AUSTRALIAN PRODUCT INFORMATION – SALAZOPYRIN® and SALAZOPYRIN® EN-TABS (sulfasalazine)

1. NAME OF THE MEDICINE

Sulfasalazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SALAZOPYRIN tablets contain 500 mg of sulfasalazine

SALAZOPYRIN EN-TABS enteric coated tablets contain 500 mg of sulfasalazine

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

SALAZOPYRIN (sulfasalazine) 500 mg tablets

Yellow-orange, round, scored tablets; marked with `KPh' on the one side and `101' on the other side.

SALAZOPYRIN EN-TABS (sulfasalazine) 500mg enteric coated tablets

Yellow-orange, elliptical convex, enteric coated tablets; marked with `KPh' on the one side and `102' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative Colitis and Crohn's Disease

Adjunct in the treatment of ulcerative colitis with the usual supportive and dietary measures. For the management of severe, acute attacks of ulcerative colitis, rectal and systemic corticosteroid therapy appears to be clinically superior to sulfasalazine, but sulfasalazine may be more effective than corticosteroids in reducing the number of relapses in patients on maintenance therapy.

In the treatment of active Crohn's disease, especially in patients with colonic involvement.

Rheumatoid Arthritis

SALAZOPYRIN EN-TABS are indicated for rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs).

4.2 Dose and method of administration

Inflammatory Bowel Disease

Oral: SALAZOPYRIN or SALAZOPYRIN EN-TABS (enteric coated) should be given preferably after meals in evenly divided doses over a 24 hour period with no more than 8 hours between overnight doses. The enteric coated tablets should not be crushed or broken.

Initial Dosage

Adults: 1 to 2 g four times daily.

Children: 40 to 60 mg/kg bodyweight daily in three to six divided doses.

Maintenance Dosage

Adults: 2 g daily in four divided doses.

Children: 40 mg/kg bodyweight daily in four divided doses. The daily maintenance dose should be continued unless contraindicated by side effects.

SALAZOPYRIN EN-TABS may be used to minimise gastrointestinal intolerance to the drug.

Rheumatoid Arthritis

Oral: Two SALAZOPYRIN EN-TABS, two or three times a day, i.e. 2 to 3 g daily. The enteric coated tablets should not be crushed or broken. For adults starting therapy, it is advisable to raise the daily dose according to the following schedule:

Adults

	1st WEEK	2nd WEEK	3rd WEEK	4th WEEK
Morning		1 tablet	1 tablet	2 tablets
Evening	1 tablet	1 tablet	2 tablets	2 tablets*
* etc. to 3 g/day maximum.				

Children: At present no dosage recommendation regarding treatment with SALAZOPYRIN EN-TABS in rheumatoid arthritis in children can be given.

4.3 Contraindications

Haematological, renal or hepatic dysfunction, allergic drug fever or skin eruptions due to sulphonamide derivatives including antibacterial sulphonamides, oral hypoglycaemics and thiazides.

Patients hypersensitive to sulfasalazine, its metabolites, or any other component of the product, sulfonamides, or salicylates.

Intestinal or urinary obstruction.

Patients with porphyria should not receive sulphonamides, as these drugs have been reported to precipitate an acute attack.

Children aged 2 years and younger.

4.4 Special warnings and precautions for use

Serious Infections

Serious infections associated with myelosuppression, including sepsis and pneumonia, have been reported. Patients who develop a new infection while undergoing treatment with sulfasalazine should be monitored closely. Administration of sulfasalazine should be discontinued if a patient develops a serious infection. Caution should be exercised when considering the use of sulfasalazine in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.

Potential Toxicity

Deaths associated with the administration of sulfasalazine have been reported, resulting from hypersensitivity reactions, agranulocytosis, aplastic anaemia, renal and liver damage, irreversible neuromuscular and CNS changes, and fibrosing alveolitis. The presence of clinical signs such as sore throat, fever, pallor, purpura or jaundice may be indications of myelosuppression, hepatotoxicity, haemolysis or other serious blood disorders. The patient should be advised to report any untoward symptoms immediately. If serious toxic or hypersensitivity reactions occur, discontinue treatment with sulfasalazine immediately while awaiting the results of blood tests. Urticaria, other skin rashes and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids.

Monitoring for Toxicity

Sulfasalazine should be administered under constant medical supervision.

