AUSTRALIAN PRODUCT INFORMATION

MESASAL®

(mesalazine) enteric coated tablets

1 NAME OF THE MEDICINE

Mesalazine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains 250 mg of mesalazine as the active ingredient.

Excipients of known effect: contains 47.7 mg elemental sodium per enteric coated tablet.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

MESASAL 250 mg enteric coated tablets are round, biconvex and tan coloured.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Treatment of acute inflammatory large bowel disease
- Maintenance therapy of Crohn's colitis and ulcerative colitis in patients sensitive to sulfasalazine

4.2 DOSE AND METHOD OF ADMINISTRATION

In acute ulcerative colitis, remissions will usually occur within 8 weeks.

Adults

Treatment of Acute Ulcerative Colitis and Crohn's Disease

500 mg (2 x 250 mg tablets) three times daily, (or as directed by a physician). Total daily dose 1.5 g. The tablets should be taken at least 30 minutes before meals with plenty of fluid.

Prevention of Relapses in Ulcerative Colitis

250 mg three times daily.

Maintenance of Remission of Crohn's Disease

250 mg three times daily.

4.3 CONTRAINDICATIONS

- A history of hypersensitivity to mesalazine, other salicylates or any of the excipients in MESASAL
- Severe renal impairment (glomerular filtration rate < 20 mL/min)
- Pathological tendency to bleeding, or concomitant anticoagulants
- Active peptic ulceration

MESASAL is contraindicated in the last weeks of pregnancy (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION - Use in Pregnancy).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Caution should be exercised when administering mesalazine to patients with:

- a history of hypersensitivity to sulfasalazine; although in general, hypersensitivity reactions to mesalazine appear to be less frequent than those observed for sulfasalazine

Do not administer mesalazine with preparations which lower stool pH, such as lactulose.

If toxic or hypersensitivity reactions occur, mesalazine should be discontinued.

Although rare, blood dyscrasias may develop during therapy. Practitioners should be aware of the possibility of their occurrence and be prepared to cease treatment immediately.

Keratoconjunctivitis sicca has been observed rarely in dogs chronically dosed with mesalazine. There have been no spontaneous clinical reports of keratoconjunctivitis sicca in man.

Long-term administration (> 1 year) of 5-aminosalicylic acid (up to 320 mg/kg/day) to rats resulted in renal nephropathy, gastric ulceration and increased plasma levels of 5-aminosalicylic acid and acetyl-5-aminosalicylic acid. The clinical significance of these findings to man has not been determined.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g. in toilets cleaned with sodium hypochlorite contained in certain bleaches).

Use in Pulmonary Function Impairment

MESASAL should be used with caution in patients with pulmonary function impairment, particularly asthma and in patients with known hypersensitivity to sulfasalazine containing preparations. Treatment in the latter patients should be instituted with careful medical supervision. Treatment should be discontinued immediately if symptoms of acute intolerance e.g. cramps, acute abdominal pain, fever, severe headache and skin rash occur.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with mesalazine content. Ensure adequate fluid intake during treatment.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Steven-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment. Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reaction, such as skin rash, mucosal lesions, or any other signs of hypersensitivity.

Special Instructions to Patients

MESASAL tablets should be taken with plenty of fluid. The tablets should not be crushed or chewed but swallowed whole.

Use in Hepatic Impairment

Caution should be exercised when administering mesalazine to patients with:

- hepatic impairment, as mesalazine is metabolised in the liver

- mesalazine might cause blood dyscrasias, although rarely reported, and hepatic impairment due to hypersensitivity reactions. Blood parameters, like blood counts and liver function and cholestasis parameters (e.g. ALT, AST, alkaline phosphatase, γGT) may be monitored like the renal parameters. Epigastric pain, also commonly associated with inflammatory bowel disease and prednisone or

sulfasalazine therapy, should be investigated in order to exclude pericarditis, hepatitis and pancreatitis either as adverse drug reactions to 5-ASA or secondary manifestations or inflammatory bowel disease

Use in Renal Impairment

Caution should be exercised when administering mesalazine to patients with:

- renal failure, elevated blood urea nitrogen (BUN) and proteinuria.

