

Salazopyrin[®] **Salazopyrin[®] EN**

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Salazopyrin[®]

Salazopyrin[®] EN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Salazopyrin[®] uncoated tablet for oral administration contains 500 mg of sulfasalazine.

Each Salazopyrin[®] EN coated gastro-resistant tablet for oral administration contains 500 mg of sulfasalazine.

Excipient with known effect:

Salazopyrin[®] EN contains 5 mg propylene glycol in each tablet.

For the full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Tablets: Yellow-orange round embossed “KPh” on one side and “101” and a score line on the other.

Enteric coated tablets: Yellow-orange film-coated, elliptical, convex, embossed “Kph” on one side and “102” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Salazopyrin[®] : Treatment of ulcerative colitis and Crohn’s disease.

Salazopyrin[®] EN: For active rheumatoid arthritis which is not controlled by antiinflammatory drugs. Ulcerative colitis, Crohn's disease and Pyoderma gangrenosum.

4.2. Posology and Method of Administration

The dosage of Salazopyrin[®] should be individually adjusted according to the patient's tolerance and response to treatment.

EN-tabs must be swallowed intact, preferably after meals, and should not be crushed or broken.

Elderly Patients

No special precautions are necessary.

A) Ulcerative colitis

Adults

Severe Attacks

Salazopyrin[®] 2-4 tablets four times a day may be given in conjunction with steroids as part of an intensive management regime. Rapid passage of the tablets may reduce effect of the drug.

Night-time interval between doses should not exceed 8 hours.

Moderate Attack

2-4 tablets four times a day may be given in conjunction with steroids.

For the EN tablets: Mild Attack: 2 tablets four times a day with or without steroids.

Maintenance Therapy

With induction of remission reduce the dose gradually to 4 tablets per day. This dosage should be continued indefinitely since discontinuance even several years after an acute attack is associated with a four fold increase in risk of relapse-

Children

The dose is reduced in proportion to body weight.

Acute Attack or relapse

40- 60mg/kg per day

Maintenance Dosage

20 - 30mg/kg per day

B) Crohn's Disease

In active Crohn's Disease, Salazopyrin[®] should be administered as in attacks of ulcerative colitis (see above).

Systemic treatment of Rheumatoid Arthritis with sulfasalazine EN-tabs

Patients with rheumatoid arthritis, and those treated over a long period with NSAIDs, may have sensitive stomachs and for this reason enteric-coated Salazopyrin[®] (EN-Tabs) are recommended for this disease, as follows:

Adults (Including Elderly):

The patient should start with one tablet daily, increasing his dosage by a tablet a day each week until one tablet four times a day, or two three times a day are reached, according to tolerance and response. Onset of effect is slow and a marked effect may not be seen for six weeks.

A reduction in ESR and C-reactive protein should accompany an improvement in joint mobility. NSAIDs may be taken concurrently with Salazopyrin[®].

Children (6 years or older):

30 to 75 mg/kg/day divided into 2 equal doses. Typically, the maximum dose is 2 g/day. To reduce possible gastrointestinal intolerance, begin with a quarter to a third of the planned maintenance dose and increase weekly until reaching the maintenance dose at one month (see Section 4.4 Special warnings and precautions for use).

4.3. Contraindications

Sulfasalazine is contraindicated in:
infants under the age of 2 years.

Patients with known hypersensitivity to sulfasalazine, its metabolites, or any other component of the product as well as sulfonamides, or salicylates.

Patients with Porphyria.

4.4. Special warnings and precautions for use

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.

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.

Baseline assessment of renal function (including urinalysis) is required to be performed in all patients initiating treatment with sulfasalazine. For patients with baseline renal impairment, treatment with sulfasalazine should only be initiated if the benefits are considered to outweigh risk. Thereafter, periodic renal function monitoring, especially in the early months of treatment, should be conducted based on clinical judgment taking baseline renal function into account. Treatment should be discontinued if renal function deteriorates. The patient should also be counselled to report immediately with the presence of clinical signs such as sore throat, fever, pallor, purpura, jaundice, malaise or unexpected non-specific illness during sulfasalazine treatment, this may indicate myelosuppression, hemolysis, or hepatotoxicity. Treatment should be stopped immediately while awaiting the results of blood tests. Please see section 4.4 “Interference with laboratory testing”.

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

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

Severe hypersensitivity reactions may include internal organ involvement, such as hepatitis, nephritis, myocarditis, mononucleosis-like syndrome (i.e., pseudomononucleosis), hematological abnormalities (including hematophagic histiocytosis), and/or pneumonitis including eosinophilic infiltration.

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

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.

Sulfasalazine should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

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

Since sulfasalazine may cause haemolytic anaemia, it should be used with caution in patients with G-6-PD deficiency.

Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency (see Section 4.6), potentially resulting in serious blood disorders (e.g., macrocytosis and pancytopenia). This can be normalised by administration of folic acid or folinic acid (leucovorin).

