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180 mm.

SALAZINE Enteric Coated Tablet 500mg

CONTENT
Each enteric-coated tablet contains Sulfasalazine 500 mg.

DESCRIPTION
Yellow oval biconvex enteric film coated tablet embossed with "S21" on one side and "SPS" on the other side.

PHARMACODYNAMICS
Sulfasalazine is metabolized by bacteria in the colon into its active metabolites, sulfapyridine and 5-aminosalicylic acid (mesalazine), the rest remains as unchanged sulfasalazine. The three compounds are having active pharmacological effects, principally immunomodulatory, antibacterial and alteration of the arachidonic acid cascade and the activity of certain enzymes. The net result clinically is a reduction in the activity of the inflammatory diseases namely ulcerative colitis, Crohn's disease and rheumatoid arthritis. A disease modifying effect is evident in rheumatoid arthritis in one to three months, but mesalazine is not believed to be responsible for this effect. There are improvements in CRP and other indicators of inflammation together with significant reduction in progression (Larsen or Sharp Index) in early patients compared with placebo or hydroxychloroquine treatment over two years. The benefit appears to be maintained even when the drug is stopped.

PHARMACOKINETICS
Absorption: 15% of the dose is absorbed from small intestine; the rest reaches the colon where the azo bond is cleaved by the intestinal flora, producing sulfapyridine and 5-aminosalicylic acid (mesalazine). About 60% of the sulfapyridine and 10-30% of the mesalazine is absorbed from the colon.

Distribution: Sulfasalazine is extensively protein bound (> 99.3%), while sulfapyridine is only about 70% protein bound and distributed to most body tissues. Acetylsulfapyridine (AcSP), the principle metabolite of sulfapyridine, is approximately 90% bound to plasma proteins. Sulfapyridine crosses the placenta and found in breast milk.

Metabolism: Sulfasalazine is metabolized by intestinal bacteria to sulfapyridine and mesalazine. Upon absorption, sulfapyridine undergoes extensive metabolism via acetylation to form acetylsulfapyridine and the rate of metabolism depends on acetylator phenotype. In fast acetylators, the mean plasma half-life of sulfapyridine is 10.4 hours while in slow acetylators, the mean plasma half-life is 14.8 hours. Slow acetylators are 2-3 times more likely to experience adverse effects compared to fast acetylators. Sulfapyridine can be metabolized to 5-hydroxy-sulfapyridine and N-acetyl-5-hydroxy-sulfapyridine via hydroxylation, and glucuronidation. Absorbed 5-aminosalicylic acid undergoes metabolism in both the liver and intestine to N-acetyl-5- aminosalicylic acid via a non-acetylation phenotype acetylation.

Excretion: About 15% of sulfasalazine is excreted via urine unchanged. About 60% of sulfasalazine is excreted in the form of sulfapyridine and its metabolites and about 20-33% in the form of mesalazine and its metabolites.

INDICATION
SALAZINE is indicated for the management of mild to moderate and severe ulcerative colitis, Crohn's disease and rheumatoid arthritis.

RECOMMENDED DOSAGE
Dosage should be adjusted in accordance to disease severity and to patient's tolerance to the drug. **SALAZINE** should be taken orally with or after meal at regular intervals. Ensure adequate fluid intake. The enteric-coated tablet should not be crushed or broken. Sulfasalazine is effective in Crohn's disease particularly in patients with colonic involvement.

Inflammatory Bowel Disease:
Adult
Severe attacks: 2 to 4 tablets, 3 to 4 times a day and may be given in conjunction with steroids as part of an intensive management regime.

Mild to moderate: 2 tablets, 3 to 4 times a day may be given in conjunction with steroids.

Maintenance: With induction of remission in ulcerative colitis, reduce the dose gradually to 2 tablets, 2 times a day in divided dose. This dosage should be continued indefinitely.

Children
For children 2 years of age or older, the dose should be given in proportion to body weight.

Acute attack or relapse: 40-60 mg/kg per day in 3 to 6 divided doses.
Maintenance: 20-30 mg/kg per day in 3 to 6 divided doses.

Rheumatoid arthritis:
Adult
Initiate dose at 1 tablet daily for the 1st week and increased by 1 tablet every week. Maximum of 3 gm daily in 2-4 divided doses.

CONTRAINDICATIONS
Sulfasalazine is contraindicated in:
• Children under the age of 2 years due to risk of kernicterus.
• Patients with intestinal or urinary obstruction.
• Patients with porphyria, as the sulfonamides have been reported to precipitate an acute attack.
• Patients with known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sulfonamides or salicylates.

