Randomized"), the per-protocol population, as defined above, and the modified ITT population (mITT), as defined above. The Applicant concluded that Giazo is noninferior to Asacol because the lower bound of the 95% interval of the difference between Giazo and Asacol in the per protocol population analysis was (b) (4)

Table 4. Percentages of Patients with Clinical Response at Week 6/EOT in Study BZUC3003

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Per-Protocol	**61.7%** (b) (4)	**60.8%** (b) (4)	**0.9%** (b) (4)
mITT	**56.3%** (b) (4)	**56.2%** (b) (4)	**0.1%** (b) (4)
All Randomized*	**53.3%** (b) (4)	**54.6%** (b) (4)	**-1%** (b) (4)

*Statistical Reviewer's analysis (second review cycle), with all dropouts coded as failures.

The FDA Statistical reviewer determined that the Applicant hadn't adequately justified the (b) (4) noninferiority (NI) margin. She found that only one study in the Applicant's meta-analysis of 16 placebo-controlled studies (Sninski, et al.) was suitable to determine an NI margin. The other studies differed substantively in their design from Study BZUC3003 (different primary endpoints, duration of treatment and patient populations). The noninferiority margin derived from the Sninski study, -3%, was much smaller than that used by the Applicant. The treatment effect for Asacol in the Sninski study was estimated to be 26%, with a 95% confidence interval of (6%, 45%). Halving of the lower bound of the confidence interval resulted in the 3% margin. Using the 3% margin, the Statistical reviewer concluded that Study BZUC3003 did not establish that Giazo is noninferior to Asacol.

Given the differences in outcome by gender observed in Study BZUC3002, the response rates by gender were of particular interest in Study BZCU3003. The analyses of the primary endpoint by gender are summarized in the table below.

Table 5. Analysis of Efficacy by Gender, mITT Population Study BZU3003

	Giazo 6.6 g/day % (# response/N)	Asacol 2.4 g/day % (# response/N)	Difference (Giazo – Asacol) (95% C.I.)
Males	**51%** (b) (4)	**49%** (b) (4)	**2%** (b) (4) (b) (4)

The reviewers noted that the lack of a placebo arm renders this study unable to address the gender issue raised in the review of Study BZCU3002. The lower limit of the confidence intervals for the comparison of Giazo and Asacol is lower in females than males in this study,

(b) (4) The Statistical reviewer explored pooling the data from Studies BZCU3002 and BZCU3003 and found that the pooled female response rate from the two trials for Giazo remained indistinguishable from the placebo arm from BZCU3002.

The first resubmission received a CR, and the Applicant resubmitted again on October 26, 2010. In the second resubmission the Applicant attempted to address the noninferiority margin issue from BZCU3003 through re-derivation of the noninferiority margin, and argued that reanalysis of both Studies BZCU3002 and BZU3003 showed that females with mildly to moderately active ulcerative colitis have a disease response to Giazo therapy. The Applicant presented a reanalysis of BZCU3003 using an endpoint from a historical study to show that a (b) (4) noninferiority margin was met. The reviewers did not find this reanalysis persuasive. With regard to the gender discrepancy in efficacy, the Applicant provided an analysis of the placebo controlled trial, Study BZU3002, and continued to argue that the absence of observed treatment effect in females was secondary to a spuriously high placebo response for the primary endpoint. The Applicant argued that there was a consistent treatment effect observed in females in the secondary efficacy endpoints and that the gender difference was driven by the MMDAI subcomponent stool frequency. However, the Clinical reviewer noted that the post hoc analysis of each MMDAI subcomponent revealed a consistent gender disparity.

The Clinical reviewer, Dr. Leptak, investigated trials that supported approval of other mesalamine related products for ulcerative colitis looking for previously documented evidence of gender disparity in this drug class. He noted that in most of the trials in which he found apparent differences between genders, the differences appeared to be compatible with subgroup variability. However, the results of the four-week placebo controlled study of the balsalazide formulation Colazal were considered particularly noteworthy, in that they also suggest a discrepancy in balsalazide efficacy based on gender (see Table below, which is reproduced from the CDTL review). The endpoints for which differences are most apparent are stool frequency, abdominal pain and patient functional assessment.

