NAME OF THE DRUG
MESASAL
5-aminosalicylic acid (5-ASA).

Mesalazine has been identified as the active component of sulfasalazine in inflammatory bowel disease and is thought to have a topical action. Chemically, mesalazine is 5-amino-2hydroxybenzoic acid and may be represented structurally as:

![Chemical structure of mesalazine]

Molecular weight: 153.1
CAS number: 89-57-6

DESCRIPTION
MESASAL tablets contain 250mg of mesalazine.

MESASAL tablets also contain the following inactive ingredients: sodium carbonate anhydrous, glycine, povidone, microcrystalline cellulose, silica colloidal – anhydrous, calcium stearate. The tablet coating contains povidone, methacrylic acid copolymer, talc purified (talc micronized), titanium dioxide, iron oxide yellow CI 77492, iron oxide red CI 77491, macrogol 6000.

PHARMACOLOGY
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 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 PRECAUTIONS).

**Pharmacokinetics**

**Healthy Volunteers**

In fasted, healthy subjects given a single oral dose of mesalazine (500mg), 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 500mg tid, the mean steady state plasma concentrations of 5-ASA and Ac-5-ASA averaged 0.7 and 1.2 $\mu$g/mL respectively.

After oral doses of mesalazine 250mg tid, the mean steady state plasma concentration of 5-ASA and Ac-5-ASA averaged 0.4 and 1.0 $\mu$g/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 (250-500mg) neither maximum plasma concentration, nor area under the plasma concentration versus time curve for mesalazine indicated any deviation from dose linearity at steady state.

**Elimination**

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

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 Use in Pregnancy).

PRECAUTIONS
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.

• hepatic impairment, as mesalazine is metabolised in the liver.
• 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, MESASAL 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.

Pregnancy and Lactation

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 adverse reaction section)

Use in Pregnancy (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 foetal 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. MESASAL 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.

INTERACTIONS
There have been no specific studies on interactions of mesalazine with other drugs that may be coadministered.
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 frusemide and spironolactone and may affect the action of rifampicin.

There is also in vitro evidence that mesalazine is a weak inhibitor of the azathioprine metabolising enzyme thiopurine methyltransferase (TPMT). An enhancement of the myelosuppressive effects of azathioprine or 6-mercaptopurine may occur rarely in patients who are receiving concomitant treatment with mesalazine.

ADVERSE REACTIONS

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 fertility section under Pregnancy and lactation)

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.

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.
**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.

**DOSAGE AND ADMINISTRATION**
In acute ulcerative colitis, remissions will usually occur within 8 weeks.

**Adult**
- 500 mg (2 x 250 mg tablets) three times daily, (or as directed by a physician) for the treatment of acute ulcerative colitis and Crohn's Disease. Total daily dose 1.5 g. The tablets should be taken at least 30 minutes before meals with plenty of fluid.
- For prevention of relapses in the case of ulcerative colitis, 250 mg three times daily.
- For maintenance of remission of Crohn's Disease, 250 mg, three times daily.

**Paediatric**
Administration in children is not recommended.

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

**OVERDOSAGE**

**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. There is no specific antidote.

**STORAGE CONDITIONS**
Store below 30°C and protect from light and moisture. Shelf life under these conditions is 18 months.

**SPECIAL INSTRUCTIONS TO PATIENTS**
MESASAL tablets should be taken with plenty of fluid. The tablets should not be crushed or chewed, but swallowed whole.

**PRESENTATION**
250 mg mesalazine - round, tan, enteric-coated tablets in PVC/aluminium blister platforms of 20 tablets in packs of 100.

SPONSOR
GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

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