

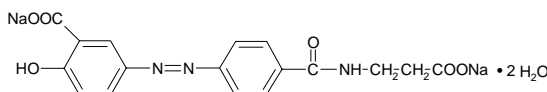
NDA 20-610—7/18/00

Page 1

COLAZAL™ (balsalazide disodium) Capsules

(kôl a zal)

DESCRIPTION: Each Colazal capsule contains 750 mg of balsalazide disodium, a prodrug that is enzymatically cleaved in the colon to produce mesalamine (5-aminosalicylic acid), an anti-inflammatory drug. Each daily dose of COLAZAL™ (6.75 grams) is equivalent to 2.4 grams of mesalamine. Balsalazide disodium has the chemical name (E)-5-[[[-4-[[[(2-carboxyethyl) amino]carbonyl] phenyl]azo]-2-hydroxybenzoic acid, disodium salt, dihydrate. Its structural formula is:



Molecular Weight: 437.32

Molecular Formula: C₁₇H₁₃N₃O₆Na₂ • 2H₂O

Balsalazide disodium is a stable, odorless orange to yellow microcrystalline powder. It is freely soluble in water and isotonic saline, sparingly soluble in methanol and ethanol, and practically insoluble in all other organic solvents.

Inactive Ingredients: Each hard gelatin capsule contains colloidal silicon dioxide and magnesium stearate. The sodium content of each capsule is approximately 86 mg.

CLINICAL PHARMACOLOGY: Balsalazide disodium is delivered intact to the colon where it is cleaved by bacterial azoreduction to release equimolar quantities of mesalamine, which is the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine. The recommended dose of 6.75 grams/day, for the treatment of active disease, provides 2.4 grams of free 5-aminosalicylic acid to the colon.

The 4-aminobenzoyl-β-alanine carrier moiety released when balsalazide disodium is cleaved is only minimally absorbed and largely inert. The mechanism of action of 5-aminosalicylic acid is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanooids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that 5-aminosalicylic acid diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

Pharmacokinetics: COLAZAL™ capsules contain granules of balsalazide disodium which are insoluble in acid and designed to be delivered to the colon intact. Upon reaching the colon, bacterial azoreductases cleave the compound to release 5-aminosalicylic acid the therapeutically active portion of the molecule, and 4-aminobenzoyl-β-alanine.

Absorption: In healthy individuals, the systemic absorption of intact balsalazide was very low and variable. The mean C_{max} occurs approximately 1-2 hours after single oral doses of 1.5 grams or 2.25 grams. The absolute bioavailability of this compound was not determined. In a study of ulcerative colitis patients receiving balsalazide, 1.5 grams twice daily, for over one year, systemic drug exposure, based on mean AUC values, was up to 60 times greater (8 ng*hr/mL to 480 ng*hr/mL) after equivalent multiple doses of 1.5 grams twice daily when compared to healthy subjects who received the same dose. There was a large intersubject variability in the plasma concentration of balsalazide versus time profiles in all studies, thus its half-life could not be determined. The effect of food intake on the absorption of this compound was not studied.

Distribution: The binding of balsalazide to human plasma proteins was ≥ 99%.

Metabolism: The products of the azoreduction of this compound, 5-aminosalicylic acid and 4-aminobenzoyl-β-alanine, and their N-acetylated metabolites have been identified in plasma, urine and feces.

Elimination: Less than 1% of an oral dose was recovered as parent compound, 5-aminosalicylic acid or 4-aminobenzoyl-β-alanine in the urine of healthy subjects after single and multiple doses of COLAZAL™, while up to 25% of the dose was recovered as the N-acetylated metabolites. In a study with 10 healthy volunteers, 65% of a single 2.25 grams dose of COLAZAL™ was recovered as 5-aminosalicylic acid, 4-aminobenzoyl-β-alanine, and the N-acetylated metabolites in feces, while <1% of the dose was recovered as parent compound.