Complete blood counts (including differential white cell count) and liver function tests should be performed before starting sulfasalazine tablets and every second week during the first three months of therapy. During the second three months, the same tests should be done once monthly and thereafter once every three months, and as clinically indicated. Assessment of renal function (including urinalysis) should be performed in all patients initially and at least monthly for the first three months of treatment. Thereafter, monitoring should be performed as clinically indicated.

Hepatic or Renal Impairment and Blood Dyscrasias

Sulfasalazine should not be given to patients with impaired hepatic or renal function or with blood dyscrasias.

Hypersensitivity

Sulfasalazine should be given with caution in patients with severe allergy or bronchial asthma.

Severe hypersensitivity reactions may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome (i.e. pseudomononucleosis),

haematological abnormalities (including haematophagic histiocytosis), and/or pneumonitis including eosinophilic infiltration.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking various drugs including sulfasalazine. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Sulfasalazine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Serious Skin Reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of sulfasalazine. Patients appear to be at highest risk for these events early in the course of therapy, the onset of the event occurring in the majority of cases within the first month of treatment. Sulfasalazine should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Effects on Folic Acid

Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious blood disorders (e.g. macrocytosis and pancytopenia) and the possibility of harming the foetus during pregnancy (see Section 4.6 Fertility, pregnancy and lactation, Use in Pregnancy).

G-6-PD Deficiency

Patients with a deficiency of erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) have been noted to develop haemolytic anaemia during treatment with sulfasalazine (Cohen et al., 1968; Gabor, 1973) and should be closely observed.

Fluid Intake

Adequate fluid intake must be maintained in order to reduce the risk of crystalluria and stone formation.

Patients with Atopic Disease

Sulfasalazine should be given with caution to patients with history of atopic disease in view of the increased likelihood of hypersensitivity reactions in atopic patients.

Interactions

Sulphonamides should be administered with caution to patients receiving other drug therapy (see 4.5 Interactions with other medicines and other forms of interactions).

Reversible Male Infertility

Several recent reports have suggested that sulfasalazine may cause reversible infertility in males (Grieve, 1979; Levi et al., 1979; Toth, 1979; Traub et al., 1979; Toovey et al., 1981). Sulfasalazine therapy has been associated with a reduction in sperm counts, reduced sperm motility, morphologically abnormal sperm and an increased proportion of immature sperm. The mechanism by which sulfasalazine might affect sperm production is not understood. Until

such time as this suggested association can be elucidated, a drug associated cause should be considered when investigating infertility in men taking sulfasalazine. Withdrawal of the drug usually reverses these effects within 2 to 3 months.

Use in the elderly

No data available.

Paediatric use

Use in children with systemic onset juvenile rheumatoid arthritis may result in a serum sickness-like reaction; therefore, sulfasalazine is not recommended in these patients.

Effects on laboratory tests

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing a false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalazine.

Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, and may cause interference with some laboratory assays that use nicotinamide adenine dinucleotide [NAD(H)] or nicotinamide adenine dinucleotide phosphate [NADP(H)] to measure ultraviolet absorbance. Examples of such assays may include alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), ammonia, thyroxine, or glucose. Consult with the testing laboratory regarding the methodology used. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine. Results should be interpreted in conjunction with clinical findings.

4.5 Interactions with other medicines and other forms of interactions

Sulphonamides may potentiate oral anticoagulants, methotrexate, and oral hypoglycaemics of the sulphonylurea type by displacing these drugs from their binding sites.

An increased incidence of gastrointestinal adverse events, especially nausea, has been reported with co-administration of oral sulfasalazine and methotrexate to rheumatoid arthritis patients.

Increased sulphonamide blood levels may occur in patients who are receiving urinary acidifiers, oral anticoagulants, indomethacin or salicylates.

Antacids

Decreased absorption of sulphonamides from the gastrointestinal tract may occur if antacids are given concurrently.

Penicillins

It has been reported that sulphonamides interfere with oral absorption of oxacillin and may inhibit the serum protein binding of penicillins.

Local Anaesthetics Derived from Para-aminobenzoic Acid

Local anaesthetics which are derivatives of para-aminobenzoic acid may antagonise sulphonamide activity.

Digoxin

Reduced absorption of digoxin, resulting in non-therapeutic serum levels, has been reported when used concomitantly with sulfasalazine.

Folic Acid

Folate deficiency may occur as sulfasalazine inhibits the absorption of folate.

