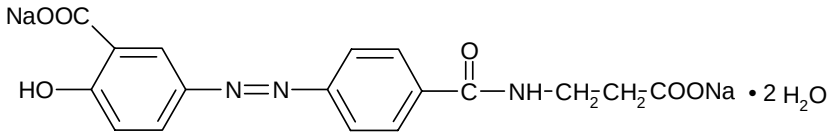
COLAZAL® (balsalazide disodium) Capsules
(kôl a zal)

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 or 5-ASA), 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: $C_{17}H_{13}N_3O_6Na_2 \cdot 2H_2O$

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-ß-alanine. The recommended dose of 6.75 grams/day, for the treatment of active disease, provides 2.4 grams of free 5-ASA to the colon.

The 4-aminobenzoyl-ß-alanine carrier moiety released when balsalazide disodium is cleaved is only minimally absorbed and largely inert. The mechanism of action of 5-ASA is unknown, but appears to be local to the colonic mucosa rather than systemic. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, 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-ASA diminishes inflammation by blocking production of arachidonic acid metabolites in the colon.

Pharmacokinetics: *COLAZAL* capsules contain a powder of balsalazide disodium that is insoluble in acid and designed to be delivered to the colon as the intact prodrug. Upon reaching the colon, bacterial azoreductases cleave the compound to release 5-ASA, the therapeutically active portion of the molecule, and 4-aminobenzoyl-ß-alanine. 5-ASA is further metabolized to yield N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA), a second key metabolite.

Absorption: The plasma pharmacokinetics of balsalazide and its key metabolites from a crossover study in healthy volunteers are summarized in Table 1. In this study, a single oral dose of *COLAZAL* 2.25 g was administered to healthy volunteers as intact capsules (3 x 750 mg) under fasting conditions, as intact capsules (3 x 750 mg) after a high-fat meal, and unencapuslated (3 x 750 mg) as sprinkles on applesauce.

Table 1: Plasma Pharmacokinetics for Balsalazide and Key Metabolites (5—ASA and N-Ac-5-ASA) with Administration of *COLAZAL* Following a Fast, a High-Fat Meal, and Drug Contents Sprinkled on Applesauce (Mean ± SD)

	Fasting n = 17	**High-fat Meal n = 17**	**Sprinkled n = 17**
C_{max} (µg/mL)			
Balsalazide	0.51 ± 0.32	0.45 ± 0.39	0.21 ± 0.12
5-ASA	0.22 ± 0.12	0.11 ± 0.136	0.29 ± 0.17
N-Ac-5-ASA	0.88 ± 0.39	0.64 ± 0.534	1.04 ± 0.57
AUC_{last} (µg·hr/mL)			
Balsalazide	1.35 ± 0.73	1.52 ± 1.01	0.87 ± 0.48
5-ASA	2.59 ± 1.46	2.10 ± 2.58	2.99 ± 1.70
N-Ac-5-ASA	17.8 ± 8.14	17.7 ± 13.7	20.0 ± 11.4
T_{max} (h)			
Balsalazide	0.8 ± 0.85	1.2 ± 1.11	1.6 ± 0.44
5-ASA	8.2 ± 1.98	22.0 ± 8.23	8.7 ± 1.99
N-Ac-5-ASA	9.9 ± 2.49	20.2 ± 8.94	10.8 ± 5.39

A relatively low systemic exposure was observed under all three administered conditions (fasting, fed with high-fat meal, sprinkled on applesauce), which reflects the variable, but minimal absorption of balsalazide disodium and its metabolites. The data indicate that both C_{max} and AUC_{last} were lower, while tmax was markedly prolonged, under fed (high-fat meal) compared to fasted conditions. Moreover, the data suggest that dosing balsalazide disodium as a sprinkle or as a capsule provides highly variable, but relatively similar mean pharmacokinetic parameter values. No inference can be made as to how the systemic exposure differences of balsalazide and its metabolites in this study might predict the clinical efficacy under different dosing conditions (i.e., fasted, fed with high-fat meal, or sprinkled on applesauce) since clinical efficacy after balsalazide disodium administration is presumed to be primarily due to the local effects of 5-ASA on the colonic mucosa.

In a study of 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.

In a separate study of ulcerative colitis, patients received balsalazide, 1.5 grams twice daily, for over 1 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.

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

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

Elimination: Following single-dose administration of 2.25 g COLAZAL (three 750-mg capsules) under fasting conditions in healthy subjects, mean urinary recovery of balsalazide, 5-ASA, and N-Ac-5-ASA was 0.20%, 0.22% and 10.2%, respectively.

