PRODUCT MONOGRAPH

[Pr]pms-SULFASALAZINE
Sulfasalazine Tablets USP
500 mg

[Pr]pms-SULFASALAZINE-E.C.
Sulfasalazine Delayed-Release Tablets USP
500 mg

Anti-inflammatory

Treatment of Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease (all dosage forms)

Rheumatoid Arthritis (pms-SULFASALAZINE-E.C. Tablets only)

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(Sulfasalazine Tablets USP)

[Pr]pms-SULFASALAZINE-E.C.
(Sulfasalazine Delayed-Release Tablets USP)

PART I: HEALTH PROFESSIONAL INFORMATION

THERAPEUTIC CLASSIFICATION

Anti-inflammatory drug

ACTION AND CLINICAL PHARMACOLOGY

About 20% of sulfasalazine is absorbed in the small intestine after oral administration. A small percentage of the absorbed sulfasalazine is excreted in the urine and the rest via the bile into the small intestine (enterohepatic circulation). This portion together with the unabsorbed sulfasalazine enters the colon where it is split by bacteria into two main metabolites, sulfapyridine and 5-amino-salicylic acid (5-ASA). The peak serum concentration is reached after 3-5 hours. The mean serum half-life after a single dose is about 6 hours; after repeated doses, it is about 8 hours. After intake of sulfasalazine delayed-release tablets, sulfasalazine has been detected in serum somewhat later than after intake of plain tablets, as expected, the peak serum concentration being observed between 3 and 12 hours.

Sulfapyridine is absorbed, partially acetylated and/or hydroxylated in the liver and/or conjugated with glucuronic acid. In patients who are slow acetylators, the serum concentration of free sulfapyridine is higher than that in fast acetylators. The major part is excreted in the urine. Non-acetylated sulfapyridine is bound to serum proteins and reaches a maximum serum concentration after 12 hours. Sulfapyridine has a tendency to accumulate. It does not disappear completely from the serum until 3 days after withdrawal of the drug.

The total urinary recovery of sulfasalazine and its sulfapyridine metabolites in healthy subjects during 3 days after the administration of a single 2 g dose of sulfasalazine averaged 91%.

The absorbed 5-aminosalicylic acid is partly excreted in the urine, mainly as acetyl-5-aminosalicylic acid. A larger portion of 5-aminosalicylic acid is excreted in the feces.

The mode of action of sulfasalazine is unclear and is suggested as being: anti-inflammatory, immunosuppressive and bacteriostatic.

In clinical cases of inflammatory bowel disease (IBD), the anti-inflammatory effects seem to relieve the acute symptoms of diarrhea, gut inflammation, mucosal edema and bleeding. The long-

term protection afforded by therapy with sulfasalazine may be due to immunosuppressive properties of the drug.

Anti-inflammatory Effects

Sulfasalazine inhibits superoxide production by granulocytes stimulated with immune complexes or formyl peptides. In addition, 5-ASA is a powerful scavenger of oxygen free radicals. Other granulocyte functions inhibited by sulfasalazine include degranulation, chemotaxis and random migration. These inhibitory effects on inflammatory cell functions may contribute to the beneficial clinical activity of sulfasalazine.

Sulfasalazine is a relatively weak inhibitor of the cyclo-oxygenase enzyme, but a potent inhibitor of 15-prostaglandin dehydrogenase (PGDH), the main metabolic pathway for the prostaglandins.

On the lipoxygenase side of the arachidonic acid cascade, sulfasalazine has been shown to exert an inhibitory effect on several enzymes including 5- Lipoxygenase (5-LO) and Leukotriene C4 (LTC_4) synthetase. In line with this effect, sulfasalazine has been shown to inhibit the release of lipoxygenase product from inflammatory cells and tissue.

Taken together, the effects of sulfasalazine on arachidonic acid metabolizing enzymes would lead to a decrease in pro-inflammatory lipoxygenase products with a simultaneous increase in immunosuppressive, anti-inflammatory prostaglandins, which may have a bearing on the clinical activity.

Effects on Immunological Functions

Since the disorders in which sulfasalazine has clinical activity are considered to be of autoimmune nature, the effect of sulfasalazine on immune-competent cells is of interest. Both natural killer cell activity and T-cell proliferation are inhibited by sulfasalazine in *in vitro* systems.

Antibacterial Effects

In-vitro studies have shown that both sulfasalazine and its main metabolites inhibit bacterial growth. A reduction in several bacterial species of the gut flora has also been observed after clinical treatment with sulfasalazine.

Pharmacokinetics in Patients with Rheumatoid Arthritis

The pharmacokinetics of sulfasalazine and its metabolites after a single oral 2 g dose was compared in patients with rheumatoid arthritis and in patients with ulcerative colitis. The study showed a large individual variability, which is also found in studies in healthy volunteers, but no difference between the two patient groups was observed, except for a significantly higher peak concentration of sulfapyridine in rheumatoid arthritis patients. The area under the plasma concentration curve (AUC) for sulfapyridine was also increased, but the difference was not significant.