Table 6. Results of Placebo-Controlled Trial of Colazal in UC (Study CP069101)

Efficacy Endpoints		Colazal 6.75 g/day Men (n=46) Women (n=26)	Placebo Men (n=19) Women (n=16)	Difference Giazo - Placebo
Stool Blood	Men	33%	21%	12%
	Women	54%	44%	10%
Stool Frequency	Men	42%	26%	16%
	Women	27%	31%	-4%
Patient Functional Assessment	Men	44%	16%	28%
	Women	35%	38%	-3%
Abdominal Pain	Men	22%	16%	6%
	Women	27%	44%	-17%
Symptom Assessment	Men	30%	21%	9%
	Women	39%	38%	1%
Sigmoidoscopy	Men	48%	47%	1%
	Women	39%	37%	2%
Physician's Global Assessment	Men	35%	47%	-12%
	Women	39%	50%	-11%

Adapted from Table 22 of Clinical Review for the second review cycle, which was modified from Colazal Applicant's NDA 20-610 submission, 1988, Vol 7.1, p. 164. Missing values are counted as failures.

The Clinical and Statistical reviewers concluded that the gender analysis from this placebo controlled trial of the previously approved balsalazide product, Colazal, also suggested discrepant gender effects. This additional information provided some support for limiting the indication of Giazo to males.

I concur with the Dr. Hyde's summary comments in his review of the second resubmission regarding the evidence of efficacy of Giazo presented in this NDA. That discussion can be found in Section 11. Other Relevant Regulatory Issues of his CDTL review. I agree with the Clinical and Statistical reviewers from the previous review cycles that Study BZCU3003 did not establish noninferiority to Asacol with a margin that could be supported. I agree with Dr. Hyde's position that the second study (the noninferiority trial) is not critical for approval. Oral balsalazide has previously been shown to be efficacious for the indication proposed in this NDA. A statistically highly persuasive p-value should not be required for BZCU3002 since it is for a new dosing format for balsalazide (tablets administered twice a day), a product already marketed as capsules (three times a day dosing), and a pro-drug for a drug, mesalamine, which has been shown to be effective for the same indication in other marketing applications.

I agree that the gender discrepancy in efficacy observed in Study BZCU3002 remains unexplained. It is difficult to take the position that Giazo is not efficacious, in light of the favorable outcome for the primary endpoint for the overall study population and that balsalazide has been shown to be effective for treatment of ulcerative colitis in the past. I believe that the reviewers' recommendation in the previous resubmission to limit product labeling to treatment of men can be supported in light of the discrepant efficacy outcome in females treated in BZCU3002, and the gender analysis of the placebo controlled trial for the approved balsalazide product Colazal, which also suggests the presence of disparity of

treatment effect by gender. I agree that the Indications and Usage section of the product label should include the language, "Effectiveness in female patients was not demonstrated in clinical studies."

The reviewers recommended a post marketing commitment (PMC) placebo controlled trial of female patients with active ulcerative colitis to assess the efficacy of an eight week course of Giazo therapy for the treatment of active disease in this patient population. The previous reviewers recommended that this trial include a Colazal (balsalazide capsules) arm to further evaluate the efficacy of that balsalazide product in females. The applicant agreed to that trial as a PMC during the previous review cycle, but questioned whether study of Colazal product should be included in the PMC for Giazo during this review cycle. The wording of the PMC was revised to a more general statement, and the applicant and Division agreed to table discussion of whether a Colazal arm should be included until the protocol is submitted for review. See final wording of this PMC in the action letter and at the end of this review.

I concur with the reviewers' recommendation to retain the PMC (agreed to by the applicant in the previous review cycle) to study the impact of antibiotic use on Giazo metabolism. The product is metabolized to active moieties in the gut lumen by gut bacteria. For this reason, it is possible that antibiotic use could alter the production of the active metabolites of Giazo, which could negatively impact efficacy.

8. Safety

The total safety data base was comprised of 565 patients treated with Giazo, of whom 430 had been exposed for more than eight weeks, 331 for at least six months, and 140 for at least a year. I concur with the Clinical reviewers' previous conclusion that the overall safety profile of Giazo is similar to that of the approved capsule dosage form of balsalazide. The Clinical reviewer assessed the adverse event data based on gender and found that a lower proportion of males had adverse events than females.

I concur with the Clinical reviewers' recommendations that the adverse reaction information from postmarketing experience with the other balsalazide formulation, Colazal, and important adverse reaction information from postmarketing experience with products that contain mesalamine should be included in the Giazo label. Those recommendations are reflected in labeling negotiated with the Applicant.

9. Advisory Committee Meeting

There was no Advisory Committee to discuss this application.

