AUSTRALIAN PRODUCT INFORMATION – COLAZIDE® (BALSALAZIDE SODIUM)

1 NAME OF THE MEDICINE

Balsalazide sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient	**mg/capsule**
Balsalazide sodium*	750.0
Excipient	
Magnesium stearate	14.0
Silica - colloidal anhydrous	8.0
Hard gelatin capsules	
Gelatin	114.5
Titanium dioxide	3.36
Iron oxide yellow (CI77492)	0.115
Iron oxide red (CI77491)	0.02
Printing ink	
Iron oxide black (CI77499)	q.s.
Shellac	q.s.

*Capsules containing 750 mg balsalazide sodium, equivalent to 612.8 mg of balsalazide and 262.5 mg of mesalazine.

3 PHARMACEUTICAL FORM

COLAZIDE® capsules are size 00 hard gelatine capsules (beige body and cap), containing an orange/yellow powder with "CZ" printed in black on the cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild-to-moderate active ulcerative colitis and maintenance of remission, in patients who are intolerant to sulfasalazine.

4.2 Dose and method of administration

COLAZIDE® capsules should be swallowed whole with food.

ADULTS

Treatment of active disease:
3 capsules three times daily until remission or for 12 weeks maximum.
Maintenance treatment:

2 capsules twice daily. The dose can be adjusted based on each patient's response. An additional benefit has been shown with a dose of 8 capsules daily. Rectal or oral steroids can be given concomitantly if necessary.

4.3 Contraindications

Hypersensitivity to any component of the product or its metabolites, including mesalazine. History of hypersensitivity to salicylates. Severe hepatic impairment, moderate-severe renal impairment. Last weeks of pregnancy. Patients with a pathological tendency to bleeding, those on concomitant anticoagulants and those with active peptic ulceration.

4.4 Special warnings and precautions for use

General

Balsalazide should be used with caution in patients with asthma.

Blood Dyscrasias

During treatment with Colazide blood counts, BUN/creatinine and urine analysis should be performed. Blood dyscrasias have been reported rarely with other mesalazine-releasing products. Patients receiving balsalazide should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Use in hepatic impairment

Balsalazide should be used with caution in patients with mild to moderate hepatic impairment.

Use in renal impairment

Renal toxicity has been observed in animals and in patients given other mesalazine products. Balsalazide is therefore contraindicated in patients with moderate to severe renal impairment. Caution should be exercised when administering balsalazide to patients with mild renal impairment or a history of renal disease.

Use in the elderly

No dose adjustment is required in elderly patients.

Paediatric use

Balsalazide is not recommended for use in children < 18 years old.

Effects on laboratory tests

No data available

4.5 Interactions with other medicines and other forms of interactions

No formal drug interaction studies have been conducted with balsalazide.

The acetylated metabolites of balsalazide are actively secreted in the renal tubule to a high degree. Therefore, plasma levels of co-prescribed drugs also eliminated by this route may be raised and this should be noted in the case of those with a narrow therapeutic range, such as methotrexate.

Pharmacodynamic interactions have not been studied. However, while balsalazide, mesalazine and N-acetylmesalazine are salicylates chemically, their properties and kinetics make classical salicylate interactions such as those found with acetylsalicylic acid very unlikely.

The uptake of digoxin has been impaired in some individuals by concomitant treatment with sulfasalazine. Even if it is not known whether this would occur also during treatment with balsalazide, it is recommended that plasma levels of digoxin should be monitored in digitalised patients starting COLAZIDE®.

The use of orally administered antibiotics could, theoretically, interfere with the release of mesalazine in the colon.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Studies in rats showed no adverse effects of balsalazide on fertility or general reproductive performance at oral doses up to 2 g/kg/day (about 2.4 times the maximum recommended clinical dose of 6.75 g/kg, based on body surface area).

Use in pregnancy

Pregnancy Category C

Studies in rats and rabbits revealed no evidence for fetotoxicity of balsalazide at oral doses up to 2 and 1.2 g/kg/day, respectively (approximately 3 times the maximum recommended clinical dose of 6.75 g/kg, based on body surface area). Adequate human data on use during pregnancy are not available. In common with other anti-inflammatory agents, mesalazine (released from COLAZIDE®) may produce premature closure of the ductus arteriosus and may, if given at term, prolong labour and delay parturition. Mesalazine is a salicylate and salicylates (for example aspirin (acetylsalicylic acid) may increase bleeding tendency both in the newborn child and the mother. COLAZIDE® is therefore contraindicated in the last weeks of pregnancy. Colazide® should only be given during pregnancy if the benefits clearly outweigh the risks.

Use in lactation

Balsalazide should not be given to breast feeding women as the active metabolite mesalazine has produced adverse effects in nursing infants. It is not known whether balsalazide is excreted into human or animals milk.

