PRODUCT MONOGRAPH

ratio-SULFASALAZINE
tablets

ratio-SULFASALAZINE EN
(enteric-coated) tablets

500mg

Sulfasalazine tablets USP

Treatment of inflammatory bowel disease, ulcerative colitis, Crohn's disease and rheumatoid arthritis

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ANCTIONS 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. 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 **ratio-SULFASALAZINE EN** (enteric-coated) 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 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 towards accumulation. 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 faeces.

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

In clinical cases, the anti-inflammatory effects seem to relieve the acute symptoms of diarrhoea, gut inflammation, mucosal oedema and bleeding. The long-term protection afforded by therapy with Sulfasalazine tablets/Sulfasalazine (enteric-coated) tablets 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 week 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 activity on several enzymes including 5-LO and 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, these 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:

Studies in-vitro 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 2 g single oral dose was compared in patients with rheumatoid arthritis and 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 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. For sulfasalazine the only difference found between the two age groups was a prolonged $t_{1/2}$ in the elderly, but no significant difference in either the plasma concentration at steady state and 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 but the acetylation phenotype is much more important.

INDICATIONS AND CLINICAL USE

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.

ratio-SULFASALAZINE EN (enteric-coated) tablets is indicated for the treatment of active rheumatoid arthritis, when treatment with an adequate conventional first line therapy has failed.

CONTRAINDICATIONS

Hypersensitivity to sulphonamides or salicylates.

In infants under 2 years.

Intestinal and urinary obstructions.

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

ratio-SULFASALAZINE tablets/**ratio-SULFASALAZINE EN** (enteric-coated) tablets should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or

other allergic manifestations are precipitated by ASA or other non-steroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS

ratio-SULFASALAZINE tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets 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 **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets 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 may be indications of serious blood disorders. Complete blood counts as well as urinalysis with careful microscopic examination should be done frequently in patients receiving **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets.

Oligospermia with infertility have been observed in men treated with **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets. Withdrawal of the drug appears to reverse these effects.

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.

PRECAUTIONS

Patients hypersensitive to furosemide, thiazides diuretics, carbonic anhydrase inhibitors, may also be hypersensitive to this medication.

ratio-SULFASALAZINE tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets should be administered under medical supervision. Sulfasalazine shares the toxic potentialities of other sulfonamides, especially sulfapyridine and the usual precautions of sulfonamide therapy should be observed.

Bone marrow depression (most often expressed as leukopenia) has been reported, usually within the first 3 months of starting treatment. In the majority of the patients this has been reversible on 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. Thereafter patients should be screened if their condition changes or if they present with any symptoms of infection. A falling trend in the blood count is a better indicator than a single value.

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

ratio-SULFASALAZINE tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets should be used with caution in patients with reduced kidney or liver function. Liver function tests and urinalysis should be carried out before and periodically during therapy.

When concurrent therapy with other drugs is administered, as in rheumatoid arthritis, the recommended frequency of monitoring is as follows: initially, every second week during first three months after onset of treatment, every six months thereafter.

ratio-SULFASALAZINE tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets may produce an orange-yellow colour of the urine. Similar discolouration of the skin and yellow staining of soft contact lenses have occasionally be reported.

Isolated instances have been reported when **ratio-SULFASALAZINE EN** (enteric-coated) tablets have passed undisintegrated. This may be due, in part, to a lack of intestinal esterase in these patients. If this is observed, the administration of **ratio-SULFASALAZINE EN** (enteric-coated) tablets should be discontinued.

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

Pregnancy and Reproduction

Teratogenic Effects:

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.

Sulfasalazine should be used during pregnancy only if clearly needed.

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 **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets 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.

Drug Interactions:

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate):

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

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

- 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; concurrent use is not recommended)

- Oxyphenbutazone or Phenylbutazone

  (effects may be potentiated when used concurrently with sulfonamides because of displacement from plasma protein binding sites)

- Photosensitizing medications, other

  (caution in concurrent use of sulfasalazine with these medications is recommended because of possible additive photosensitizing effects)

- Probenecid

  (decreases renal tubular secretion of sulfonamides when used concurrently, 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

  (concurrent 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 sulinpyrazone therapy).

Medical Problems:

Use of this medication should be carefully considered when the following medical problems exist (reasons given where appropriate):

- Blood dyscrasias
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Hepatic function impairment
- Intestinal and urinary tract obstruction
- Porphyria
- Renal function impairment

Laboratory Tests:

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

Complete blood count, including differential white blood cell count and platelets, should be carried out before starting treatment and monitored closely during the first 3 months of treatment. Thereafter patients should be screened if their condition changes or if they present with any symptom of infection. A falling trend in the blood count is a better indicator than a single value.

Liver function tests and urinalysis with careful microscopic examination should be carried out before and periodically during therapy.

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

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 are seen with daily dosage of 4 g or more, or total serum sulfapyridine levels above 50 µg/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 **ratio-SULFASALAZINE** tablets are markedly reduced when using **ratio-SULFASALAZINE EN** (enteric-coated) tablets.

The most commonly reported adverse reactions are: nausea, vomiting, gastric distress, methaemoglobinaemia, 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 in a frequency of one in every thirty patients or less.