Bioavailability in Elderly Patients with Rheumatoid Arthritis

The pharmacokinetics of sulfasalazine and its metabolites was compared in young (mean age 40.5 years) and elderly (mean age 74.4 years) rheumatoid arthritis patients after a single oral (2 g) dose taken fasting and at steady state. The only difference found between the two groups was a prolonged $t_{1/2}$ in the elderly, but no significant difference in either the plasma concentration at steady state or in the renal clearance. For sulfapyridine, both t_{max} and volume of distribution were significantly increased in the elderly after the single doses, but this difference with age disappeared at chronic dosing. The data indicates that there is no major age-dependent difference in the pharmacokinetics of sulfasalazine. However, the effect of acetylation phenotype is much more important.

INDICATIONS AND CLINICAL USE

pms-SULFASALAZINE (sulfasalazine) and pms-SULFASALAZINE-E.C. (sulfasalazine delayed-release tablets)) are indicated as an adjunctive therapy in the treatment of severe ulcerative colitis, proctitis or distal ulcerative colitis and Crohn's disease. It is especially useful for chronic administration.

pms-SULFASALAZINE-E.C. is also indicated for the treatment of active rheumatoid arthritis, when treatment with an adequate conventional first line therapy has failed.

CONTRAINDICATIONS

pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. are contraindicated:

- In patients with hypersensitivity to sulfasalazine, its metabolites, or any other component of the product (see Composition), sulfonamides, or salicylates.
- In infants under 2 years of age.
- In patients with intestinal and urinary obstructions.
- In patients with porphyria, as these drugs have been reported to precipitate an acute attack.
- In patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by acetyl salicylic acid (ASA) or other non-steroidal anti-inflammatory agents. Fatal anaphylactic reactions have occurred in such individuals.
- In patients with severe renal impairment (GFR< 30 mL/min/1.73m^2) and/or severe hepatic impairment (see WARNINGS AND PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General

pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. should be administered under medical supervision. Sulfasalazine shares the potential toxic effects of other sulfonamides (e.g., hypersensitivity, renal/hepatic impairment, hematologic disorders), especially sulfapyridine and

the usual precautions of sulfonamide therapy should be observed (see specific sections under WARNINGS AND PRECAUTIONS).

pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. 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 anemia, 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 during sulfasalazine treatment may indicate myelosuppression, hemolysis, or hepatotoxicity. Discontinue treatment with sulfasalazine while awaiting the results of blood tests.

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-Laboratories Test Interactions).

The risk of serious-life-threatening events, including drug rash with eosinophilia and systemic symptoms (DRESS), appears to be highest during the first 3 months of sulfasalazine therapy. Closer monitoring of patients during this period is of importance for early diagnosis and appropriate management.

Complete blood counts, including differential white cell count and liver function tests, should be performed 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. A falling trend in the blood count is a better indicator than a single value (see Monitoring and Laboratory Tests).

pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. 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.

Gastrointestinal

Isolated instances have been reported when sulfasalazine delayed-release tablets. have passed undisintegrated through the digestive tract. This may be due, in part, to a lack of intestinal esterase in these patients. If this is observed, the administration of pms-SULFASALAZINE-E.C should be discontinued.

Hematologic

Patients, especially those with glucose-6-phosphate dehydrogenase deficiency, should be observed closely for signs of hemolytic anemia. This reaction is frequently dose-related. If toxic or hypersensitivity reactions occur, the drug should be discontinued immediately.

Bone marrow depression (most often manifested as leucopenia) has been reported, usually within the first 3 months of starting treatment. In the majority of the patients, this has been reversible upon stopping the drug. A full blood count, including differential white blood cell count, should be carried out before starting treatment and monitored closely during the first 3 months of treatment. A falling trend in the count of any formed blood element is a better indicator than a single value.

Afterwards, patients should be screened if their condition changes or if they present with any symptoms of infection.

Serious infections associated with myelosuppression, including sepsis and pneumonia, have been reported.

Red cell and platelet counts should be carried out before and periodically during therapy.

Hepatic

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with 5-ASA/Mesalazine products. Therefore, pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. are contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised, and pms-SULFASALAZINE or pms-SULFASALAZINE-E.C. should only be used if the expected benefit clearly outweighs the risks to the patients. Liver function tests should be carried out before and periodically during therapy.

Hypersensitivity Reactions

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
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), hematological abnormalities (including hematophagic 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 etiology for the signs or symptoms cannot be established.

There have been reports of hepatic failure and increased liver enzymes in patients with pre-existing liver disease when treated with 5-ASA/Mesalazine products. Therefore, pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. are contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS). In patients with mild to moderate liver function impairment, caution should be exercised and pms-SULFASALAZINE or pms-SULFASALAZINE-E.C. should only be used if the expected benefit clearly outweighs the risks to the patients.

Serious Skin Reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported 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.