4.7 Effects on ability to drive and use machines

Balsalazide does not affect the ability to drive and use machines.

4.8 Adverse effects (Undesirable effects)

In clinical trials with balsalazide in ulcerative colitis, the most commonly reported adverse effects were headache, and gastrointestinal symptoms such as abdominal pain, diarrhoea, nausea and vomiting.

Adverse events reported by 1% or more of patients treated with balsalazide 6.75 g/day in three controlled clinical studies are presented by treatment group (Table 1):

Table 1: Adverse Events Occurring in 1% of COLAZIDE® (Balsalazide) Patients in Controlled Trials

Adverse Event	Balsalazide 6.75 g/day [N = 175]	Mesalazine 2.4 g/day [N = 100]	Placebo [N = 35]
Headache	13 (7%)	20 (20%)	3 (9%)
Abdominal pain	11 (6%)	4 (4%)	1 (3%)
Diarrhoea	8 (5%)	3 (3%)	1 (3%)
Nausea	6 (3%)	7 (7%)	2 (6%)
Respiratory	6 (3%)	5 (5%)	5 (14%)
Arthralgia	5 (3%)	3 (3%)	-
Vomiting	5 (3%)	4 (4%)	2 (6%)
Cramps	3 (2%)	1 (1%)	-
Dyspepsia	3 (2%)	5 (5%)	-
Fatigue	3 (2%)	2 (2%)	-
Flu-like disorder	3 (2%)	5 (5%)	-
Haemorrhage rectum	3 (2%)	3 (3%)	1 (3%)
Stools frequent	3 (2%)	-	1 (3%)
Anorexia	2 (1%)	-	-
Back pain	2 (1%)	5 (5%)	1 (3%)
Bowel irregularity	2 (1%)	-	-
Colitis ulcerative aggravated	2 (1%)	5 (5%)	-
Constipation	2 (1%)	1 (1%)	-
Dizziness	2 (1%)	2 (2%)	2 (6%)
Dyspnoea	2 (1%)	1 (1%)	-
Ear infection	2 (1%)	-	-
Fever	2 (1%)	3 (3%)	-
Insomnia	2 (1%)	1 (1%)	-
Melaena	2 (1%)	1 (1%)	-
Dry mouth	2 (1%)	-	-
Myalgia	2 (1%)	2 (2%)	-
Pain	2 (1%)	5 (5%)	1 (3%)

Pruritus	2 (1%)	-	1 (3%)
Rhinitis	2 (1%)	2 (3%)	-

Generally, adverse effects are expected to be those of mesalazine. Reactions reported during treatment with oral mesalazine are listed below.

Blood and lymphatic system disorders: Blood dyscrasias, aplastic anaemia, leucopenia, neutropenia, agranulocytosis, thrombocytopenia

Nervous system disorders: Headache, neuropathy

Cardiac disorders: Myocarditis, pericarditis

Respiratory, thoracic and mediastinal disorders: Bronchospasm, allergic alveolitis

Gastrointestinal disorders: Abdominal pain, diarrhoea, nausea, vomiting, aggravation of ulcerative colitis, acute pancreatitis

Hepatobiliary disorders: Hepatitis, cholelithiasis, increased liver enzymes

Skin and subcutaneous tissue disorders: Alopecia, rash, angioedema

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus-like syndrome, arthralgia, myalgia

Renal and urinary disorders: Interstitial nephritis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

There is limited experience with overdosing. Possible symptoms include nausea, vomiting, diarrhoea as well as intensification of the described adverse effects. In the event of an overdose the mainstay of treatment is supportive and symptomatic care. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Balsalazide is a prodrug of the active metabolite, mesalazine, which is linked to a carrier molecule (4-aminobenzoyl-β-alanine) via an azo bond. It is believed that mesalazine is released in the colon by bacterial azo-reduction. Mesalazine is an intestinal anti-inflammatory agent acting locally on the colonic mucosa. Its precise

mechanism of action is unknown. Balsalazide and the carrier molecule are not thought to contribute to the pharmacological action of the drug.