WARNINGS AND PRECAUTIONS
Sulfasalazine should be administered under medical supervision. Sulfasalazine shares the potential toxic effects of other sulfonamides (e.g. hypersensitivity, renal/hepatic impairment, haematologic disorders), especially sulfapyridine and the usual precautions of sulfonamide therapy should be observed.

Sulfasalazine should be used only after critical appraisal of the risk to benefit in patients with hepatic or renal damage, blood dyscrasias, severe allergy or bronchial asthma. Pancreatitis has been observed in some susceptible individuals.

Deaths associated with the administration of sulfasalazine have been reported from hypersensitivity reactions, agranulocytosis, aplastic anaemia, other blood dyscrasias, 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.

• Hypersensitivity
Severe life-threatening hypersensitivity reactions have been reported in patients taking various drugs including sulfasalazine. They may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome (i.e., pseudomononucleosis), haematological abnormalities (including haematophagic histiocytosis), pneumonitis including eosinophilic infiltration and systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS).

It is important to note that early manifestations of hypersensitivity, such as fever, elevated liver function tests and/or hepatomegaly and eosinophilia 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 aetiology for the signs or symptoms cannot be established.

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.

• Blood Dyscrasia, Liver and Kidney Impairment
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. Bone marrow depression (most often manifested as leukopenia) has been reported, usually within the first three months of starting treatment. In the vast majority of patients, this has been reversible on stopping the drug.

Complete blood counts, including differential white blood cell count, and liver function tests should be carried out before starting sulfasalazine 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. The patient should also be counselled to report immediately with any sore throat, fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness during sulfasalazine treatment, this may indicate myelosuppression, haemolysis or hepatotoxicity. Treatment should be stopped immediately while awaiting the results of blood tests.

Sulfasalazine should not be given to patients with impaired hepatic or renal function or with blood dyscrasias, unless the potential benefit outweighs the risk.

• Allergy or Bronchial Asthma
Sulfasalazine should be given with caution to patients with severe allergy or bronchial asthma.

• Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency
Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency should be closely observed for signs of haemolytic anaemia. This reaction is frequently dose-related. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately.

• Crystalluria / Kidney Stone
Adequate fluid intake must be maintained in order to prevent crystalluria and kidney stone formation.

• Infertility
Oligospermia and infertility have been observed in men treated with sulfasalazine. Withdrawal of the drug appears to reverse these effects within two to three months.

• Folate Deficiency
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). This can be normalised by administration of folic acid or folinic acid (leucovorin).

• Use in Children
The safety and effectiveness of sulfasalazine in paediatric patients below the age of 2 years with ulcerative colitis have not been established. 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.

FRONT SIDE ▲

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• Interference with Laboratory Testing
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, mesalamine/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)]. Caution should be exercised in the interpretation of these laboratory results in patients who are receiving sulfasalazine (see Drug Interactions).

Sulfasalazine may produce an orange-yellow colour of the urine. Similar discolouration of the skin and yellow staining of soft contact lenses have occasionally been reported.

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

DRUG INTERACTIONS
• 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. Folic acid requirements may be increased in patients receiving sulfasalazine.

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

• Oral Hypoglycaemic Agents
Sulfonamides bear certain chemical similarities to some oral hypoglycaemic agents. Hypoglycaemia has occurred in patients receiving sulfonamides. Patients receiving sulfasalazine and hypoglycaemic agents should be closely monitored.

• Methotrexate
Co-administration of oral sulfasalazine and methotrexate to rheumatoid arthritis patients did not alter the pharmacokinetic disposition of the drugs. However, an increased incidence of gastrointestinal adverse events, especially nausea, was reported.

• Drug / Laboratory Test Interactions
Sulfasalazine or its metabolites may interfere with ultraviolet absorbance, particularly at 340 nm, and may cause interference with some laboratory assays that use NAD(H) or 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 (see Warnings and Precautions).

PREGNANCY AND LACTATION
Pregnancy
Sulfasalazine should not be used during pregnancy unless the benefits to the mother clearly outweigh the risks to the foetus. Reproduction studies have been performed in rats and rabbits at doses up to 6 times the human dose and have revealed no evidence of impaired female fertility or harm to the foetus due to sulfasalazine.