Other
Patients hypersensitive to furosemide, thiazides diuretics, carbonic anhydrase inhibitors, may also be hypersensitive to this medication. Patients should be monitored for signs of skin rash, mucosal lesions, or any other signs of hypersensitivity.

Immune

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.

Renal

Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with mesalamine products and pro-drugs of mesalamine. pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. are contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS). In patients with mild to moderate renal dysfunction, caution should be exercised, and pms-SULFASALAZINE or pms-SULFASALAZINE-E.C. should be used only if the benefits outweigh the risks. Urinalysis should be carried out before and periodically during therapy.

Adequate fluid intake must be maintained in order to prevent crystalluria and kidney stone formation.

Sexual Function/Reproduction

Oligospermia with infertility have been observed in men treated with sulfasalazine. Withdrawal of the drug appears to reverse these effects within 2 to 3 months.

Monitoring and Laboratory Tests

The following may be especially important in patient-monitoring (other tests may be warranted in some patients, depending on their condition):

Bone marrow depression (most often manifested as leucopenia) has been reported, usually within the first 3 months of starting treatment. In the majority of the patients this has been reversible upon stopping the drug.
Complete blood counts, including differential white cell count and liver function tests, should be performed 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.
A falling trend in the blood count is a better indicator than a single value (see WARNINGS AND PRECAUTIONS).

Proctoscopy and sigmoidoscopy may be required periodically during treatment to determine patient response and dosage adjustments.

Special Populations

Pregnancy and Reproduction

Sulfasalazine should not be used during pregnancy unless the benefits to the mother clearly outweigh the risks to the fetus.

Teratogenic Effects
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.

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 fetus due to sulfasalazine.

The outcome of pregnancy in a group of pregnant women with intestinal bowel disease (IBD) treated with sulfasalazine alone or sulfasalazine and concomitant steroid therapy was compared with untreated IBD pregnancies. The incidence of fetal morbidity and mortality was comparable between the groups and to the expected outcome in the general population.

Non-teratogenic Effects
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.

A case of agranulocytosis has been reported in an infant whose mother was taking both sulfasalazine and prednisone throughout pregnancy.

Nursing Mothers
Caution should be exercised when sulfasalazine is administered to a nursing woman, since it is excreted in the milk. The concentration of sulfapyridine in milk is about 30 - 60% of that in serum. However, since sulfapyridine has a poor bilirubin displacing capacity, the risk for kernicterus in healthy suckling children may be low with therapeutic doses. Sulfasalazine and sulfapyridine are found in low levels in breast milk. Caution should be used, particularly if breastfeeding premature infants or those deficient in Glucose-6-Phosphate Dehydrogenase (G-6-PD). There have been reports of bloody stools or diarrhea in infants who were breastfeeding from mothers on sulfasalazine. In cases where the outcome was reported, bloody stools or diarrhea resolved in the infant after discontinuation of sulfasalazine in the mother.

Pediatrics
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.

ADVERSE REACTIONS

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 be alleviated by reducing the dosage. Increased incidence of adverse reactions is 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.

It has been shown that the frequency and severity of the rather common dyspeptic manifestations experienced by patients with gastric intolerance to sulfasalazine tablets are markedly reduced when using delayed-release sulfasalazine.

The most commonly reported adverse reactions are: nausea, vomiting, gastric distress, methemoglobinemia, anorexia, headache and apparently reversible oligospermia. These occur in about one-third of patients. Less frequent adverse reactions are skin rash, erythema, pruritus, urticaria, fever, Heinz-body anemia, hemolytic anemia, leukopenia, megaloblastic (macrocytic) anemia, and cyanosis, which may occur at a frequency of one in every thirty patients or less.

Although the listing that follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the sulfonamides require that each of these reactions be considered when sulfasalazine is administered.

Other adverse reactions which occur rarely, in approximately 1 in 1,000 patients or less are:

Blood dyscrasias: aplastic anemia, agranulocytosis, purpura, thrombocytopenia and hypoprothrombinemia, pancytopenia, macrocytosis, congenital neutropenia, and myelodysplastic syndrome.

Hypersensitivity reactions: erythema multiforme (Stevens Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, anaphylaxis, serum sickness syndrome, pneumonitis with or without eosinophilia, vasculitis, fibrosing alveolitis, pleuritis, pericarditis with or without tamponade, allergic myocarditis, polyarteritis nodosa, hepatitis and hepatic necrosis with and without immune complexes, parapsoriasis varioliformis acuta (Mucha-Habermann syndrome), rhabdomyolysis, photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection, alopecia and induction of autoantibodies.

Skin reactions: facial edema, exanthema, lichens planus, toxic pustuloderma, drug rash with eosinophilia and systemic symptoms (DRESS), angioedema.

Gastrointestinal reactions: hepatitis, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, mouth ulceration, diarrhea, abdominal pain, aggravation of ulcerative colitis, pseudomembranous colitis, and neutropenic enterocolitis.