10. Pediatrics

The Applicant requested full waiver of the PREA requirement for pediatric studies, stating that Giazo doesn't represent a meaningful benefit over existing available therapy for the pediatric population. The Applicant's balsalazide disodium product, Colazal, which is formulated in a capsule, is approved for treating active UC in pediatric patients ages 5 through 17 years. The capsules can be opened to sprinkle on food. The Pediatric Research Committee (PeRC), on

October 29, 2008 (in the second review cycle), agreed with waiving requirements under the age of 12 years, but felt that the BID dosing option (vs. TID with Colazal capsules) should be available to pediatric patients who can take tablets. The PeRC told the reviewers that if they believed that adequate information already exists to permit labeling for children aged 12 and over, a waiver could be granted. They deferred to the review team as to whether additional studies would be needed.

In the third review cycle (second resubmission), in response to negotiations with the FDA review team, the Applicant proposed a pediatric plan to conduct a PK study in male patients ages 12 through 17 years. The application was presented to PeRC on April 14, 2010, and the committee concurred with the plan, but suggested considering including children of even younger ages who still might be able to swallow the tablet.

During the current review cycle, the review team noted that balsalazide disodium (trade name Colazal) was designated an Orphan Drug Product on August 12, 2005 for the "treatment of **pediatric patients** with ulcerative colitis" [emphasis added] prior to the submission of this NDA for Giazo (balsalazide disodium in a tablet dosage form) on July 16, 2007. The review team consulted with Office of Orphan Products Development and with the Pediatric and Maternal Health Staff and was informed that the orphan designation for balsalazide capsules (Colazal) also applies to balsalazide tablets. Based on the orphan designation for the active moiety (also made by Salix Pharmaceuticals, Inc.), which predated the submission of the current NDA, PREA does not apply to this application. This issue was not identified during previous review cycles of this NDA. As the CDTL for this resubmission, Dr. Fiorentino notes in his review, "As a related historical precedent, DGIEP has had recent experience with a separate BLA application (Remicade, BLA#103772) in which OCC interpreted the Act to mean that PREA does not apply to adult approvals in which the same indication has orphan designation in pediatrics. During the review of the pediatric study for Remicade (conducted under the assumption that PREA applied), the Office of Chief Counsel (OCC) provided DGIEP a memorandum (dated August 18, 2011) noting that, "per section 505B(k) of the Act, PREA was not triggered and there should not have been a required PREA PMR" at the time of the adult approval."

For this reason, even though the applicant had agreed in the previous review cycle (on April 2, 2010) to a required pediatric study under PREA (a PK study in pediatric patients ages 12 through 17), the study can only be requested as a PMC under the reporting requirements under Section 506B (not PREA).

The reviewers and members of the Pediatric and Maternal Health staff met to re-evaluate the type of pediatric study that should be requested as a PMC during this review cycle. The Applicant's balsalazide capsule product, Colazal, is approved for treatment of both adults and pediatric patients with ulcerative colitis. The Colazal label includes the following information regarding use in the pediatric population:

1 INDICATIONS AND USAGE
COLAZAL is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 5 years of age and older. Safety and effectiveness of COLAZAL beyond 8 weeks in children (ages 5-17 years) and 12 weeks in adults have not been established.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dose

For treatment of active ulcerative colitis in adult patients, the usual dose is three 750 mg COLAZAL capsules to be taken 3 times a day (6.75 g per day) for up to 8 weeks. Some patients in the adult clinical trials required treatment for up to 12 weeks.

2.2 Pediatric Dose

For treatment of active ulcerative colitis in pediatric patients, aged 5 to 17 years, the usual dose is EITHER:

• three 750 mg COLAZAL capsules 3 times a day (6.75 g per day) for up to 8 weeks;

OR:

• one 750 mg COLAZAL capsule 3 times a day (2.25 g per day) for up to 8 weeks.

Use of COLAZAL in the pediatric population for more than 8 weeks has not been evaluated in clinical trials. [See Clinical Studies Section (14)]

8.4 Pediatric Use

(b) (4)

[redacted]

• a clinical trial of 68 patients ages 5-17 years comparing two doses of COLAZAL (6.75 g/day and 2.25 g/day), and

(b) (4)

[redacted] Based on the limited data available, dosing can be initiated at either 6.75 or 2.25 g/day.

Safety and efficacy of COLAZAL in pediatric patients below the age of 5 years have not been established.