Sulfasalazine and sulfapyridine pass the placental barrier. Although sulfapyridine has been shown to have a poor bilirubin displacing capacity, the potential for kernicterus in newborns should be kept in mind. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency. 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 definitely established. Because the possibility of harm cannot be ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Lactation
Sulfasalazine and sulfapyridine are found in low levels in breast milk. Caution should be used, particularly if breastfeeding premature infants or those deficient in G6PD. There have been reports of bloody stools or diarrhoea in infants who were breastfeeding from mothers on sulfasalazine. In cases where the outcome was reported, bloody stools or diarrhoea resolved in the infant after discontinuation of sulfasalazine in the mother.

SIDE EFFECTS
Adverse reactions with sulfasalazine may be more frequent and more severe in patients who are slow acetylators. Most side effects are dose-dependent, and the symptoms can often be alleviated by reducing the dosage. Increased incidence of adverse reactions are seen with daily dosage of 4 g or more, or total serum sulfapyridine levels above 50 mcg/mL. Hypersensitivity reactions have been noted, in which a dose reduction is irrelevant.

The following events have been reported in patients receiving sulfasalazine:

Infections and Infestations
Not known: aseptic meningitis, pseudomembranous colitis

Blood and lymphatic system disorders
Common: leukopenia
Uncommon: thrombocytopenia†
Not known: pancytopenia, agranulocytosis, aplastic anaemia, pseudomononucleosis*†, haemolytic anaemia, macrocytosis, megaloblastic anaemia

Immune system disorders
Not known: anaphylaxis*, serum sickness

Metabolism and nutrition system disorders
Common: loss of appetite
Not known: folate deficiency*†

Psychiatric disorders
Uncommon: depression

Nervous system disorders
Common: dizziness, headache, taste disorders
Not known: encephalopathy, peripheral neuropathy, smell disorders

Ear and labyrinth disorders
Common: tinnitus

Cardiac disorders
Not known: myocarditis*†, pericarditis, cyanosis

Vascular disorders
Not known: pallor*†

Respiratory, thoracic and mediastinal disorders
Common: cough
Uncommon: dyspnoea
Not known: interstitial lung disease*, eosinophilic infiltration, fibrosing alveolitis, oropharyngeal pain*†

Gastrointestinal disorders
Very common: gastric distress, nausea
Common: abdominal pain, diarrhoea*, vomiting*
Not known: aggravation of ulcerative colitis*, pancreatitis

Hepatobiliary disorders
Uncommon: jaundice*†
Not known: hepatic failure*, hepatitis fulminant*, hepatitis†, hepatitis cholestatic*, cholestasis*

Skin and subcutaneous tissue disorders
Common: purpura*†, pruritus
Uncommon: alopecia, urticaria
Not known: drug rash with eosinophilia and systemic symptoms (DRESS)*†, epidermal necrolysis (Lyell's syndrome)*, Stevens-Johnson syndrome†, exanthema, exfoliative dermatitis†, angioedema*, toxic pustuloderma, lichen planus, photosensitivity, erythema

Musculoskeletal and connective tissue disorders
Common: arthralgia
Not known: system lupus erythematosus, Sjogren's syndrome

Renal and urinary disorders
Common: proteinuria
Not known: nephrotic syndrome, interstitial nephritis, nephrolithiasis*, haematuria, crystalluria†

Reproductive system and breast disorders
Not known: reversible oligospermia†

General disorders and administration site conditions
Common: fever†
Uncommon: facial oedema
Not known: yellow discoloration of skin and body fluids*

Investigations
Uncommon: elevation of liver enzymes
Not known: induction of autoantibodies

* Adverse effects identified post-marketing.
† See section Warnings and Precautions.

SYMPTOMS AND TREATMENT OF OVERDOSE
Similar to those of any sulfonamides, 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 should be symptomatic and supportive, including alkalinisation of urine. Patients should be observed for development of methaemoglobinaemia or sulfhaemoglobinaemia. If these occur, treat appropriately. Serum sulfapyridine concentrations may be used to monitor progress of recovery from overdosage. There is evidence that the incidence and severity of toxicity following overdosage are directly related to the total serum sulfapyridine concentration.

PACK SIZES
Aluminium-PVC blister strip of 10 tablets per strip, pack in box of 5 x 10 tablets, 10 x 10 tablets and 50 x 10 tablets.

STORAGE CONDITIONS
Store in a cool and dry place, below 30°C.
Protect from light.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

SHELF LIFE
36 months

Manufactured by:
SRIPRASIT PHARMA CO., LTD.
216 Moo 6, Suanluang, Krathum Baen,
Samut Sakhon 74110, Thailand.

Date of Revision: January 2021

PIS0019 Rev: 1

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