Respiratory reactions: cough, dyspnea, interstitial lung disease (some with fatal outcome).

CNS reactions: transverse myelitis, convulsions, transient lesions of the posterior spinal column, cauda equina syndrome, Guillain-Barré syndrome, peripheral neuropathy, encephalopathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus and drowsiness. Three cases of aseptic meningitis have been reported during the use of delayed-release sulfasalazine in the treatment of rheumatic diseases.

Nervous system reactions: smell and taste disorders.

Hepatic reactions: elevation of liver enzymes, hepatic failure, hepatitis fulminant, sometimes leading to liver transplantation, Jaundice, cholestatic jaundice, cirrhosis, and possible hepatocellular damage including liver necrosis and liver failure.

Renal reactions: toxic nephrosis with oliguria and anuria, nephrotic syndrome, hematuria, crystalluria proteinuria, and interstitial nephritis, hemolytic-uretic syndrome.

Musculoskeletal/connective tissue reactions: Sjögren's syndrome, systemic lupus erythematosus.

Other reactions: urine discoloration and skin discoloration. The sulfonamides bear certain

chemical similarities to some goitrogens, diuretics, acetazolamide and the thiazides, and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents. Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides and long-term administration has produced thyroid malignancies in this species.

Post-Marketing Reports

The following events have been identified during post-approval use of products which contain (or are metabolized to) mesalamine in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to mesalamine:

Blood dyscrasias: pseudomononucleosis

Cardiac disorders: myocarditis

Hepatobiliary disorders: hepatitis cholestatic, cholestasis

Metabolism and nutrition system disorders: folate deficiency

Renal and urinary disorders: nephrolithiasis

Respiratory, thoracic and mediastinal disorders: oropharyngeal pain

Vascular disorders: pallor

DRUG INTERACTIONS

Drug-Drug Interactions

Combinations containing any of the following medications, depending on the amount present, may interact with this medication.

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance:

- Antibiotics
- Anticoagulants, coumarin- or indandione-derivative
- Anticonvulsants, hydantoin
- Antidiabetic agents, oral

The following drug interactions and/or related problems have been selected on the basis of their possible mechanism of action (detailed in parentheses):

- Digitalis Glycosides or Folic Acid
  (sulfasalazine may inhibit absorption and lower the serum concentrations of these medications; folic acid requirements may be increased in patients receiving sulfasalazine) (patients taking digitalis glycosides should be monitored closely for evidence of altered digitalis effect. Reduced absorption of digoxin resulting in non-therapeutic serum levels, has been reported in patients taking digoxin concomitantly with oral sulfasalazine)

- Methenamine
  (in acid urine, methenamine breaks down into formaldehyde, which may form an insoluble precipitate with certain sulfonamides and may also increase the danger of crystalluria; concomitant use is not recommended)

- Methotrexate
  (may be displaced from protein binding sites and/or metabolism may be inhibited by sulfonamides, resulting in increased or prolonged effects and/or toxicity; dosage adjustments may be necessary during and after sulfonamide therapy; 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)

- Oxyphenbutazone, Phenylbutazone
  (effects may be potentiated when used concomitantly with sulfonamides because of displacement from plasma protein binding sites)

- Photosensitizing Medications
  (caution in concomitant use of sulfasalazine with these medications is recommended because of potential additive photosensitizing effects)

- Probenecid
  (decreases renal tubular secretion of sulfonamides when used concomitantly, resulting in increased and more prolonged sulfonamide concentrations and/or toxicity; sulfonamide dosage adjustments may be necessary during and after probenecid therapy and sulfonamide serum determinations may be useful in prolonged probenecid therapy)

- Sulfinpyrazone
  (concomitant use may displace sulfonamides from protein binding sites and may decrease renal excretion, resulting in increased sulfonamide concentrations and/or toxicity; sulfonamide dosage adjustments may be necessary during and after sulfinpyrazone therapy)

- Thiopurine Methyltransferase (TPMT)
  (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)

Drug-Laboratories Test Interactions

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 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, General).

OVERDOSAGE

Symptoms

Similar to those of any sulfonamide, the most likely symptoms being gastrointestinal disturbances (nausea and vomiting), drowsiness, convulsions, hematuria, crystalluria or anuria. Patients with impaired renal function are at increased risk of serious toxicity. Patients should be observed for development of methemoglobinemia or sulfhemoglobinemia. If these occur, treat appropriately. Serum sulfapyridine concentrations may be used to monitor progress of recovery from overdosage.

Treatment

Gastric lavage or emesis plus catharsis as indicated. Alkalinize urine. If kidney function is normal, force fluids. If anuria is present, restrict fluids and salt, and treat appropriately. Catheterization of the ureters may be indicated for complete renal blockage by crystals. The low molecular weight of sulfasalazine and its metabolites may facilitate their removal by dialysis. For agranulocytosis, discontinue the drug immediately, hospitalize the patient and institute appropriate therapy.