In a study that examined the disposition of balsalazide in patients who were taking 3-6 grams of COLAZAL™ daily for more than one year and who were in remission from ulcerative colitis, less than 1% of an oral dose was recovered as intact balsalazide in the urine. Less than 4% of the dose was recovered as 5-aminosalicylic acid, while virtually no 4-aminobenzoyl-β-alanine was detected in urine. The urinary recovery of the N-acetylated metabolites comprised 20-25% of the balsalazide dose. No fecal recovery studies were performed in this population.

Special Populations

Geriatric: No information is available for the geriatric population.

Pediatric: The safety and effectiveness of balsalazide in the pediatric population have not been established.

Gender: No adequate and well-controlled studies which examine balsalazide in males versus females are available.

Renal Insufficiency: No adequate and well-controlled studies which examine balsalazide disposition in patients with mild, moderate, and severe renal impairment are available.

Hepatic Insufficiency: No information is available for patients with hepatic impairment.

Race: No information is available which examines balsalazide in different races.

Pharmacodynamic/Pharmacokinetic Relationship: No information is available.

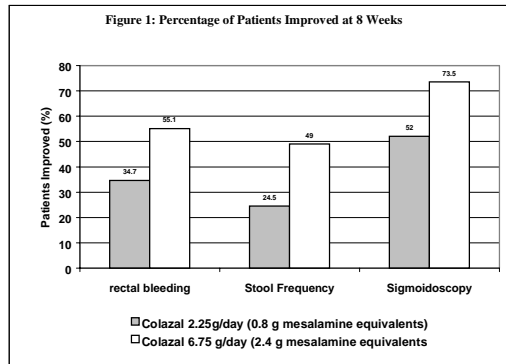
Drug-Drug Interactions: Neither in vitro nor in vivo drug-drug interaction studies have been performed with balsalazide.

CLINICAL TRIALS: Two randomized, double blind studies were conducted.

In the first trial, 103 patients with active mild to moderate ulcerative colitis with sigmoidoscopy findings of friable or spontaneously bleeding mucosa were randomized and treated with balsalazide 6.75 grams/day or balsalazide 2.25 grams/day. The primary efficacy endpoint was reduction of rectal bleeding and improvement of at least one of the other assessed symptoms (stool frequency, patient functional assessment, abdominal pain, sigmoidoscopic grade, and physician's global assessment (PGA)). Outcome assessment for rectal bleeding at each interim period (week 2, 4, and 8) encompassed a 4 day period (96 hours). Results demonstrated a statistically significant difference between high and low doses of COLAZAL™ (Figure 1).

Figure 1 :Percentage of Patients Improved at 8 Weeks

NDA 20-610—7/18/00
Page 2



A second study, conducted in Europe, confirmed findings of symptomatic improvement.

INDICATIONS AND USAGE: COLAZAL™ is indicated for the treatment of mildly to moderately active ulcerative colitis. Safety and effectiveness of Colazal beyond 12 weeks has not been established.

CONTRAINDICATIONS: COLAZAL™ is contraindicated in patients with hypersensitivity to salicylates or to any of the components of COLAZAL™ capsules or balsalazide metabolites.

PRECAUTIONS: Of the 259 patients treated with COLAZAL™ 6.75 grams/day in controlled clinical trials of active disease, exacerbation of the symptoms of colitis, possibly related to drug use, has been reported by 3 patients.

General: Patients with pyloric stenosis may have prolonged gastric retention of Colazal Capsules.

Renal: There have been no reported incidents of renal impairment in patients taking COLAZAL™. At doses up to 2000 mg/kg (approximately 21 times the recommended 6.75 grams/day dose on a mg/kg basis for a 70 kg person), COLAZAL™ had no nephrotoxic effects in rats or dogs. Renal toxicity has been observed in animals and patients given other mesalamine products. Therefore, caution should be exercised when administering COLAZAL™ to patients with known renal dysfunction or a history of renal disease.

