

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Sulfasalazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Salazopyrin tablet: Each tablet contains 500 mg sulfasalazine.

Salazopyrin-EN enteric coated tablet: Each tablet contains 500 mg sulfasalazine.

Excipient(s) with known effect

Salazopyrin-EN tablets contain:

- Propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Salazopyrin 500 mg tablet: Yellow-orange, round, scored tablets; marked with 'KPh' on the one side and '101' on the other side.

Salazopyrin-EN 500 mg enteric coated tablet: 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 tablets are indicated for rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs).

4.2 Dose and method of administration

Dose

The dosage of sulfasalazine should be individually adjusted according to the patient's tolerance and response to the treatment.

Inflammatory Bowel Disease

Salazopyrin or Salazopyrin EN (enteric coated) tablets 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 tablets may be used to minimise gastrointestinal intolerance to the drug.

Rheumatoid Arthritis

Oral: Two Salazopyrin EN tablets, 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 tablets 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 during sulfasalazine treatment 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.

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.

Folic Acid Metabolism

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 possibly harming the fetus during pregnancy (see section 4.6).

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 section 4.3).

Hepatic Impairment

Sulfasalazine should not be given to patients with impaired hepatic function.

Renal Impairment

Sulfasalazine should not be given to patients with impaired renal function.

Blood Dyscrasias

Sulfasalazine should not be given to patients with blood dyscrasias.

Paediatric Population

Use of sulfasalazine 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, particularly at 340 nm, 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 around that wavelength. 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 Interaction with other medicines and other forms of interaction

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 oral 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

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 possibly 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.

Breast-feeding

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. Caution should be used, particularly if breastfeeding premature infants or those deficient in G-6-PD. 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.

There have been reports of bloody stools or diarrhoea in infants of mothers on sulfasalazine who were breastfeeding. In cases where the outcome was reported, bloody stools or diarrhoea resolved in the infant after discontinuation of sulfasalazine in the mother.

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.

Fertility

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.

4.7 Effects on ability to drive and use machinery

The effect of sulfasalazine on the ability to drive and use machinery has not been systematically evaluated.

4.8 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 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 section 4.4)

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 section 4.4).

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 section 4.4), pericarditis, cyanosis[#].

Vascular Disorders

Pallor* (see section 4.4).

Respiratory, Thoracic and Mediastinal Disorders (see section 4.4)

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 section 4.4)

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

Skin and Subcutaneous Tissue Disorders (see section 4.4)

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 section 4.4), nephrotic syndrome, interstitial nephritis, nephrolithiasis*.

Reproductive System

Reversible oligospermia (see section 4.4).

General Disorders

Fever (see section 4.4), 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 of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

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; treatment with sulfasalazine is contraindicated in these patients (see section 4.3). 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 "*Antibacterial Effect*" below).

Pharmacodynamic Effects

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 *C. 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 *Clostridium 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.

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/Elimination

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.

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

Biotransformation

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.

5.3 Preclinical safety data

No data available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Salazopyrin tablets:

Silicon dioxide

Magnesium stearate

Povidone

Pregelatinised maize starch

Salazopyrin-EN tablets:

Carnauba wax

Cellacefate

Silicon dioxide

Macrogol 20000

Magnesium stearate

Povidone

Propylene glycol

Purified talc

Self-emulsifying glyceryl monostearate

Starch

White beeswax

6.2 Incompatibilities

No data available.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Salazopyrin Tablets 500 mg, available in HDPE bottles of 100 tablets.

Salazopyrin-EN Tablets 500 mg, available in HDPE bottles of 100 tablets.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF THE TEXT

29 May 2019

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance
4.4	Revised to include information regarding the interference of sulfasalazine with NADH/NADPH based bioassays per Company CDS