For hypersensitivity reactions, discontinue treatment immediately. Such reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Dosing Consideration

The dosage of pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. should be adjusted according to the response to the treatment and the patient's tolerance to the drug. The tablets / delayed-release tablets should be taken at regular and even intervals over the 24-hour period. pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. tablets should preferably be taken with a meal. For intestinal inflammatory diseases, the night-time doses interval should not exceed 8 hours.

Patients not previously treated with sulfasalazine should increase the dose gradually during the first few weeks. The incidence of adverse reactions tends to increase with daily dosages of 4 g or more; patients receiving these doses should be advised of this possibility and should be carefully observed for the appearance of adverse reactions.

Recommended Dose and Dosage Adjustment

Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease

1. Acute attacks:

   Adults:
   Severe attacks: 2–4 tablets, 3–4 times daily
   Moderate and mild attacks: 2 tablets, 3–4 times daily.

   Children:
   25–35 kg body weight: 1 tablet, 3 times daily
   35–50 kg body weight: 2 tablets, 2-3 times daily

2. Prophylaxis:

   Adults:
   In the state of remission in ulcerative colitis the maintenance dose recommended for keeping the patient free from symptoms is 2 tablets 2–3 times a day. Treatment with this dosage should continue indefinitely, unless adverse effects are observed. In case of deterioration, raise the dosage to 2–4 tablets, 3–4 times a day.

   Children:
   25–35 kg body weight: 1 tablet twice daily
   35–50 kg body weight: 1 tablet 2–3 times daily

Patients experiencing gastrointestinal side effects with the uncoated pms-SULFASALAZINE tablet should use pms-SULFASALAZINE-E.C. tablets or a lower dose.

Rheumatoid Arthritis

1. Adults:
   2 delayed-release tablets, 2 times daily.
   When starting therapy, it is suggested to increase the daily dose as follows:

	1st Week	2nd Week	3rd Week	4th Week and after
Morning		1 Delayed-release tablet	1 Delayed-release tablet	2 Delayed-release tablets
Evening	1 Delayed-release tablet	1 Delayed-release tablet	2 Delayed-release tablets	2 Delayed-release tablets

   If no response has been seen after two months treatment, dose may be increased to 3 g/day. Some patients may do well with 1.5 g/day.

   A clinical effect generally appears 1–2 months after initiation of treatment. Concomitant therapy with analgesics and/or anti-inflammatory agents is recommended until the therapeutic effect of pms-SULFASALAZINE-E.C. tablets is apparent. pms-SULFASALAZINE-E.C. tablets are effective and well-tolerated in long-term treatment.

2. Children:
   The use of sulfasalazine in Juvenile Rheumatoid Arthritis is not recommended since its efficacy / safety has not been established.

Special Population

1. Elderly patients:
   Based on pharmacokinetic studies, no special dosage instructions are required for elderly patients.

2. Patients with renal deficiency:
   pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. should be used with caution in patients with renal deficiency.

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

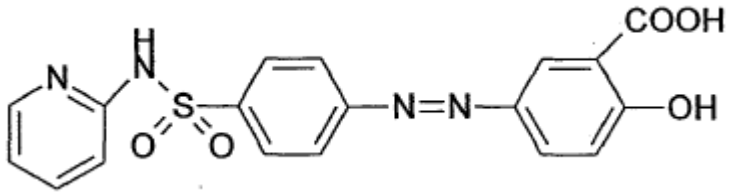
Proper Name: Sulfasalazine, USP

Chemical Name: 2-Hydroxy-5-[[4-[(2-pyridinylamino) sulfonyl]phenyl]azo]benzoic acid

Molecular Formula: $C_{18}H_{14}N_4O_5S$

Molecular Mass: 398.40 g/mol
C 54.27%, H 3.54%, N 14.06%, 020.08%,
S 8.05%

Structural Formula:



Physicochemical Properties:

Description: Minute, brownish-yellow crystals

Melting Point: Decomposes at 240–245°C.

Solubility: Slightly soluble in ale. Practically insoluble in water, benzene, chloroform, and ether.

UV max: 237 and 359 nm.

STORAGE AND STABILITY

Store between 15-30°C. Avoid freezing.

AVAILABILITY OF DOSAGE FORMS

pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. are available in the following dosage forms:

pms-SULFASALAZINE 500 mg:
Each dark-yellow, round, biconvex tablet scored on one side, identified PMS on other side contains: 500 mg Sulfasalazine. Available in bottles of 100 and 500.

pms-SULFASALAZINE-E.C. 500 mg:
Each dark-yellow, oval enteric-coated tablet, contains: 500 mg Sulfasalazine. Available in bottles of 100 and 500.

Composition

The non-medicinal ingredients in pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. are:

pms-SULFASALAZINE 500 mg:
Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Povidone.

pms-SULFASALAZINE-E.C. 500 mg:
Acrylic Resin, Croscarmellose Sodium, Iron Oxide Red, Iron Oxide Yellow, Macrogol, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Propylene Glycol, Sodium Carboxy-methylcellulose, Sodium Citrate Dihydrate, Talc, Titanium Dioxide.