Drug Interactions: No drug interaction studies have been conducted for COLAZAL™, however the use of orally administered antibiotics could, theoretically, interfere with the release of mesalamine in the colon.

Carcinogenesis, Mutagenesis, Impairment of Fertility: 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.

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

4-aminobenzoyl-β-alanine, a metabolite of balsalazide disodium, was not genotoxic in the Ames test, and the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test but was positive in the human lymphocyte chromosomal aberration test. N-acetyl-4-aminobenzoyl-β-alanine, a conjugated metabolite of balsalazide disodium, was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation tests, or the human lymphocyte chromosomal aberration test. Balsalazide disodium at oral doses up to 2 grams/kg/day, 2.4 times the recommended human dose based on body surface area, was found to have no effect on fertility and reproductive performance in rats.

Pregnancy - Teratogenic Effects: Pregnancy Category B. Reproduction studies were performed in rats and rabbits at oral doses up to 2 grams/kg/day, 2.4 and 4.7 times the recommended human dose based on body surface area for the rat and rabbit, respectively, and revealed no evidence of impaired fertility or harm to the fetus due to balsalazide disodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether balsalazide disodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when COLAZAL™ is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of COLAZAL™ in pediatric patients have not been established.

ADVERSE REACTIONS: Over 1000 patients received treatment with COLAZAL™ in domestic and foreign clinical trials. In four controlled clinical trials patients receiving a COLAZAL™ dose of 6.75 grams/day most frequently reported the following events (reporting frequency ≥3%), headache (8%), abdominal pain (6%), diarrhea (5%), nausea (5%), vomiting (4%), and respiratory infection (4%), arthralgia (4%). Withdrawal from therapy due to adverse events was comparable among patients on COLAZAL™ and placebo.

Adverse events reported by 1% or more of patients who participated in the four well-controlled, Phase 3 trials are presented by treatment group (Table 1).

Table 1 : Adverse Events Occurring in at Least 1% of COLAZAL™ and Ulcerative Colitis Patients in Controlled Trials

Adverse Event	COLAZAL™ 6.75 grams/day [N = 259]	Placebo [N = 35]
Headache	22 (8%)	3 (9%)
Abdominal pain	16 (6%)	1 (3%)
Nausea	14 (5%)	2 (6%)
Diarrhea	14 (5%)	1 (3%)
Vomiting	11 (4%)	2 (6%)
Respiratory	9 (4%)	5 (14%)
Arthralgia	9 (4%)	--
Rhinitis	6 (2%)	--
Insomnia	6 (2%)	--

NDA 20-610—7/18/00

Page 3

Adverse Event	COLAZAL™ 6.75 grams/day [N = 259]	Placebo [N = 35]
Fatigue	6 (2%)	--
Rectal bleeding	5 (2%)	1 (3%)
Flatulence	5 (2%)	--
Fever	5 (2%)	--
Dyspepsia	5 (2%)	--
Pharyngitis	4 (2%)	-
Pain	4 (2%)	1 (3%)
Coughing	4 (2%)	--
Back pain	4 (2%)	1 (3%)
Anorexia	4 (2%)	--
Urinary Tract	3 (1%)	--
Sinusitis	3 (1%)	1 (3%)
Myalgia	3 (1%)	--
Frequent stools	3 (1%)	1 (3%)
Flu-like disorder	3 (1%)	--
Dry mouth	3 (1%)	--
Dizziness	3 (1%)	2 (6%)
Cramps	3 (1%)	--
Constipation	3 (1%)	--

The number of placebo patients is too small for valid comparisons. Some adverse events, such as abdominal pain, fatigue, and nausea were reported more frequently in women subjects than in men. Abdominal pain, rectal bleeding, and anemia can be part of the clinical presentation of ulcerative colitis.