Ferrous Sulphate

Ferrous sulphate may impair the absorption of sulfasalazine however, the clinical significance of this interaction is doubtful.

Thiopurine 6-Mercaptopurine or Azathioprine

Due to inhibition of thiopurine methyltransferase (TPMT) by sulfasalazine, bone marrow suppression and leucopenia have been reported when thiopurine 6-mercaptopurine or its prodrug, azathioprine, and oral sulfasalazine were used concomitantly.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category [A]

Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency, potentially resulting in serious blood disorders (e.g. macrocytosis and pancytopenia) and the possibility of harming the foetus during pregnancy.

There have been reports of babies with neural tube defects born to mothers who were exposed to sulfasalazine during pregnancy, although the role of sulfasalazine in these defects has not been established. Because the possibility of harm cannot be completely ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Use in lactation

The amount of sulfasalazine that passes into the maternal milk is negligible, however, the concentration of sulfapyridine in milk is about 40% of that in serum. The risk of kernicterus in breast-fed infants has been assessed as low with therapeutic doses, since sulfapyridine has been shown to have a poor bilirubin displacing capacity.

As with all drugs, sulfasalazine should not be given to nursing mothers unless the expected benefits to the mother outweigh the potential risk to the infant. Caution should be used, particularly if breastfeeding premature infants or those deficient in G-6-PD. There have been

reports of bloody stools or diarrhoea in infants of mothers on sulfasalazine who were breastfeeding.

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)

Sulfasalazine shares the toxic potentialities of other sulphonamides, especially sulfapyridine, and the usual precautions of sulphonamide therapy should be observed. Moreover, it may be difficult to evaluate an adverse reaction in the individual case, since several of the untoward symptoms and signs encountered in conjunction with treatment with sulfasalazine may be part of the disease. In assessing liver and joint complications, it should also be borne in mind that such are often associated with ulcerative colitis.

The acetylation rate of sulfapyridine is determined by genetic factors. Slow acetylators can be expected to show higher serum levels of sulfapyridine, and thus may show an increased tendency towards adverse reactions.

Many side effects are dose dependent, and the symptoms can often be alleviated by reducing the dosage by greater subdivision of the dose.

The most common side effects are: nausea, vomiting and anorexia (which occur more frequently in patients receiving non-enteric coated sulfasalazine. To minimise the risk of gastrointestinal adverse reactions enteric coated tablets are used, which means that they do not disintegrate until they reach the small intestine); raised temperature; erythema and pruritus; headache; reversible oligospermia (oligospermia and infertility have been described in men treated with sulfasalazine. Withdrawal of the drug will reverse these effects).

The majority of the adverse reactions listed below have only seldom been reported, primarily in treatment of inflammatory bowel diseases and are typical of sulphonamides.

Infections and Infestations

Aseptic meningitis, pseudomembranous colitis.

Blood and Lymphatic System Disorders (see 4.4 Special warnings and precautions for use)

Red cell abnormalities[#] (e.g. haemolytic anaemia, macrocytosis), aplastic anaemia, megaloblastic anaemia, pseudomononucleosis*, hypoprothrombinaemia, methaemoglobinaemia, bone marrow depression with leucopenia (e.g. agranulocytosis, thrombocytopenia), pancytopenia.

Immune System Disorders

Serum sickness.

Hypersensitivity Reactions

Anaphylaxis*/anaphylactoid reactions, periorbital or facial oedema, conjunctival and scleral injection and nephrotic syndrome.

Metabolism and Nutrition Disorders

Anorexia, folate deficiency* (see 4.4 Special warnings and precautions for use).

Psychiatric Disorders

Mental depression.

Nervous System Disorders

Dizziness[#], smell and taste disorders, peripheral neuropathy, headache, peripheral neuritis, convulsions, hallucinations, vertigo, insomnia, transient lesions of posterior column and transverse myelitis, encephalopathy.

Ear and Labyrinth Disorders

Tinnitus[#].

Cardiac Disorders

Myocarditis* (including allergic myocarditis) (see 4.4 Special warnings and precautions for use), pericarditis, cyanosis[#].

Vascular Disorders

Pallor* (see 4.4 Special warnings and precautions for use).

Respiratory, Thoracic and Mediastinal Disorders (see 4.4 Special warnings and precautions for use)

Lung complications (fibrosing alveolitis with e.g. dyspnoea, cough, eosinophilic infiltration), interstitial lung disease*, oropharyngeal pain*.