DETAILED PHARMACOLOGY

As the etiology of ulcerative colitis and Crohn's disease is unclear, it is difficult to establish the significance of the different pharmacological actions of sulfasalazine.

Sulfasalazine has been used for more than four decades in the treatment of inflammatory bowel disease. Like other azo compounds, sulfasalazine exhibits an affinity for connective tissue. It also has an antibacterial as well as anti-inflammatory effect. An effect on prostaglandin synthetase and metabolism has also been suggested. Significant changes in immunological variables proved the immunosuppressive effect of sulfasalazine.

The absence of etiologic treatment for ulcerative colitis and Crohn's disease is evidenced throughout all studies. The success of the therapy depends on the site of the inflammation. In their studies, Gabel and Goldstein *et al* found that optimal results were obtained with sulfasalazine

when it was tolerated with minimal side effects (13%). From the data of Goldstein et al, it was suggested that sulfasalazine alone was an effective drug treatment for Crohn's disease.
A dosage of 2 g daily was a satisfactory maintenance treatment for ulcerative colitis and should be continued unless contraindicated by side effects. A dose of 2 g daily may give good results in patients with ulcerative colitis and Crohn's disease where treatment with corticosteroids and azathioprine have failed.

It is difficult to evaluate in the individual case whether the adverse effects are due to sulfasalazine or to the symptoms of ulcerative colitis or Crohn's disease.

The most common side effects are related to gastric intolerance and upper gastrointestinal (GI) tract response to the drug (i.e., nausea, vomiting, gastric distress and anorexia).

Lowering the dose may decrease the frequency of adverse reactions. The use of delayed-release sulfasalazine (pms-SULFASALAZINE-E.C.) is also an alternative to plain tablets to reduce the frequency of adverse reactions.

Holdsworth has reported that patients having side effects not related to dosage (such as rash, fever, allergy) can be easily desensitized. Patients could continue their sulfasalazine therapy using 2–3 g daily, thereafter.

TOXICOLOGY

Single-Dose Toxicity

In single-dose toxicity studies in the mouse, rat and rabbit, the oral toxicity was low for all three-species examined, the LD_{50} being greater than the maximum tolerated dose (i.e., 15 g/kg for the mouse and 7.5 g/kg for the rat and rabbit).

Toxicity at Repeated Dose Administration

Rat
A 200 mg/kg dose was well-tolerated in rats, the only finding being a reversible thyroid influence. At 500 and 800 mg/kg there were drug-induced effects on different parameters (body weight gain, organ weights, thyroid function and morphology). Most of these effects were normalized after the recovery period.

Dog
Doses of 250 and 500 mg/kg were well-tolerated in dogs, the only finding being increased relative weight of thyroid glands. Two dogs given 800 mg/kg also had an atrophy of testicular epithelium. (Impairment of male fertility has been reported in animals and man, and has been shown to be of a reversible type B [see Reproduction toxicity]).

Reproduction Toxicity

In the **rat fertility study** using doses of 200, 500 and 800 mg/kg, there was a drug induced impairment of male fertility which was shown to be of a reversible type. Only at a dose of 800 mg/kg were there other adverse reactions in the parent generation and in the offspring.

In the **rat teratology study** the 200 mg/kg dose was without adverse reactions. The 500 mg/kg dose had an influence on maternal and fetal body weight gain, the 800 mg/kg dose also influenced the skeletal growth and implantation rate.

In the **rabbit teratology study**, using the same doses, a maternal transient body weight loss was found at doses of 500 and 800 mg/kg, but, there was no influence on the offspring.

In the **rat peri- and post-natal study,** the 200 mg/kg dose was without adverse reactions. At doses of 500 and 800 mg/kg, there were materno-toxic effects - lower body weight gain and at 800 mg/kg, there was also an aggravation of labour (dystocia). As a consequence, there was also an increased pup mortality rate and lower pup weight gain.

Mutagenicity

A mutagenicity testing program including ***in vitro*** tests for point mutations and chromosome aberrations showed that sulfasalazine did not possess any mutagenic activity under the conditions of these tests.

Carcinogenicity

No carcinogenicity studies have been performed based upon the following criteria:

- The chemical structure of sulfasalazine does not indicate any suspected carcinogenic risk and sulfasalazine has no relationship with other carcinogens.
- Results from mutagenicity studies were negative.
- Results from chronic toxicity studies did not indicate a potential drug induced involvement in tumour development.
- Human therapeutic experience with sulfasalazine for more than 40 years is not associated with suspected tumor development.

