# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**022205Orig1s000**

# PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

# PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22,205

SERIAL NUMBER: 000

DATE RECEIVED BY CENTER: July 17, 2007

DRUG NAME: Balsalazide disodium / Colazal, tablets

INTENDED CLINICAL POPULATION: Patients with mildly to moderately active ulcerative colitis.

SPONSOR: Salix Pharmaceuticals, Inc.
Morrisville, NC

DOCUMENTS REVIEWED: EDR - Module 4

REVIEW DIVISION: Division of Gastroenterology Products (HFD-180)

PHARM/TOX REVIEWER: Ke Zhang, Ph.D.

PHARM/TOX SUPERVISOR: Sushanta Charkder, Ph.D.

DIVISION DIRECTOR: Daniel A Shames, M.D.

PROJECT MANAGER: Ms Kristen Everett

Date of review submission to Division File System (DFS):
January 10, 2008

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## Executive Summary

1. Recommendations

1.1 Recommendation on approvability

From a preclinical standpoint, approval of Balsalazide disodium, 1.1 g tablets is recommended for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

1.2 Recommendation for nonclinical studies: None

1.3 Recommendation on labeling: The proposed labeling is adequate.

2. Summary of nonclinical findings:

Treatment with Colazal increased the incidence of corticomedullary (females) or pelvic (males) minerlization, papillary urothelial heperplasia and mineralization (males), and urothelial hyperplasia (males and females) at doses of 600 mg/kg/day or higher in the 26-week oral (gavage) toxicity study in rats and in the 24-month dietary carcinogenicity study in rats.

In the 24-month rat carcinogenicity study, oral (dietary) balsalazide disodium at doses up to 2 g/kg/day was not tumorigenic.

Balsalazide disodium was not genotoxic in the Ames test, the human lymphocyte chromosomal aberration test, and the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, or the mouse micronucleus test. However, it was genotoxic in the in vitro Chinese hamster lung cell (CH V79/HGPRT) forward mutation test.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### *2.6.1 INTRODUCTION AND DRUG HISTORY*

NDA number: 22,205
Review number: 01
Sequence number/date/type of submission: 000 / July 17, 2007
Information to sponsor: Yes () No (x)
Sponsor and/or agent:

Salix Pharmaceuticals, Inc.
Morrisville, NC

Manufacturer for drug substance:

(b) (4)

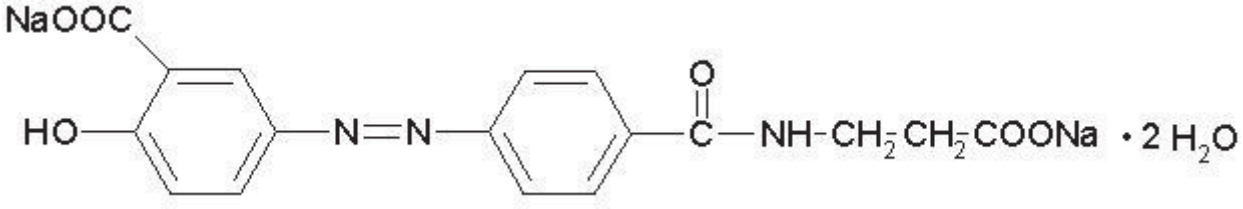
Reviewer name: Ke Zhang
Division name: Division of Gastroenterology Products
HFD #: 180
Review completion date: January 10, 2008

Drug: Balsalazide disodium / Colazal, Tablets

Balsalazide is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid or 5-ASA),

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

Structure:




Molecular Weight: 437.32

Molecular Formula: $C_{17}H_{13}N_3O_6Na_2 \bullet 2H_2O$

Relevant INDs/NDAs/DMFs: IND 38,492 / NDA 20,601

Drug class: Anti-inflammatory drug.

Indication: Balsalazide disodium is indicated for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

Clinical formulation:

Each film-coated tablet contains 1.1 g balsalazide disodium.

Route of administration: Oral tablets

Studies reviewed within this submission: None.

Studies not reviewed within this submission: None.

LABELING:

The sponsor's proposed labeling is in accordance with the current Structured Product Labeling Format for Balsalazide disodium, 1.1 g tablets. However, the following information should be included in the proposed labeling: "Treatment with Colazal increased the incidence of pelvic and corticomedullary mineralization in kidney and urothelial hyperplasia in rats at oral doses of 600 mg/kg/day (about 0.7 fold the recommended human dose based on body surface area) or higher. Therefore, caution should be exercised when administering Colazal to patients with known renal dysfunction or a history of renal disease".

The sentence of [redacted] (b) (4) should be removed.

*3.6 OVERALL conclusions and recommendations*

Balsalazide contains an active moiety, 5-aminosalicylic acid (5-ASA) and a carrier molecule, 4-aminobenzoyl-β-alanine (4-ABA). 5-ASA and 4-ABA are attached via azo bond. Balsalazide is cleaved by bacterial azoreduction in the colon to release equi-molar quantities of 5-ASA and 4-ABA. 5-ASA is an anti-inflammatory agent. It reduces inflammatory response by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. The sponsor submitted a NDA application for Balsalazide disodium, 1.1 g tablets and is seeking for approval to market Balsalazide disodium, 1.1 g tablets for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. The proposed dosage is three 1.1 g two times a day at a total daily dose of 6.6 g.

Balsalazide disodium is currently marketed as oral capsule (750 mg) under a trade name of Colazal for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older. The recommended adult oral dosage of Colazal is three 750 mg capsules three times daily (total daily dose is 6.75 g). The proposed clinical dose of 6.6 g/day is consistent with the recommended oral dosage for Colazal. Therefore, from a preclinical standpoint, this NDA is approvable. The proposed labeling should be revised as recommended.

Recommendations:

1. From a preclinical standpoint, approval of Balsalazide disodium, 1.1 mg tablets at a total daily dose of 6.6 g is recommended for the treatment of mildly to moderately active ulcerative colitis in patients 18 years of age and older.

2. The proposed labeling should be revised as recommended.

_____ _____
Ke Zhang, Ph.D. Date
Pharmacologist, HFD-180

Comments:

_____ _____
Sushanta Chakder, Ph.D. Date
Acting Supervisory Pharmacologist
HFD-180

CC:
IND
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Zhang

R/D Init.: SChakder 12/28/07

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/s/
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1/10/2008 08:22:56 AM
PHARMACOLOGIST

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1/10/2008 09:49:46 AM
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