- renal impairment (given that 5-ASA is primarily eliminated through acetylation and subsequent urinary excretion). Interstitial nephritis has been reported following treatment with mesalazine. Hence, patients with compromised renal function, impaired renal reserve or individuals with an increased risk of developing renal dysfunction due to use of nephrotoxic drugs or other co-morbid conditions should be carefully monitored throughout the duration of therapy, and especially during the early months of treatment. Treatment with mesalazine should be discontinued promptly if renal function significantly deteriorates. Care should be taken to ensure adequate hydration in patients with compromised renal function during exacerbations of inflammatory bowel disease

In view of the rare risk of interstitial nephritis associated with mesalazine treatment, it is recommended that all patients have their renal function monitored (with serum creatinine levels measured) prior to treatment start. Renal function should then be periodically monitored during chronic treatment, based on individual patient history. Treatment with mesalazine should be discontinued promptly if renal function deteriorates.

Use in the Elderly

Regular monitoring of renal function in the elderly is essential as renal function deteriorates with age (see Section 4.3 CONTRAINDICATIONS).

Paediatric Use

Administration in children is not recommended.

Effects on Laboratory Tests

False-positive liquid chromatography assay results for urinary normetanephrine have been reported in patients receiving sulfasalazine or its metabolite, mesalazine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

There have been no specific studies on interactions of mesalazine with other drugs that may be co-administered.

In common with other salicylates, mesalazine may potentiate the effect of coumarin anticoagulants and the blood sugar reducing effect of sulphonylureas. Mesalazine may delay the excretion of methotrexate and may antagonise the effects of probenecid and sulphinpyrazone. There is also the theoretical possibility that mesalazine may decrease the diuretic effect of furosemide and spironolactone and may affect the action of rifampicin. Lactulose or similar preparations may cause a possible reduction of mesalazine release from tablets due to decreased pH caused by bacterial metabolism.

There is in vitro evidence that mesalazine is a weak inhibitor of the azathioprine metabolising enzyme thiopurine methyltransferase (TPMT). Enhancement of the myelosuppressive effects of azathioprine or 6-mercaptopurine may occur rarely in patients who are treated concomitantly with mesalazine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Decreased sperm count and impaired sperm motility, which may affect male fertility, have been reported with mesalazine. This effect may be reversible when treatment is discontinued (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Use in Pregnancy

Pregnancy category: C

Adequate human data on use during pregnancy are not available. There is a small theoretical risk that, in common with other non-steroidal anti-inflammatory agents, mesalazine may produce premature closure of the ductus arteriosus; may cause fetal renal impairment; and may, if given at term, prolong labour and delay parturition. The intake of aspirin (acetylsalicylic acid) increases the bleeding tendency both in the newborn child and in the mother.

Mesalazine is a salicylate and therefore is not recommended during pregnancy unless in the physician's opinion, benefits outweigh the potential risk in the first stages of pregnancy. Mesalazine is contraindicated in the last weeks of pregnancy.

Use in Lactation

It is recommended that breast-feeding be discontinued during maternal use of mesalazine. While adequate human data on use during lactation and adequate animal reproduction studies are not available, there are reports of mesalazine and its acetylated metabolite being excreted in human breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical trials totalling 2,164 patients, adverse reactions related to treatment with mesalazine occurred in 5.3% of patients; these were severe enough to lead to withdrawal in 1.4% of patients. A further 1.5% of patients had adverse reactions that were possibly drug related. The incidence of adverse reactions was lower amongst patients receiving mesalazine than the comparator drug (sulfasalazine).

Reproductive system and breast disorder: decreased sperm count and impaired sperm motility (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Effects on Fertility)

Gastro-Intestinal System

Common nausea, abdominal pain and diarrhoea have been reported. Acute, reversible pancreatitis and exacerbation of the symptoms of colitis have been reported rarely.

Nervous System

Headache, neuropathy.

Skin and Appendages

Rash (including pruritis and urticaria).

Renal

There have been rare reports of renal disorders including cases of acute and chronic interstitial nephritis and renal failure with various mesalazine formulations. Cases of nephrolithiasis have also been reported.

Hepatobiliary

In common with other salicylates, transitory abnormal liver function tests or hepatitis may occur rarely.

Haematological Effects

Alterations in peripheral blood counts (e.g., leucopenia, neutropenia, thrombocytopenia, aplastic anaemia, agranulocytosis) have been reported rarely for various mesalazine formulations.

Reproductive System Disorders

Oligospermia (reversible)

Hypersensitivity

In common with other salicylates, hypersensitivity reactions including pulmonary and cardiac changes may occur rarely. These reactions include fever, myalgia, arthralgia, alveolitis, myocarditis and pericarditis although these have also been reported as extra-intestinal manifestations of the underlying bowel disease.