Although the listing which 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.

Hypersensitivity reactions:

erythema multiform (Stevens Johnson syndrome), exfoliative dermatitis, epidermal necrolysis (Lyell's syndrome) with corneal damage, anaphylaxis, serum sickness syndrome, transient pulmonary changes with eosinophilia and decreased pulmonary function, allergic myocarditis, polyarteritis nodosa, L.E. syndrome, hepatitis with immune complexes, parapsoriasis varioliformis acuta (Mucha Habermann syndrome), photosensitization, arthralgia, periorbital edema, conjunctival and scleral injection and alopecia.

Gastrointestinal reactions:

hepatitis, pancreatitis, bloody diarrhea, impaired folic acid absorption, impaired digoxin absorption, stomatitis, diarrhea and abdominal pains.

CNS reactions:

transverse myelitis, convulsions, transient lesions of the posterior spinal column, peripheral neuropathy, mental depression, vertigo, hearing loss, insomnia, ataxia, hallucinations, tinnitus and drowsiness.

Renal reactions:

toxic nephrosis with oliguria and anuria, nephrotic syndrome, hematuria, crystalluria and proteinuria.

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.

Desensitization:

Rash, often associated with fever, may occur as a side effect of **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric coated) tablets. Such patients can frequently be desensitized by treatment with graduated doses of sulfasalazine increasing slowly from 1 - 500 mg per day over at least 23 days. Normal maintenance dose of 2 - 3 g daily can then be reached by progressively increasing the daily dose.

Desensitization should not be attempted in patients with a history of agranulocytosis, or who have experienced an anaphylactic reaction on a previous course of therapy with **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

Similar to those of any sulfonamide, the most likely symptoms being gastrointestinal disturbances, drowsiness, convulsions, haematuria, crystalluria or anuria. 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 **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets 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.

When in the physician's opinion, reinstitution of **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets is warranted, regimens modeled upon desensitization procedures may be attempted approximately two weeks after **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets have been discontinued and symptoms have disappeared (see **"DOSAGE and ADMINISTRATION"**).

DOSAGE AND ADMINISTRATION

The dosage of **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets should be adjusted according to the response to the treatment and the patient's tolerance to the drug. The tablets/enteric coated tablets should be taken at regular and even intervals over the 24 hour period. **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) 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 **ratio-SULFASALAZINE** tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets 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 actions.

Elderly patients:

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

Patients with renal deficiency:

ratio-SULFASALAZINE tablets/ **ratio-SULFASALAZINE EN** (enteric-coated) tablets should be used with caution in patients with renal deficiency.

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 **ratio-SULFASALAZINE** tablets should use **ratio-SULFASALAZINE EN** (enteric-coated) tablets or a lower dose.

Rheumatoid Arthritis

1. Adults

2 enteric coated 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 Enteric coated tablet	1 Enteric coated tablet	2 Enteric coated tablets
Evening	1 Enteric coated tablet	1 Enteric coated tablet	2 Enteric coated tablets	2 Enteric coated tablets

If no response has been seen after two months treatment, dose may be increased to 3 g per day.

Some patients may do well with 1.5 g/day.

A clinical effect generally appears 1 - 2 months after initiation of treatment. Concurrent therapy with analgesics and/or anti-inflammatory agents is recommended until the therapeutic effect of **ratio-SULFASALAZINE EN** (enteric-coated) tablets is apparent. **ratio-SULFASALAZINE EN** (enteric-coated) tablets is 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.

PATIENT INFORMATION

Read the bold information first:

Then go back and read the rest. If you do not recognize the names of medical conditions or medicines included in this information, check with your physician, nurse, or pharmacist. Brand names for the generic drug names listed can also be found in the index. It is a good idea for you to learn both the generic and brand names of your medicines and to write them down for future use.

Sulfasalazine (sul-fa-SAL-a-zeen), a sulfonamide or sulfa medicine, belongs to the general family of medicines called anti-infectives. It is taken by mouth to help control active rheumatic arthritis and inflammatory bowel disease such as enteritis or colitis.

Sulfasalazine is available only with your physician's prescription.

Remember:

- This medicine has been prescribed for your present medical problem only. Even though other people may have the same symptoms as you, they may have a different kind of problem. Your medicine may not work for them and may even cause them harm. **Therefore, your medicine must not be given to other people or used for other problems** unless you are otherwise directed by your physician.

- In order for this medicine to work, it must be taken as directed.
- Keep all medicines out of the reach of children.
- If you want more information about this medicine, ask your physician, nurse, or pharmacist.
- If any of the following information causes you special concern, do not decide against taking this medicine without first checking with your physician.

Before Using This Medicine

In order to decide on the best treatment for your medical problem, your physician should be told:

- if you have ever had any unusual or allergic reaction to any of the sulfonamides, furosemide or thiazide diuretics (water pills), dapsone, sulfoxone, oral hypoglycemics (diabetes medicine you take by mouth), glaucoma medicine you take by mouth (for example, acetazolamide, dichlorphenamide, methazolamide), or salicylates (for example, aspirin).