In a multiple dose study in healthy subjects receiving a COLAZAL dose of two 750 mg capsules twice daily (3 g/day) for 10 days, mean urinary recovery of balsalazide, 5-ASA, and N-Ac-5-ASA was 0.1%, 0%, and 11.3%, respectively. During this study, subjects received their morning dose 0.5 hours after being fed a standard meal, and subjects received their evening dose 2 hours after being fed a standard meal.

In a study with 10 healthy volunteers, 65% of a single 2.25 gram dose of *COLAZAL* was recovered as 5-ASA, 4-aminobenzoyl-ß-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-ASA, while virtually no 4-aminobenzoyl-ß-alanine was detected in urine. The mean urinary recovery of N-Ac-5-ASA and N-acetyl-4-aminobenzoyl-ß-alanine comprised <16% and <12% of the balsalazide dose, respectively. No fecal recovery studies were performed in this population.

All pharmacokinetic studies with COLAZAL are characterized by large variability in the plasma concentration versus time profiles for balsalazide and its metabolites, thus half-life estimates of these analytes are indeterminate.

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.

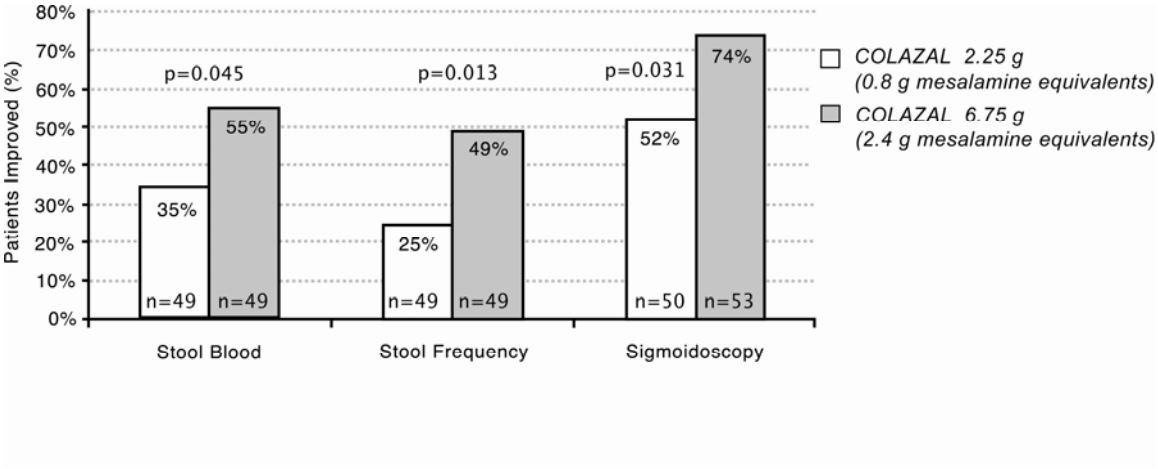
Pharmacodynamic/Pharmacokinetic Relationship: No information is available.

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



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: 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-ß-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-ß-alanine, a conjugated metabolite of balsalazide disodium, was not genotoxic in Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, 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: The 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%), respiratory infection (4%), and 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 2).

Table 2: 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 infection	9 (4%)	5 (14%)
Arthralgia	9 (4%)	--
Rhinitis	6 (2%)	--
Insomnia	6 (2%)	--
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 infection	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, ulcerative colitis 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, thrombocythemia

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: creatine phosphokinase increased, hypocalcemia, hypokalemia, hypoproteinemia, LDH increase, weight decrease, weight increase

Musculoskeletal: arthritis, arthropathy, stiffness in legs

Nervous: aphasia, dysphonia, gait abnormal, hypertonia, hypoesthesia, paresis, 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-ß-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.

COLAZAL capsules may also be administered by carefully opening the capsule and sprinkling the capsule contents on applesauce. The entire drug/applesauce mixture should be swallowed immediately; the contents may be chewed, if necessary, since contents of *COLAZAL* are NOT coated beads/granules. Do not store drug/applesauce mixture for future use.

HOW SUPPLIED: *COLAZAL* is available as beige capsules containing 750 mg balsalazide disodium and CZ imprinted in black.

NDC 65649-101-02 Bottles of 280 capsules.
NDC 65649-101-50 Bottles of 500 capsules.

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). See USP Controlled Room Temperature.

Rx only

Manufactured for Salix Pharmaceuticals, Inc., Morrisville, NC 27560
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