12 CLINICAL PHARMACOLOGY

Pediatric Population

In studies of pediatric patients with mild-to-moderate active ulcerative colitis receiving three 750 mg COLAZAL capsules 3 times daily (6.75 g/day) for 8 weeks, steady state was reached within 2 weeks, as observed in adult patients. Likewise, the pharmacokinetics of balsalazide, 5-ASA, and N-Ac-5-ASA were characterized by very large inter-patient variability, which is also similar to that seen in adult patients. The pro-drug moiety, balsalazide, appeared to exhibit dose-independent (i.e., dose-linear) kinetics in children, and the systemic exposure parameters (C_{max} and AUC_{0-8}) increased in an almost dose-proportional fashion after the 6.75 g/day versus the 2.25 g/day doses. However, the absolute magnitude of these exposure parameters was greater relative to adults. The C_{max} and AUC_{0-8} observed in pediatric patients were 26% and 102% greater than those observed in adult patients at the 6.75 g/day dosage level. In contrast, the systemic exposure parameters for the active metabolites, 5-ASA and N-Ac-5-ASA, in pediatric patients increased in a less than dose proportional manner after the 6.75 g/day dose versus the 2.25 g/day dose. Additionally, the magnitude of these exposure parameters was decreased for both metabolites relative to adults. For the metabolite of key safety concern from a systemic exposure perspective, 5-ASA, the C_{max} and AUC_{0-8} observed in pediatric patients were 67% and 64% lower than those observed in adult patients at the 6.75 g/day dosage level. Likewise, for N-Ac-5-ASA, the C_{max} and AUC_{0-8} observed in pediatric patients were 68% and 55% lower than those observed in adult patients at the 6.75 g/day dosage level.

14 CLINICAL STUDIES

14.2 Pediatric Studies

A clinical trial was conducted comparing two doses (6.75 g/day and 2.25 g/day) of COLAZAL in 68 pediatric patients (age 5 to 17, 23 males and 45 females) with mildly to moderately active ulcerative colitis. 28/33 (85%) patients randomized to 6.75 g/day and 25/35 (71%) patients randomized to 2.25 g/day completed the study. The primary endpoint for this study was the proportion of subjects with clinical improvement (defined as a reduction of at least 3 points in the Modified Sutherland Ulcerative Colitis Activity Index [MUCAI] from baseline to 8 weeks). Fifteen (45%) patients in the COLAZAL 6.75 g/day group and 13 (37%) patients in the COLAZAL 2.25 g/day group showed this clinical improvement. In both groups, patients with higher MUCAI total scores at baseline were likely to experience greater improvement.

Rectal bleeding improved in 64% of patients treated with COLAZAL 6.75 g/day and 54% of patients treated with COLAZAL 2.25 g/day. Colonic mucosal appearance upon endoscopy improved in 61% of patients treated with COLAZAL 6.75 g/day and 46% of patients treated with COLAZAL 2.25 g/day.

The pediatric program from Colazal was re-examined to determine whether merely performing pediatric PK trials with Giazo would be adequate to establish a safe and effective dose of Giazo for pediatric use. The reviewers noted that the PK of Colazal was different between children and adults. (Children had higher balsalazide exposures and lower active metabolite exposures.) Two pediatric doses are labeled for Colazal, the adult dose and a lower dose, both of which were the only doses studied in the pediatric efficacy trial (which did not include a placebo control). Although there was a numerically higher response rate in the higher dose group, the difference was not statistically significant. Ultimately, the reviewers concluded that FDA could not determine a safe and effective pediatric dose based on pharmacokinetic studies alone, and that the PMC should be revised to include pharmacodynamic evaluation to support exposure/response assessments. By this, the team intends that the applicant will include evaluation of endpoints such as clinical response and/or mucosal healing in the trial. The Applicant agreed to inclusion of pharmacodynamic evaluation in the PMC. They agreed to conduct a pediatric trial as a PMC under the reporting requirements of Section 506B. The PMC will state:

> PMC 1627-1: A single- and repeated-dose pharmacodynamics and pharmacokinetics trial of Giazo tablets administered orally to pediatric patients ages 12 years to less than 17 years with mildly to moderately active ulcerative colitis to support pediatric labeling.

I concur with the CDTL and the previous Clinical Reviewers' conclusions regarding the limitations for use of Giazo in children younger than age 12 years, in light of the large pill size.

11. Other Relevant Regulatory Issues

DSI inspected sites from both BZUC3002 and BZUC3003. The clinical data from BZUC3002 were found to be acceptable in the first review cycle. The Clinical Inspection Summary memo from DSI for BZUC3003, in the second review cycle, concluded that the data from both inspected sites could be used in support of the NDA.

I concur with the Clinical reviewers' conclusion that a QT evaluation for Giazo is not necessary.