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PART III: CONSUMER INFORMATION

[Pr]pms-SULFASALAZINE and
pms-SULFASALAZINE-E.C.
sulfasalazine and sulfasalazine delayed-release tablets

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. contain sulfasalazine, which are anti-inflammatory drugs indicated as an adjunctive therapy in the treatment of severe ulcerative colitis (bowel inflammation), proctitis (inflammation of the rectum) or distal ulcerative colitis and Crohn's disease.

pms-SULFASALAZINE-E.C. contains sulfasalazine in delayed-release tablets, indicated for the treatment of active rheumatoid arthritis, when treatment with an adequate conventional first line therapy has failed.

What it does:
The way in which pms-SULFASALAZINE and pms-SULFASALAZINE work is unclear and thought to involve three actions:

- anti-inflammatory action, which blocks the production and effect of certain substances in the body (cyclooxygenase, prostaglandins and others), which are involved in producing inflammation;
- bacteriostatic (anti-bacterial) action, which prevents the growth of several kinds of bacteria which are possibly involved in inflammation;
- immunosuppressive action (which reduces a patient's overly active immune response, which has been linked to inflammatory diseases).

All of these actions likely work together to reduce symptoms of gut inflammation, diarrhea, swelling and bleeding.

When it should not be used:
Do not use pms-SULFASALAZINE or pms-SULFASALAZINE-E.C. if you have:

- a hypersensitivity (allergic reactions) to sulfasalazine, its metabolites, sulfonamides, salicylates or any other component of this product (see What the non- medicinal ingredients are);
- an intestinal or urinary obstruction;
- porphyria (disease of pigment production in tissues).
- experienced sudden asthmatic attacks, urticaria, rhinitis, or other allergic-type reactions to acetylsalicylic acid or other nonsteroidal anti-inflammatory, as these attacks are serious and can be fatal (see WARNINGS AND PRECAUTIONS for a complete list of conditions where pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. should not be used);
- severe kidney (renal) impairment and/or severe liver (hepatic) impairment (see Side Effects and What to Do About Them)

This drug is not to be used in infants under 2 years of age.

What the medicinal ingredient is:
Sulfasalazine

What the non-medicinal ingredients are:
pms-SULFASALAZINE tablets contain: Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose, Povidone.

pms-SULFASALAZINE-E.C contain: Acrylic Resin, Croscarmellose Sodium, Iron Oxide Red, Iron Oxide Yellow, Macrogol, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Propylene Glycol, Sodium Carboxymethylcellulose, Sodium Citrate Dihydrate, Talc, Titanium Dioxide.

What dosage forms it comes in:

- pms-SULFASALAZINE: Tablets.
  Available in bottles of 100 and 500.
- pms-SULFASALAZINE-E.C: Delayed-release tablets.
  Available in bottles of 100 and 500.

WARNINGS AND PRECAUTIONS

BEFORE you use pms-SULFASALAZINE or pms-SULFASALAZINE-E.C., talk to your doctor or pharmacist if you:

- have had any allergic reactions to any sulfonamides, furosemide or thiazide diuretics (water pills), dapsone, sulfoxone, oral hypoglycemics (diabetes drugs you take by mouth), glaucoma medicines you take by mouth (for example, acetazolamide, dichlorophenamide, methazolamide), or salicylates (for example, acetylsalicylic acid);
- are pregnant or intend to become pregnant while taking this medicine;
- are breastfeeding an infant. Sulfonamides pass into the breast milk in small amounts and may cause unwanted effects in infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency. There have been reports of bloody stools or diarrhea in infants who were breastfeeding from mothers on sulfasalazine.
- intend to father a child (low sperm count);
- have any of the following medical problems:
  - Blockage of the stomach, intestines, or urinary tract
  - Blood problems
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Kidney disease
  - Liver disease
  - Porphyria

- History of recurring or chronic infections. If you develop a new infection while taking pms-SULFASALAZINE or pms-SULFASALAZINE-E.C., talk to your doctor.
- are now taking any other medicines (See Interactions with this medicine).
- before having any kind of surgery, including dental surgery, with a general anesthetic, tell the physician or dentist in charge that you are taking a sulfonamide.

Stop taking pms-SULFASALAZINE or pms-SULFASALAZINE-E.C. immediately and tell your doctor if you develop the following symptoms:

- Skin rash, fever, swollen lymph nodes, lesions inside your mouth or nose;
- Sore throat, fever, pallor (pale skin), swollen lymph nodes, purple discoloration of the skin which does not blanch under pressure or jaundice (yellowing of your skin or white porting of your eye).

Do not give this medication to infants under 2 years of age.