Gastrointestinal Disorders

Gastric distress[#], abdominal pain[#], nausea, vomiting*, diarrhoea*, pancreatitis, stomatitis, impaired folic acid absorption, aggravation of ulcerative colitis*.

Hepatobiliary Disorders (see 4.4 Special warnings and precautions for use)

Hepatic failure*, hepatitis fulminant*, hepatitis, jaundice*, hepatitis cholestatic*, cholestasis*.

Skin and Subcutaneous Tissue Disorders (see 4.4 Special warnings and precautions for use)

Toxic epidermal necrolysis (Lyell's syndrome), erythema multiforme, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)*, toxic pustuloderma, alopecia, erythema, exanthema, exfoliative dermatitis, angioedema*, lichen planus, photosensitivity, purpura*, pruritus, urticaria, generalised skin eruptions.

Musculoskeletal and Connective Tissue Disorders

Systemic lupus erythematosus, Sjögren’s syndrome, arthralgia.

Renal and Urinary Disorders

Proteinuria[#], haematuria[#], crystalluria[#] (see 4.4 Special warnings and precautions for use), nephrotic syndrome, interstitial nephritis, nephrolithiasis*.

Reproductive System

Reversible oligospermia (see 4.4 Special warnings and precautions for use).

General Disorders

Fever (see 4.4 Special warnings and precautions for use), yellow discolouration of skin and body fluids*, petechiae and drug fever, periarteritis nodosum and LE phenomenon have occurred.

Investigations

Induction of autoantibodies, elevation of liver enzymes.

[#] Adverse effects are possibly dose-related.

* Adverse effects identified post-marketing.

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

The drug has low acute per oral toxicity in the absence of hypersensitivity. There is evidence that the incidence and severity of toxicity following overdosage are directly related to the total serum sulfapyridine concentration.

Signs and Symptoms

Similar to those of any sulphonamides. The most likely symptoms would be gastrointestinal disturbances (nausea, vomiting and abdominal pain), haematuria, crystalluria or anuria. In more advanced cases, central nervous system symptoms such as drowsiness, convulsions, etc., may be observed. Patients with impaired renal function are at increased risk of serious toxicity. There are no documented reports of deaths due to ingestion of large single doses of sulfasalazine.

Treatment of Overdosage

There is no specific antidote and treatment is symptomatic and supportive. Alkalinize urine (2.5 to 4.0 g of sodium bicarbonate every 4 hours). If kidney function is normal, force fluids. If anuria is present, restrict fluids and salt and treat for renal failure. Sulfasalazine can be removed by haemodialysis. Catheterisation of the ureters may be indicated for complete renal blockage by crystals. For agranulocytosis discontinue the drug immediately, hospitalise the patient and institute appropriate therapy. Patients should be observed for development of methaemoglobinaemia or sulfhaemoglobinaemia. If these occur, treat appropriately.

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

Sulfasalazine has, among others, an immunosuppressive effect and has shown affinity to connective tissue. It has also been shown to have a wide range of effects in other biological systems. It is, however, difficult to judge the clinical relevance of its various pharmacological actions since the aetiology of rheumatoid arthritis is largely unknown. Moreover, the mode of action of sulfasalazine in the treatment of ulcerative colitis is also not known. A metabolite of the drug may have an inhibitory effect on an antigen-antibody process occurring in the intestinal wall and the salicylate component may act as an anti-inflammatory agent. The drug does not appear to have any long term antibacterial effect on the stool flora of patients with ulcerative colitis (see 5.1 Pharmacodynamic properties, Antibacterial Effect).

The following effects have been found in vitro: inhibition of bacterial growth; inhibition of prostaglandin synthesis; increased intestinal cytoprotection due to inhibition of prostaglandin degradation; reduction of leukotriene formation; modulation of polymorphonuclear leucocyte function; inhibition of proteolytic enzymes; inhibition of DNA synthesis; and impairment of folate absorption and metabolism.

Most of these effects have also been shown in experimental animal systems. This has led to the following alternative explanations of the clinical effects of sulfasalazine.