The following adverse events, presented by body system, have also been infrequently reported by patients taking COLAZAL™ during clinical trials (n = 513) for the treatment of active acute ulcerative colitis or from foreign post-marketing reports. In most cases no relationship to COLAZAL™ has been established.

Body as a Whole: abdomen enlarged, asthenia, chest pain, chills, edema, hot flushes, malaise

Cardiovascular and vascular: bradycardia, deep venous thrombosis, hypertension, leg ulcer, palpitations, pericarditis

Gastrointestinal: amylase increased, bowel irregularity, colitis ulcerative aggravated, diarrhea with blood, diverticulosis, epigastric pain, eructation, fecal incontinence, feces abnormal, gastroenteritis, giardiasis, glossitis, hemorrhoids, melena, neoplasm benign, pancreatitis, ulcerative stomatitis, stools frequent, tenesmus, tongue discoloration

Hematologic: anemia, epistaxis, fibrinogen plasma increase, hemorrhage, prothrombin decrease, prothrombin increase, thrombocytopenia

Liver and biliary: bilirubin increase, hepatic function abnormal, SGOT increase, SGPT increase

Lymphatic: eosinophilia, granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, lymphoma-like disorder, lymphopenia

Metabolic and nutritional: creatinine phosphokinase increased, hypocalcemia, hypokalemia, hypoproteinemia, LDH increase, weight decrease, weight increase

Musculoskeletal: arthritis, arthropathy, stiffness in legs

Nervous: aphasia, dysphonia, gait abnormal, hyposthesia, paresthesia, spasm generalized, tremor

Psychiatric: anxiety, depression, nervousness, somnolence

Reproductive: menstrual disorder

Resistance Mechanism: abscess, immunoglobulins decrease, infection, moniliasis, viral infection

Respiratory: bronchospasm, dyspnea, hemoptysis

Skin: alopecia, angioedema, dermatitis, dry skin, erythema nodosum, erythematous rash, pruritus, pruritus ani, psoriasis, skin ulceration

Special Senses: conjunctivitis, earache, ear infection, iritis, parosmia, taste perversion, tinnitus, vision abnormal

Urinary: hematuria, interstitial nephritis, micturition frequency, polyuria, pyuria

Post Marketing Reports:

The following events have been identified during post-approval use in clinical practice, of products which contain (or are metabolized to) mesalamine. Because they are reported voluntarily from a population of unknown size estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine.

Gastrointestinal: Reports of hepatotoxicity, including elevated liver function tests (SGOT/AST, SGPT/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 fatalities associated with these events were reported in COLAZAL™ clinical trials. One case of Kawasaki-like syndrome which included hepatic function changes was also reported, however, this event was not reported in COLAZAL™ clinical trials.

DRUG ABUSE AND DEPENDENCY:

Abuse: None reported

Dependency: Drug dependence has not been reported with chronic administration of mesalamine.

OVERDOSAGE: 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™ use, 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-β-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.

DOSAGE AND ADMINISTRATION: For Treatment of Active Ulcerative Colitis the usual dose in adults is three 750 mg COLAZAL™ capsules to be taken three times a day for a total daily dose of 6.75 grams for a duration of 8 weeks. Some patients in the clinical trials required treatment for up to 12 weeks.

HOW SUPPLIED: COLAZAL™ is available as beige capsules containing 750 mg balsalazide and BZ imprinted in black.

NDC XXXXX-XXXX-XX Bottles of 280 capsules

Store at 25°C (77 °F); excursions permitted to 15°C-30°C (59–86 °F). See USP Controlled Room Temperature

Rx only

NDA 20-610—7/18/00

Page 4

Manufactured for Salix Pharmaceuticals, Inc., Palo Alto, CA 94303

by: Anabolic, Inc., Irvine, CA 92712

* COLAZAL™ is a trademark of Salix Pharmaceuticals, Inc.

Copyright © 2000 Salix Pharmaceuticals, Inc.

(Identifier code 05/00)