INTERACTIONS WITH THIS MEDICATION

If taken with some other medicines, the effects of pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. or the other medications may change. Please check with your doctor or pharmacist before taking any other medications with pms-SULFASALAZINE or pms-SULFASALAZINE, such as:

- Anthralin
- Antibiotics
- Anticoagulants, coumarin- or indandione-type (blood thinners)
- Antidiabetic agents, oral (diabetes medicines you take by mouth)
- Azathioprine
- Coal tar
- Dapsone
- Digitalis glycosides (heart medicine)
- Dipyrone
- Diuretics (water pills or high blood pressure medicine)
- Ethotoin
- Folic acid
- Furazolidone
- Mephenytoin
- Methenamine
- Methotrexate
- Methoxsalen
- Nalidixic acid
- Nitrofurantoin
- Other sulfonamides
- Oxyphenbutazone
- Phenothiazines (tranquilizers)
- Phenylbutazone
- Phenytoin
- Primaquine
- Probenecid
- Sulfinpyrazone
- Sulfoxone
- Tetracyclines
- Thiopurine 6-mercaptopurine
- Trioxsalen
- Vitamin K

Drug interactions with antibiotics, anticoagulants, coumarin- or indandione-derivative, anticonvulsants, oral antidiabetic agents, digitalis glycosides or folic acid, methenamine, methotrexate, oxyphenbutazone or phenylbutazone, photosensitizing medications, probenecid, sulfinpyrazone, thiopurine methyltransferase (TPMT) are possible.

Sulfasalazine may interfere with some medical tests. Your healthcare provider will evaluate your results depending on your symptoms.

PROPER USE OF THIS MEDICATION

Usual adult dose:

Take pms-SULFASALAZINE or pms-SULFASALAZINE-E.C. as directed by your doctor, at regular and even intervals over the 24-hour period. If you are taking pms-SULFASALAZINE or pms-SULFASALAZINE E.C. tablets for an intestinal inflammatory disease, the night-time doses interval should not exceed 8 hours.

pms-SULFASALAZINE and pms-SULFASALAZINE-E.C. tablets are best taken after meals or with food to lessen stomach upset. If stomach upset continues or is bothersome, check with your doctor.

Each dose of pms-SULFASALAZINE and pms-SULFASALAZINE should also be taken with a full glass (8 ounces) of water. Several additional glasses of water should be taken every day, unless otherwise directed by your doctor. Drinking extra water helps prevent unwanted side effects of the sulfonamide.

For patients taking the delayed-release tablet form of this medicine:

- Swallow tablets whole. Do not break or chew.
- Contact your doctor if you notice any undisintegrated tablet in your stool.

Keep taking this medicine for the full time of treatment, even if you begin to feel better after a few days. Do not miss any doses.

If your symptoms (including diarrhea) do not improve within a month or two or if they become worse, check with you doctor. It is important that your doctor checks your progress at regular visits.

Laboratory and blood tests may be scheduled for you by your doctor before and during treatment.

Overdose:

If you think you have taken too much pms-SULFASALAZINE or pms-SULFASALAZINE-E.C., contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you do miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, **do not** take the missed dose or double your next dose. Instead, go back to your regular dosing schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects appear very often, when they do occur they may require medical attention.

Other side effects (than those mentioned in the following table) may occur, which usually do not require medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

More Common: Diarrhea, dizziness, loss of appetite, nausea or vomiting, headache, itching, skin rash, upset stomach.
Less Common: rash, itching, hives, fever.
Rare: blood problems

In some patients this medicine may also cause the urine to become orange-yellow, or may stain contact lenses yellow. This side effect does not require medical attention.

Some people who take sulfonamides may become more sensitive to sunlight than they are normally. When you begin to take this medicine, avoid too much sun or too much use of a sunlamp until you see how you react, especially if you tend to burn easily. You may still be more sensitive to sunlight or sunlamps for many months after you stop taking this medicine. If you have a severe reaction, check with your doctor.

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your healthcare professional		Stop taking drug and get immediately medical help
		Only if severe	In all cases	
More common	Low sperm counts (oligospermia), with infertility, have been observed with men taking sulfasalazine, which is reversible within several months of stopping the medication.			✓
	Increased sensitivity of the skin to sunlight		✓	
Less Common	Aching in joints and muscles, difficulty in swallowing, fever, pale skin, redness, blistering, peeling or loosening of the skin, sore throat, unusual bleeding or bruising, unusual tiredness or weakness, yellowing of the eyes or skin, mouth sores, ringing in the ears			✓
Rare	- Kidney problems with symptoms such as blood in the urine, lower back pain, pain or burning when urinating, swelling of the front part of the neck - Liver problems including liver failure, with symptoms such as abdominal pain, nausea, yellowing of the eyes or skin - Interstitial lung disease with symptoms such as shortness of breath and difficulty breathing - Hypersensitivity (allergic) reactions including death with symptoms such as rash, swelling of the mouth, throat, lips, other tissues, and difficulty in breathing These symptoms have been associated with sulfasalazine use			✓

This is not a complete list of side effects. For any unexpected effects while taking pms-SULFASALAZINE or pms-SULFASALAZINE-E.C., contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15-30°C. Avoid freezing and keep out of the reach and sight of children. Do not store in the bathroom medicine cabinet because the heat or moisture may cause the medicine to break down. Do not keep outdated medicine or medicine no longer needed.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Pharmascience Inc. at 1-888-550-6060.

This leaflet was prepared by:

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