Antibacterial Effect

West et al., (1974) found that the number of anaerobic bacteria in the colon lumen was markedly reduced by administration of sulfasalazine. Krook et al., (1981) showed that 1 month of sulfasalazine treatment gave a drastic reduction in the anaerobic bacteria count. After four months of continuing treatment the counts returned to normal, although a decrease in certain bacterial strains was still evident.

Rheumatoid arthritis may be an enteropathogenic arthritis. One well known observation is that experimental arthritis in pigs may be caused by Clostridium perfringens in the large bowel. Neumann et al., (1984) has recently examined the faecal flora in a normal control population and in rheumatoid arthritis patients during sulfasalazine treatment. During therapy there was a trend towards a decrease in the Cl. perfringens count in the sulfasalazine treated group which was not seen in the control group. Tremaine et al., (1984) have recently shown that patients on sulfasalazine have a significantly lower incidence of Cl. difficile infection than patients with no treatment, and that a significantly higher incidence of infection is observed after antibiotic therapy.

Anti-inflammatory and Immunoregulatory Effect

In recent years a large number of papers, predominantly on in vitro studies, have reported effects of sulfasalazine on the arachidonic acid metabolites, prostaglandins and leukotrienes.

Any equivalence to these effects in vivo, seen as an anti-inflammatory effect, has yet only partly been documented. Thus, inhibition of carrageenan inflammation could be demonstrated in the rat paw and in the rat colon. In the adjuvant arthritis model in rats, Steinwall et al.,

showed a significant inhibition at high doses of sulfasalazine. Indomethacin-induced ulceration could be reduced by sulfasalazine, and water transport was normalised by sulfasalazine both in human biopsy tissue and in the dinitrochlorobenzene (DNCB) colitis in a rat model.

With regard to possible immunoregulatory effects, Holm and Perimann (1968) published a study on the effect of sulfasalazine upon lymphocytic activity. Sulfasalazine was shown to have a specific toxicity for lymphocytes, higher than for other cells. Campbell (1973) studied the effect of sulfasalazine in immunological models, and a clear immunoregulatory effect was noted.

Laursen (1978) found that sulfasalazine in mice suppressed many immunological factors, such as serum levels of different immunoglobulins and the number of lymphocytes. Rubenstein et al., (1978) and Ali et al., (1982) have shown that sulfasalazine therapy depresses the activity of certain lymphocytes.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

After the administration of a single 2 g dose of SALAZOPYRIN (enteric or non enteric coated tablets), sulfasalazine can be detected in serum within 6 hours. Two days after administration the serum concentration is negligible. With repeated daily doses, the steady state serum level of sulfasalazine is achieved after 4 to 5 days.

Sulfasalazine is poorly absorbed from the small intestine (up to 30%), after which it is excreted into the bile. A few percent of the given dose is excreted unmetabolised into the urine. The unabsorbed drug is excreted in the faeces. This is also confirmed by the observation that around 70% of an ingested dose of sulfasalazine can be recovered in the effluent of ileostomised patients. Sulfasalazine rapidly enters the enterohepatic circulation and is returned to the gastrointestinal tract via the biliary route. Up to 80% of the absorbed intact sulfasalazine can be recovered in the bile effluent.

Distribution and Excretion

Intact sulfasalazine can be detected in serum within 6 hours after oral administration and between 2 and 10% of a single dose can be recovered as the unchanged molecule from the urine. No detectable sulfasalazine has been found in stools of normal subjects, although up to 7% of an orally administered sulfasalazine dose has been found in the faeces of patients having ulcerative colitis. Sulfasalazine and its metabolites excreted in the urine may impart an orange-yellow colour to alkaline urine.

Most of the 5-aminosalicylate moiety formed by bacterial action in the gut is excreted unchanged in the faeces. However, up to 33% of the salicylate absorbed can be recovered in the urine almost entirely as N-acetyl-5-aminosalicylic acid.

Both sulfasalazine and 5-ASA exhibit an affinity for collagen rich tissues. It has been shown that these two entities tend to concentrate primarily in the intestinal wall as well as in the

peritoneal, pleural and synovial fluids. There is also evidence that blood borne sulfasalazine can enter the intestinal lumen directly from the serum, for it has been shown by Hannagren et al., (1973) that intravenously administered sulfasalazine concentrates intestinally in rats with ligated bile ducts.