- if you are pregnant or if you intend to become pregnant while taking this medicine, although sulfasalazine has not been shown to cause birth defects and other problems do not usually occur.

- if you are breast-feeding 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.

- if you intend to father a child (oligospermia)
- if you have any of the following medical problems:

  Blockage of stomach, intestines, or urinary tract
  Blood problems
  Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  Kidney disease
  Liver disease
  Porphyria

- if you are now taking any of the following medicines or types of medicine:

  Anthralin
  Antibiotics
  Anticoagulants, coumarin- or indandione-type (blood thinners)
  Antidiabetic agents, oral (diabetes medicine you take by mouth)
  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
Trioxsalen
Vitamin K

Proper Use of This Medicine

Sulfasalazine tablets is best taken after meals or with food to lessen stomach upset. If stomach upset continues or is bothersome, check with your physician.

Each dose of 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 physician. Drinking extra water will help to prevent unwanted side effects of the sulfonamide.

For patients taking the enteric-coated tablet form of this medicine:

- Swallow tablets whole. Do not break or crush.
- Contact your physician if you notice any undisintegrated tablet in you stools.

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 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.

Do not give sulfasalazine to infants under 2 years of age unless directed to by your physician.

How to store this medicine:

- Store away from heat and direct light, out of the reach 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. Flush it down the toilet.

Precautions While Using the Medicine

If your symptoms (including diarrhea) do not improve within a month or two or if they become worse, check with your physician.

It is important that your physician check your progress at regular visits.

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.

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 physician.

Side Effects of This Medicine

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. **Stop taking this medicine and check with your physician immediately** if any of the following side effects occur:

More common:

Headache, continuing
Itching
Skin rash

Less common:

Aching of joints and muscles
Difficulty in swallowing
Fever
Pale skin
Redness, blistering, peeling, or loosening of skin
Sore throat
Unusual bleeding or bruising
Unusual tiredness or weakness
Yellowing of eyes or skin

Rare:

Blood in urine
Lower back pain
Pain or burning while urinating
Swelling of front part of neck

Also, check with your physician as soon as possible if the following side effect occurs:

More common:

Increased sensitivity of skin to sunlight

Other side effects 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 physician if any of the following side effects continue or are bothersome:

More common:

Diarrhea
Dizziness
Loss of appetite
Nausea or vomiting

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

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your physician.

AVAILABILITY

Sulfasalazine is available in the following dosage forms:

ratio-SULFASALAZINE tablets: 500 mg, scored, brownish-yellow, round, convex tablets with A107" in bottles of 100 and 300

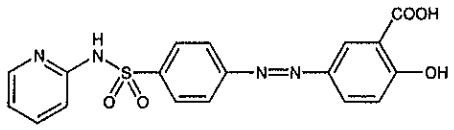
ratio-SULFASALAZINE EN (enteric-coated) tablets: 500 mg, brownish-yellow, circular, convex with A104" in bottles of 100 and 300

PHARMACEUTICAL INFORMATION

Drug Substance: **Sulfasalazine USP**

Chemical name: 5-((4-(2-Pyridylsulfamoyl)phenyl)azo)salicylic acid

Structural Formula:



Generic Names: Salicylazosulfapyridine
Sulfasalazine (USAN)
Sulphasalazine (BAN)

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

Molecular Weight: 398.39

Description: Sulfasalazine is a bright yellow to light brownish yellow odourless fine powder.

Solubility: Very slightly soluble in ethanol, practically insoluble in water, ether, chloroform and benzene. Soluble in aqueous solutions of alkali hydroxides.

PHARMACOLOGY

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

Sulfasalazine tablets/ Sulfasalazine (enteric-coated) tablets have been used for more than four decades in the treatment of inflammatory bowel disease. Like other azo compounds, sulfasalazine exhibits an affinity for connective tissues. It also has an antibacterial as well as anti-inflammatory effect. An effect on prostaglandin synthetase and metabolism has also been proposed. Significant changes in immunological variables proved the immunosuppressive effect on 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 (13%) with minimal side effects. From the data of Goldstein et al, it was suggested that sulfasalazine alone was an effective drug treatment in 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.

Most common effects are related to gastric intolerance and upper 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

Sulfasalazine (enteric-coated) tablets is also an alternative to plain tablets to reduce the frequency of adverse reactions.

Holdsworth has reported that patients have 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:

The oral toxicity was low for all three species examined. LD_0 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:

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

Dog:

Dose levels of 250 and 500 mg/kg were well tolerated by the animals, the only finding being increased relative weight of thyroids. Two dogs at 800 mg/kg also had an atrophy of testicular epithelium. (Impairment of male fertility is known from animals and man and has been shown to be of a reversible type - see Reproduction toxicity)

Reproduction toxicity:

In the **rat fertility study** using dose levels 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 dose levels 800 mg/kg were there other adverse reactions in the parent generation and in the offspring.

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

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

In the **rat peri- and post-natal study** 200 mg/kg was without adverse reactions. At 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 and lower pup weight.

Mutagenicity:

A mutagenicity testing program covering **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.
- Experience of its use in human therapy for more than 40 years is not associated with a suspected tumour development related to sulfasalazine.

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