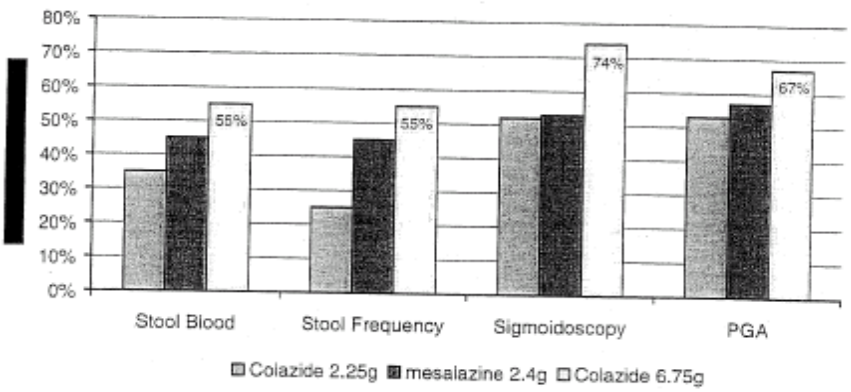
Clinical trials

Two randomized, double blind studies demonstrated the efficacy and safety of COLAZIDE® compared to mesalazine in patients with mildly to moderately active ulcerative colitis. Efficacy measurements included clinical symptoms, and endoscopic findings.

In the first trial, 154 patients were randomized and treated with daily doses of COLAZIDE® 6.75 g (equivalent to 2.4 g of mesalazine), COLAZIDE® 2.25 g (equivalent to 0.8 g of mesalazine) or mesalazine 2.4 g. After 8 weeks of treatment, COLAZIDE® 6.75 g was shown to be significantly superior to COLAZIDE® 2.25 g in improving stool blood, stool frequency, and/or sigmoidoscopic score and Physician's Global Assessment (PGA) (Figure 1).

Figure 1: Percentage of Patients Improved at 8 Weeks

(Study CP099301)

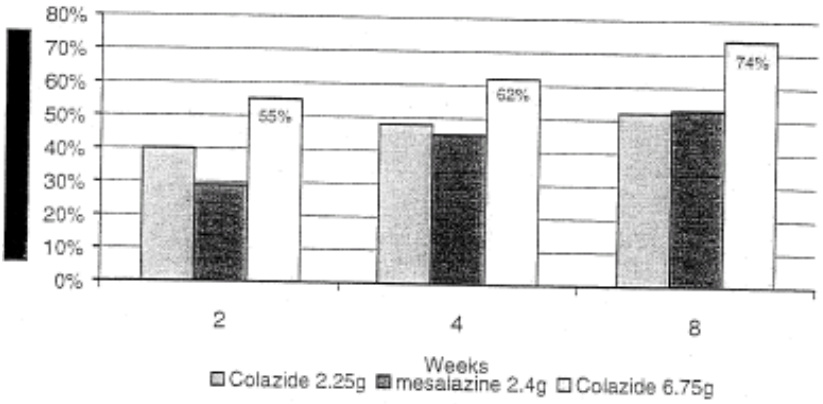


A greater percentage of patients treated with COLAZIDE® reported improvement in clinical symptoms than patients treated with mesalazine, however, these differences did not reach statistical significance.

COLAZIDE® 6.75 g was shown to be significantly better than mesalazine 2.4 g in improving sigmoidoscopic results at Weeks 2 ($p = 0.006$) and 8 ($p = 0.032$), but not at Week 4 ($p = 0.074$) (Figure 2). At all time points, a greater percentage of patients treated with COLAZIDE® 6.75 g showed sigmoidoscopic improvement, than patients treated with either mesalazine 2.4 g or COLAZIDE® 2.25 g.

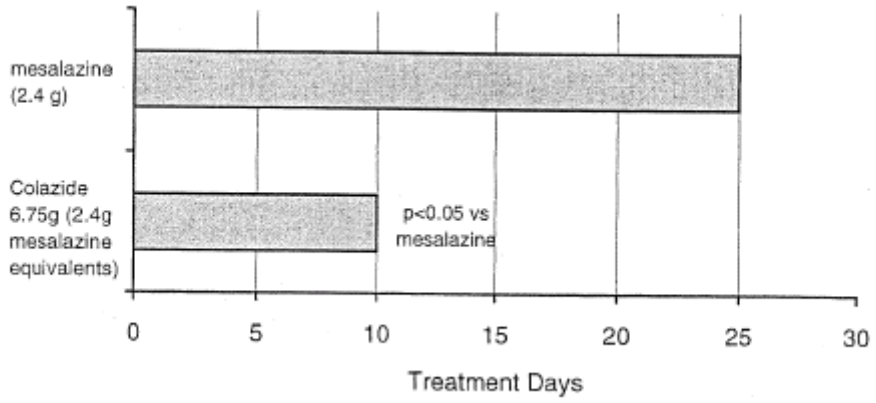
Figure 2: Percentage of Patients with Sigmoidoscopic Improvement

(Study CP099301)



In a second study, 101 patients were randomized to receive daily doses of COLAZIDE® 6.75 g or mesalazine 2.4 g for up to 12 weeks. COLAZIDE® was shown to be comparable to mesalazine in achieving symptomatic improvement of acute ulcerative colitis. The median time to complete symptom relief was 10 days for patients treated with COLAZIDE® 6.75 g, compared to 25 days for patients treated with mesalazine 2.4 g (Figure 3).

