Clinical Pharmacology Review

Submission: **NDA 20-610 / SLR-016** **Stamp Date**: 6/20/06

Trade Name: Colazal® Capsule, 750 mg **Team Leader**: Abimbola Adebowale, Ph.D.

Active Ingredient: Balsalazide disodium

Sponsor: Salix Pharmaceuticals, Inc.

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

Type of Submission: Efficacy Supplement for Pediatric Labeling

Background

NDA 20-610 for Balsalazide disodium (Colazal®) Capsule, 750 mg was approved by the Agency on July 18, 2000 for the treatment of mildly to moderately active ulcerative colitis. The recommended dosage is three 750 mg capsules three times daily for a total daily dose of 6.75 g. Balsalazide (BSZ) is a prodrug designed to deliver mesalamine (5-ASA) to the colon, where it is cleaved by bacteria azoreductases to release the active moiety (5-ASA) and the inactive carrier, 4-amino benzoyl-β-alanine (4-ABA). The mechanism of action of 5-ASA is unknown, but appears to be primarily topical rather than systemic.

To obtain needed pediatric information on balsalazide, the Agency issued a formal Pediatric Written Request (PWR) for Colazal® Capsules on 12/17/01. The PWR was further amended on 7/2/02, 12/18/02, 5/7/04 and 12/15/05. The Agency requested in the PWR that the sponsor conduct a single study to evaluate the pharmacokinetics (PK), safety and efficacy of balsalazide in no less than 40 pediatric patients, 5 to 17 yrs of age with mildly to moderately active ulcerative colitis (UC). Eligible patients were to be randomized to two dose levels of balsalazide.

In fulfillment of the amended PWR for Colazal®, the sponsor has provided the final report for study BZUC3001 for Agency review and comments.

The current review will solely address the clinical pharmacology-related findings of the study.

Study BZUC3001 is entitled,

"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"

Objectives

- To evaluate the efficacy, safety and PK of two dosage regimens of Colazal® in pediatric patients with mildly to moderately active UC over a treatment period of 8 weeks.

Study Design

A multi-center, randomized, double-blind, parallel study

Planned Enrollment	68 pediatric patients with confirmed mild to moderate active UC with a baseline Modified Sutherland UC activity index (MUCAI) score between 4 and 10 (29 per protocol completers, age 6-17 yrs)
Treatments	Subjects received one of the following treatments for 8 weeks: • 6.75 g (three Colazal 750mg Capsules administered TID) • 2.25 g (one Colazal 750mg Capsule administered TID)
PK Sampling Times	For determination of balsalazide and its metabolites, plasma samples were collected from 6 subjects/dose level at the following time points: 0 (pre-dose), 1, 2, 3, 4, 6 and 8 hrs after the first dose on treatment day 14.

Pharmacokinetic Analysis

Plasma concentrations of balsalazide and its primary metabolites (5-ASA, NASA, 4-ABA and NABA) were determined using a validated HPLC-MS/MS analytical assay. The following pharmacokinetic parameters were determined for balsalazide and its metabolites: C_{max}, t_{max}, AUC_{0-8}, $t_{1/2}$, CL/F, Cave, Cmin, Cmax/Cmin and % fluctuation.

Analytical Method

The HPLC/MS/MS method was validated for the determination of balsalazide over a concentration range of 5 to 1000 ng/mL. The analytical method was also validated for 5-ASA, NASA, 4-ABA and NABA over concentration ranges of 20-4000 ng/mL, 20-4000 ng/mL, 1-200 ng/mL and 2-400 ng/mL, respectively. The analytical method was within acceptable limits (i.e., 75-125% for the LLOQ samples and 85-115% for the low, medium and high QC samples) with respect to specificity, inter- and intra-assay precision and accuracy.

Results and Discussion

Overall, the PK data of balsalazide and its metabolites in pediatric patients are characterized by large inter-individual variability, similar to what was observed in adults. The PK parameters of balsalazide generally increased in a dose-linear manner. However, this was not observed for balsalazide metabolites (Table 1). Cmax, Cmin and AUC of balsalazide were increased by 26%, 27% and 102%, respectively in pediatric patients relative to adults. However, Cmax, Cmin and AUC of balsalazide metabolites were markedly reduced in pediatric patients relative to adults (Table 2).

Table 1. Summary of the PK parameters for balsalazide and its metabolites following one week of TID dosing with Colazal in pediatric patients

