Clinical Pharmacology BPCA Summary

Submission: NDA 20-610 / SE5-016
Stamp Date: 6/20/06
Trade Name: Colazal Capsule, 750 mg
Acting 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

1 Executive Summary

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. In the colon, balsalazide is cleaved by bacteria azoreductases to release the active moiety (5-ASA) and the inactive carrier, 4-amino benzoyl-®-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 provided the final report for study BZUC3001 for Agency review and comments. Study BZUC3001was designed as a multi-center, randomized, double-blind, and parallel study to evaluate the efficacy, safety and pharmacokinetics of two dosage regimens (6.7g/day or 2.25g/day) of Colazal in pediatric patients with mildly to moderately active UC over a treatment period of 8 weeks.

1.1 Recommendation (s):

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 for 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. Labeling recommendations for the applicant's proposed label were provided by the Agency.

1.2 Phase IV Commitments: None

1.3 Summary of Clinical Pharmacology (CP) Findings:

In summary, the study results indicated that relative to adults, administration of balsalazide in pediatric patients aged 6-17 years was associated with lower systemic exposure of mesalamine (5-aminosalicylic acid or 5-ASA) and N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA or 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 applicant 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.

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Dennis Bashaw

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