The sulfapyridine formed by cleavage of sulfasalazine during azo-reduction by the intestinal flora is absorbed in the intestinal tract and appears to be evenly distributed in the various body tissues and fluids. About two thirds of the amount of sulfapyridine present in sulfasalazine is excreted in the urine, partially as acetylated or glucuronidated metabolites. The faeces contain sulfapyridine equivalent to approximately 7% of the ingested dose. There is no detectable sulfapyridine in serum 3 days after termination of treatment.

Metabolism

The 70 to 80% of the ingested dose of intact sulfasalazine which reaches the colon is subjected to azo-reductive cleavage by the colonic flora to yield the two major metabolites, 5-amino-salicylic acid (5-ASA) and sulfapyridine. Sulfapyridine is rapidly absorbed, partly metabolised in the liver, primarily by acetylation, and subsequently excreted in the urine. Non-acetylated sulfapyridine is partly protein bound. The role of the gut bacteria in splitting sulfasalazine has been elucidated in detail by Peppercorn and Goldman (1972). Thus, the delay in appearance of sulfapyridine and 5-ASA in the serum after oral administration of sulfasalazine is consistent with the time taken for the drug to reach the microbially rich colon. The two products of cleavage, 5-ASA and sulfapyridine are subsequently metabolised.

In humans only N-acetyl-5-aminosalicylic acid has been identified as a metabolite of 5-ASA. Sulfapyridine metabolites have been identified in humans as: N4-acetylsulfapyridine; sulfapyridine-o-glucuronide; acetylsulfapyridine-o-glucuronide; 5-hydroxy-sulfapyridine-o-glucuronide; and N4-acetyl-5-hydroxy-sulfapyridine-o-glucuronide.

The rate at which sulfapyridine is acetylated in the liver is genetically determined. Patients can be readily classified as slow or fast acetylator phenotypes on the basis of the ratio of sulfapyridine and acetylsulfapyridine concentrations in serum or urine. There is also a genetic basis for differentiation of patients according to the rate at which sulfapyridine is hydroxylated. Those subjects who show relative slowness in acetylation and hydroxylation rates may be expected to show higher than normal serum concentration of sulfapyridine after administration of sulfasalazine.

Protein Binding

Greater than 95% of absorbed sulfasalazine is bound to serum proteins.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Salazopyrin

Colloidal anhydrous silica
Magnesium sterate
Maize starch
povidone

Salazopyrin EN-Tabs

Carnauba wax
Cellacefate
Colloidal anhydrous silica
Glyceryl monosterate
Macrogol 20000
Magnesium sterate
Maize starch
Povidone
Propylene glycol
Purified talc
White beeswax

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

SALAZOPYRIN tablets and SALAZOPYRIN EN tablets should be stored below 25°C.

6.5 Nature and contents of container

SALAZOPYRIN (sulfasalazine) 500 mg tablets supplied in bottles of 100 tablets.

SALAZOPYRIN EN-TABS (sulfasalazine) 500mg enteric coated tablets supplied in bottles of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

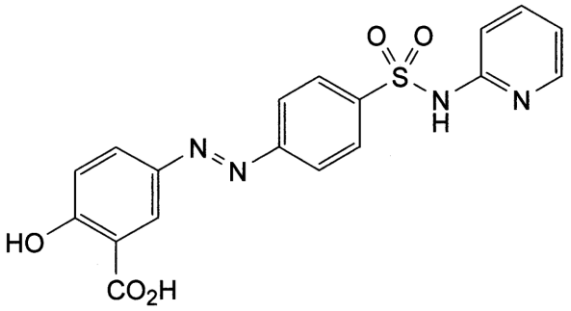
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Sulfasalazine is a bright yellow or brownish-yellow, fine powder. It is practically insoluble in water, very slightly soluble in ethanol (96 percent), practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

Chemical structure

The structural formula of sulfasalazine is shown below:



Chemical Name:	2-Hydroxy-5-[2-[4-(pyridin-2-ylsulphamoyl)phenyl]diazenyl]benzoic acid
Molecular Formula:	$C_{18}H_{14}N_4O_5S$
Molecular Weight:	398.4

CAS number

599-79-1.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

05 September 1991.

10. DATE OF REVISION

4 September 2019

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
Throughout PI	Reformatted in line with the revised Australian Form for providing product information requirements.
Section 4.4	Addition of information under 'Effects on laboratory tests' relating to the potential interference of sulfasalazine on some laboratory assay results
Section 6.1	Updated excipient name to Australian approved name
Section 8	Sponsor address udpated