Parameter	6.75 g/day				2.25 g/day			
	Mean	SD	CV%	N	Mean	SD	CV%	N
T_{max}[a], h								
Balsalazide	1.54	(1.0-6.0)	-	6	1.00	(1.0-2.0)	-	6
5-ASA	2.50	(1.0-6.0)	-	4	3.00	(2.0-6.0)	-	5
N-Ac-5-ASA	1.96	(1.0-6.0)	-	6	2.99	(2.0-8.0)	-	6
4-ABA	2.54	(1.9-8.0)	-	6	5.00	(2.0-7.9)	-	6
N-Ac-4-ABA	2.46	(1.0-6.0)	-	6	3.99	(2.0-7.8)	-	6
C_{max}, ng/mL								
Balsalazide	452	400	88.5	6	211	156	73.8	6
5-ASA	344	352	102.5	6	317	268	84.5	6
N-Ac-5-ASA	815	782	96.0	6	686	423	61.7	6
4-ABA	37.8	46.7	123.7	6	22.0	14.1	64.2	6
N-Ac-4-ABA	85.0	89.1	104.9	6	51.0	49.9	97.8	6
DN-C_{max}[b], mL^{-1}								
Balsalazide	201	178	88.5	6	281	208	73.8	6
5-ASA	153	157	102.5	6	423	357	84.5	6
N-Ac-5-ASA	362	348	96.0	6	914	564	61.7	6
4-ABA	17	21	123.7	6	29	19	64.2	6
N-Ac-4-ABA	38	40	104.9	6	68	67	97.8	6
AUC_{0-8}, ng·h/mL								
Balsalazide	2031.1	1963.7	96.7	6	624.8	473.6	75.8	6
5-ASA	1931.0	2236.0	115.8	6	2042.9	1663.9	81.4	6
N-Ac-5-ASA	4721.1	4613.2	97.7	6	4582.0	2811.5	61.4	6
4-ABA	220.0	303.6	138.0	6	137.0	93.1	68.0	6
N-Ac-4-ABA	515.5	614.8	119.2	6	349.0	359.9	103.1	6
DN-AUC_{0-8}[b], h/mL								
Balsalazide	903	873	96.7	6	833	631	75.8	6
5-ASA	858	994	115.8	6	2724	2219	81.4	6
N-Ac-5-ASA	2098	2050	97.7	6	6109	3749	61.4	6
4-ABA	98	135	138.0	6	183	124	68.0	6
N-Ac-4-ABA	229	273	119.2	6	465	480	103.1	6
% Fluctuation								
Balsalazide	172	49.0	28.5	6	252	56.3	22.4	6
5-ASA	105	93.3	88.9	4	46.5	12.4	26.7	5
N-Ac-5-ASA	95.2	65.3	68.6	6	59.3	60.7	102.3	6
4-ABA	84.6	59.2	70.0	6	62.2	16.1	25.9	6
N-Ac-4-ABA	85.2	49.1	57.7	6	51.3	24.9	48.6	6

4-ABA = 4-aminobenzoyl-β-alanine; 5-ASA = 5-aminosalicylic acid; AUC_{0-8} = area under the plasma concentration-time curve from 0 to 8 hours; C_{max} = maximum observed plasma concentration after Colazal administration; DN-AUC_{0-8} = dose-normalized AUC, calculated as AUC/TID dose administered; DN-C_{max} = dose-normalized C_{max}, calculated as C_{max}/TID dose administered; N-Ac-4-ABA = N-acetyl-4-aminobenzoyl-β-alanine; N-Ac-5-ASA; N-acetyl-5-aminosalicylic acid; T_{max} = time to maximum observed plasma concentration after Colazal administration.

Table 2. Comparative PK data in pediatric and adult patients with mild to moderate UC

	Pediatrics		Adults[b]
Parameter	**Colazal 6.75 g/day**	**Colazal 2.25 g/day**	**Colazal 6.75 g/day**
C_{max}, ng/mL	452 (89%)	211 (74%)	386 (71%)
C_{min}, ng/mL	67.9 (178%)	24.7 (125%)	53.5 (107%)
AUC_{0-8}, ng•h/mL	2031.1 (97%)	624.8 (76%)	1005 (59%)
% Fluctuation	172 (29%)	252 (24%)	273 (50%)

AUC_{0-8} = area under the plasma concentration-time curve from 0 to 8 hours; C_{max} = maximum observed plasma concentration after Colazal administration; C_{min} = minimum plasma concentration during the dosing interval; CV = coefficient of variation; Percent fluctuation = Computed as 100 x ($C_{max} - C_{min}/C_{ave}$).

In summary, the study results indicate that relative to adults, administration of balsalazide in pediatric patients aged 6-17 years was associated with lower systemic exposure of 5-ASA and NASA, the two key balsalazide metabolites of greatest interest from a safety and efficacy perspective. The study also showed that clinical improvement in UC was demonstrated in 45% and 37% of pediatric patients treated with the 6.75 g/day and 2.25 g/day dose level, respectively. However, those differences were not statistically significant. Moreover, the two dose levels employed in the study were generally safe and well tolerated in the pediatric patients. Hence, the sponsor recommends the 2.25 g/day and 6.75 g/day dose levels for use in the treatment of pediatric patients 5-17 yrs of age with mildly to moderately active UC.

Reviewer Recommendations

The final study report has been reviewed by the Office of Clinical Pharmacology (OCP/Division of Clinical Pharmacology 3), and from the view point of OCP, the sponsor has fulfilled the PK provisions of the PWR for Colazal. The sponsor's recommended dosages of 6.75 g/day and 2.25 g/day up to 8 weeks in pediatric patients 5-17 yrs of age with mildly to moderately active UC are **acceptable** from a clinical pharmacology perspective. The sponsor's proposed labeling is acceptable. See attachment 1 for the Package Insert incorporating the sponsor's proposed changes to the labeling. It should be noted that the proposed label in this supplement will need to be updated with labeling revisions introduced as a result of NDA 20-610/S-014, which provides for information on the effect of food on the PK of balsalazide.

Attachment 1

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

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/s/

Suliman Alfayoumi
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