Skin and Subcutaneous Tissue Disorders

Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reaction, such as skin rash, mucosal lesions, or any other signs of hypersensitivity.

Frequency unknown: drug reaction with eosinophilia and systemic symptoms (DRESS)

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

Symptoms

There is no specific pattern of symptoms following overdose with mesalazine. Possible symptoms may include nausea, vomiting and diarrhoea, and symptoms similar to salicylate overdose.

Treatment

Treatment consists of supportive and symptomatic measures. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific antidote.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mesalazine has been identified as the active component of sulfasalazine in inflammatory bowel disease and is thought to have a topical action.

In clinical studies, mesalazine has shown clinical efficacy similar to sulfasalazine.

The mode of the anti-inflammatory action of mesalazine is unknown. Inhibition of prostaglandin synthesis (via inhibition of cyclo-oxygenase), inhibition of chemotactic leukotriene synthesis (via inhibition of lipoxygenase), and direct inhibition of leukocyte motility may contribute to activity. More recent data suggest that the activity of mesalazine is based on a scavenging of oxygen free radicals, and that mesalazine is a biological antioxidant.

MESASAL enteric coated tablets have an acrylic based resin coating which disintegrates when the surrounding pH is consistently above 6.4, permitting release of mesalazine in the terminal ileum and colon.

The tablet coating is not affected by gastric contents or gastric residence time; but the presence of food tends to delay onward passage of the tablet.

Food may also delay the rate of absorption of mesalazine. In view of the probable topical action of mesalazine, however, this may not be therapeutically relevant.

Disintegration of the coating typically occurs about 5 hours after leaving the stomach. The simultaneous administration of agents which raise the gastric pH above 6.4, and the presence of achlorhydria, may decrease the time to release of mesalazine (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Healthy Volunteers

In fasted, healthy subjects given a single oral dose of mesalazine (500 mg), time to peak plasma concentration was 6.5 hours for mesalazine and 7 hours for acetyl-5-aminosalicylic acid (Ac-5-ASA). Urinary recovery was approximately 35%, and faecal recovery 26.5% of total dose.

Patients with Crohn's Disease or Ulcerative Colitis

Absorption

After oral administration of mesalazine 500 mg t.i.d, the mean steady state plasma concentrations of 5-ASA and Ac-5-ASA averaged 0.7 and 1.2 μg/mL respectively.

After oral doses of mesalazine 250 mg t.i.d, the mean steady state plasma concentration of 5-ASA and Ac-5-ASA averaged 0.4 and 1.0 μg/mL, respectively.

Peak concentrations of 5-ASA and Ac-5-ASA occurred at 4 to 6 hours after dosing.

Urine recovery data indicate that up to 44% of the dose is absorbed. Up to 35% of the dose remains unabsorbed and is excreted in the faeces.

Distribution

About 80% of Ac-5-ASA is bound to plasma proteins.

Metabolism

Acetylation of mesalazine takes place in the liver and in the wall of the colon independently of acetylator status. The acetylation process appears to be saturable; however, at therapeutic doses (250 – 500 mg) neither maximum plasma concentration, nor area under the plasma concentration versus time curve for mesalazine indicated any deviation from dose linearity at steady state.

Excretion

The mean elimination half-life of 5-ASA is 1.4 hours. Following oral administration, mesalazine is eliminated to a large extent as N-acetyl-5-aminosalicylic acid, both in the urine and the faeces. Following rectal administration, mesalazine is eliminated mainly as parent drug in the faeces. A poorer absorption of mesalazine from the distal colon has been suggested.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The enteric coated tablets also contain: calcium stearate, colloidal anhydrous silica, glycine, iron oxide red, iron oxide yellow, macrogol 6000, methacrylic acid copolymer, microcrystalline cellulose, povidone, purified talc, sodium carbonate, titanium dioxide and triethyl citrate.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (PVC/PVDC/Al)

Pack sizes: 100

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

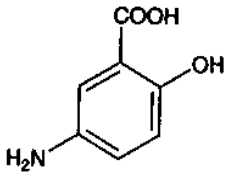
AUST R 289132 – MESASAL mesalazine 250 mg enteric coated tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Chemical name: 5-amino-2-hydroxybenzoic acid

Molecular weight: 153.1

CAS Number

89-57-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16/08/2017

10 DATE OF REVISION

24/08/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial change
4.4	Added a warning on urine discolouration after contact sodium hypochlorite and a warning regarding the risk of DRESS.
4.8	Added a warning regarding the risk of DRESS and adverse reaction of DRESS with a frequency unknown.

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