Although the Division has been advising sponsors of products intended to treat UC that NDAs for products that will be utilized for chronic management of this disease should be supported by studies of one year duration, the Applicant reached agreement with the Division in an end of phase 2 meeting in 2005 that they would only need to complete induction studies to support an NDA. The CDTL from the previous review cycles concluded that this agreement should stand, and I concur. I agree that labeling should explicitly state the limitations of the clinical studies upon which the approval was based. The Indications and Usage section of the product label will include the language, "Safety and effectiveness of Giazo therapy beyond 8 weeks have not been established." The Dosage and Administration section will state "The dose is

three 1.1 g GIAZO tablets to be taken 2 times a day with or without food (6.6 g per day) for up to 8 weeks." [emphasis added]

12. Labeling

Please see Dr. John Hyde's CDTL review from the previous resubmission for a detailed discussion of the labeling issues. The reviewers' recommendations regarding labeling were incorporated in label negotiations. I concur with limiting the indication to male patients, and stating in the indication that "effectiveness in female patients was not demonstrated in clinical studies." In addition, I agree with including the statement that "Safety and effectiveness of Giazo therapy beyond 8 weeks have not been established." I agree with only including the results of the placebo controlled trial in the product label, and that for the primary endpoint, the efficacy outcomes for both males and females should be presented so that prescribers may better understand why the product is indicated only for men.

With regard to the proprietary name, in the initial review cycle, the Division of Medication Error Prevention and Analysis (DMEPA) reviewer objected to the Applicant's proposed trade name, "Giazo" because it represented a dual trade name. During the review of the subsequent resubmission DMEPA reexamined the previously identified issues surrounding use of the name "Giazo" for a tablet form of balsalazide by an Applicant who has another balsalazide product marketed under a different name, the capsule formulation Colazal. They examined the Applicant's submission of results from a Failure Mode Effect Analysis and their arguments to justify the trade name "Giazo". DMEPA ultimately recommended that the proposed trade name is acceptable. They confirmed that the name remained acceptable in a review conducted during this review cycle. DMEPA's recommendations regarding labeling, including container and carton labeling, were incorporated and addressed in labeling negotiations in the previous review cycle.

DDMAC's recommendations for labeling revisions were incorporated in labeling negotiations.

The Study Endpoints and Labeling Division (SEALD) was consulted in this review cycle and their recommendations were incorporated in final product labeling. Changes in the wording and format of the Indications and Usage section and the Dosage and Administration section of the label referenced in my current review, relative to my previous reviews, reflect incorporation of SEALD's recommendations during this review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

I concur with the recommendations of the reviewers that the Applicant has provided sufficient information to support approval of this balsalazide product for the indication:

> GIAZO is indicated for the treatment of mildly to moderately active ulcerative colitis in male patients 18 years of age and older.
>
> Limitations of Use:

- Effectiveness of GIAZO in the treatment of female patients was not demonstrated in clinical trials.
- Safety and effectiveness of GIAZO therapy beyond 8 weeks have not been established.

The manufacturing issues identified in by the Office of Compliance in the previous review cycle have been resolved.

- Risk Benefit Assessment

The risk characteristics of Giazo appear similar to those of the currently marketed oral balsalazide product. The reviewers have determined that efficacy of Giazo has been established in male patients only, based on the results of the single, placebo controlled trial submitted in support of this application, Study BZU3002. The product will be indicated for male patients with mildly to moderately active ulcerative colitis.

- Recommendation for Postmarketing Risk Management Activities - None.

- Recommendation for other Postmarketing Study Commitments

The following post marketing commitments will be included in the approval letter. These PMCs are subject to the reporting requirements under Section 506B. (The pediatric study cannot be required under PREA due to the Orphan designation for balsalazide capsules (Colazal) for pediatric ulcerative colitis, which occurred prior to submission of this NDA.)

PMC 1627-1: A single- and repeated-dose pharmacokinetic trial of Giazo tablets administered orally to pediatric patients ages 12 years to less than 17 years with mildly to moderately active ulcerative colitis to support pediatric labeling.

Final Protocol Submission:	06/2013
Trial Completion:	06/2015
Final Report Submission:	12/2015

PMC 1627-2: A placebo-controlled clinical trial in female patients with active ulcerative colitis to assess the efficacy of an eight week course of Giazo therapy for the treatment of active disease in this patient population.

Final Protocol Submission:	01/2013
Trial Completion:	06/2015
Final Report Submission:	12/2015

PMC 1627-3: A pharmacokinetic trial in patients to evaluate the effect of concomitant therapy with antibiotics commonly used in ulcerative colitis on the metabolism of balsalazide following administration of Giazo.

Final Protocol Submission:	01/2013

Trial Completion:	01/2015
Final Report Submission:	06/2015

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/s/

DONNA J GRIEBEL
02/03/2012