Figure 3: Median Time to Complete Relief of Symptoms (Study 57-3001)



5.2 Pharmacokinetic properties

Absorption

Balsalazide is believed to achieve its action through the topical effects of mesalazine on the colonic mucosa. Systemic absorption is therefore not necessary for efficacy. However, following oral administration an undetermined proportion of the dose is absorbed. Less than 1% of this proportion appears as intact balsalazide in the systemic circulation. Most of the absorbed material is in the form of mesalazine (5-ASA) or N-acetyl 5-ASA. The absolute bioavailability of balsalazide has not been determined.

The T_{max} for intact balsalazide is 1-2 hours. The T_{max} for 5-ASA and N-acetyl 5-ASA is approximately 9-10 hours, suggesting that release of the active drug

mesalazine occurs in the colon.

Administration with food results in decreased absorption of intact balsalazide, but no change in the absorption of 5-ASA or N-acetyl 5-ASA.

Distribution

The protein binding of intact balsalazide is approximately 99%.

Metabolism

Balsalazide is believed to be broken down in the colon into the active molecule 5-ASA and the carrier molecule 4-aminobenzoyl-β-alanine (4-ABA). On systemic absorption, both the carrier molecule and 5-ASA are rapidly N-acetylated.

Excretion

Approximately 25% of an orally administered dose is eliminated in the urine, in the form of the N-acetyl metabolites. The remainder is eliminated in the faeces.

Special populations
No information is available on the effects of age, gender, hepatic impairment or renal insufficiency on the pharmacokinetics of balsalazide or its metabolites.

5.3 Preclinical safety data

Genotoxicity

Balsalazide was not genotoxic in assays for chromosomal damage (including the *in vivo* mouse micronucleus test). In assays for gene mutations, balsalazide was negative in the Ames test and mouse lymphoma cell forward gene mutation test, but gave equivocal results in the Chinese hamster lung cell forward gene mutation test.

4-aminobenzoyl-β-alanine, a metabolite of balsalazide, was not genotoxic in assays for gene mutations (Ames test and the mouse lymphoma cell forward gene mutation test) but gave equivocal results in an assay for chromosomal damage (*in vitro* human lymphocyte chromosomal aberration test). N-acetyl-4-aminobenzoyl-β-alanine, a conjugated metabolite of balsalazide, was not genotoxic in gene mutation assays (Ames test and the mouse lymphoma cell forward mutation tests) or an assay for chromosomal damage (*in vitro* human lymphocyte chromosomal aberration test).

Carcinogenicity

When balsalazide was given to rats at dietary doses up to 2 g/kg/day for 104 weeks, an increased incidence of benign adrenal phaeochromocytoma was noted in male rats at the highest dose tested (representing a systemic exposure of about 2.4 times the maximum anticipated patient exposure on a mg/m^2 basis).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refer to Section 2 - Qualitative and quantitative composition.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

Approved Shelf Life as packaged for sale

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

AUST R 77358
COLAZIDE® is registered in bottles of 130, 180, 280 capsules (not all pack sizes are available).

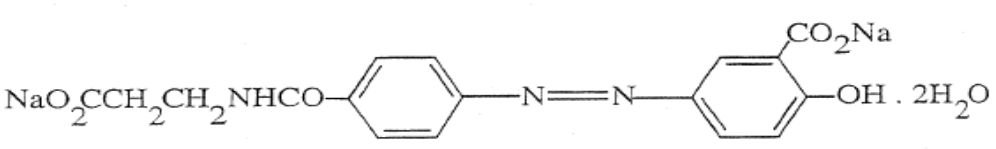
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical Name:	5-[4-(2-carboxyethylcarbamoyl)-phenylazo]-salicylic acid disodium salt dihydrate
Empirical Formula:	$C_{17}H_{13}N_3O_6Na_2.2H_20$
Molecular Weight:	401.32 (437.32 for the dihydrate)

Chemical structure



CAS number

Active Substance	CAS number
Balsalazide sodium	80573-04-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Australia: Schedule 4 – Prescription Only Medicine

8 SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai NSW 2080
Australia
Telephone: (02) 9391 5555

9 DATE OF FIRST APPROVAL

07 June 2005

10 DATE OF REVISION

3 June 2020

Summary table of changes

Section Changed	Summary of new information
All	Reformat PI as per new TGA PI form
1	Removed text “generic name “.
2	Active ingredient and excipients changed from sentence structure to a table, quantities added as per the ARTG record.
3	Added text “size 00 hard gelatine capsules (beige body and cap), containing an orange/yellow powder as per ARTG record”.
6.3	Added text “Approved Shelf Life as packaged for sale 2 years” as per ARTG record.