Because sulfasalazine causes crystalluria and kidney stone formation, adequate fluid intake must be maintained.

Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.

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 NAD(H) or NADP(H) to measure ultraviolet absorbance around that wavelength. Examples of such assays may include urea, ammonia, LDH, α -HBDH and glucose. It is possible that alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase-muscle/brain (CK-MB), glutamate dehydrogenase (GLDH), or thyroxine may also show interference when sulfasalazine treatment is given at high doses. 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.

Excipient information

Salazopyrin EN contain propylene glycol (see section 2).

Examples of propylene glycol exposure based on daily dose (see section 4.2) are as follows:

- 16 Salazopyrin[®] EN administered to an adult weighing 70 kg would result in a propylene glycol exposure of 1.14 mg/kg/day.
- 2 Salazopyrin[®] EN administered to a 6 year-old child weighing 20 kg would result in a propylene glycol exposure of 0.50 mg/kg/day.

4.5. Interaction with other medicinal products and other forms of interaction

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

Sulfonamides bear certain chemical similarities to some oral hypoglycemic agents. Hypoglycemia has occurred in patients receiving sulfonamides. Patients receiving sulfasalazine and hypoglycemic agents should be closely monitored.

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

and oral Salazopyrin® were used concomitantly. Coadministration 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.

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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in rats and rabbits have revealed no evidence of harm to the fetus. 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 established. Because the possibility of harm cannot be completely ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Breast-feeding

Sulfasalazine and sulfapyridine are found in low levels in breast milk. Patients should avoid breastfeeding while taking this medicine. 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.

4.7. Effects on ability to drive and use machines

Sulfasalazine has no influence on the ability to drive and use machines.

4.8. Undesirable effects

Overall, about 75% of ADRs occur within 3 months of starting therapy, and over 90% by 6 months. Some undesirable effects are dose-dependent and symptoms can often be alleviated by reduction of the dose.

General

Sulfasalazine is split by intestinal bacteria to sulfapyridine and 5-amino salicylate so ADRs to either sulfonamide or salicylate are possible. Patients with slow acetylator status are more likely to experience ADRs related to sulfapyridine. The most commonly encountered ADRs are nausea, headache, rash, loss of appetite and raised temperature.

Specific

The adverse reactions observed during clinical studies conducted with Sulfasalazine have been provided in a single list below by class and frequency (very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($1/10000$ to $< 1/1000$); very rare ($< 1/10000$); not known (cannot be estimated from available data)). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from post-marketing experience are included as frequency Not known (cannot be estimated from the available data) in the table below.

MedDRA System Organ Class	Frequency	Adverse Drug Reaction
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Infections and Infestations	Not known	Aseptic meningitis, Pseudomembranous colitis
Blood and lymphatic system disorders	Common	Leukopenia
	Uncommon	Thrombocytopenia**
	Not known	Agranulocytosis, Aplastic anaemia, Hemolytic anaemia, Heinz body anaemia, Hypoprothrombinaemia, Lymphadenopathy, Macrocytosis, Megaloblastic anaemia, Methaemoglobinaemia, Neutropenia, Pancytopenia, pseudomononucleosis**
Immune system disorders	Not known	Anaphylaxis*, Polyarteritis nodosa, Serum sickness
Metabolism and nutrition system disorders	Common	Loss of appetite
	Not known	folate deficiency**
Psychiatric disorders	Common	Insomnia
	Uncommon	Depression
	Not known	Hallucinations
Nervous system disorders	Common	Dizziness, Headache, Taste disorders
	Uncommon	Convulsions
	Not known	aseptic meningitis, Ataxia, Encephalopathy, Peripheral neuropathy, Smell disorders
Ear and labyrinth disorders	Common	Tinnitus
	Uncommon	Vertigo
Cardiac disorders	Not known	Allergic myocarditis**, Cyanosis, Pericarditis
Vascular disorders	Uncommon	Vasculitis
	Not known	pallor**
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Dyspnoea
	Not known	Fibrosing alveolitis, Eosinophilic infiltration, Interstitial lung disease* , oropharyngeal pain**
Gastrointestinal disorders	Very common	Gastric distress, Nausea
	Common	Abdominal pain, Diarrhea*, Vomiting*, Stomatitis
	Not known	Aggravation of ulcerative colitis*, Pancreatitis, parotitis
Hepatobiliary disorders	Uncommon	jaundice**
	Not known	Hepatic failure*, Hepatitis fulminant*, Hepatitis**, hepatitis cholestatic*, cholestasis**
Skin and subcutaneous tissue disorders	Common	Pruritus, purpura**
	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* Hematuria, Crystalluria**
Reproductive system and breast disorders	Not known	Reversible oligospermia**
General disorders and administration site conditions	Common	Fever**
	Uncommon	Facial edema
	Not known	Yellow discoloration of skin and body fluids*
Investigations	Uncommon	Elevation of liver enzymes
	Not known	Induction of autoantibodies
Frequency categories: Very common $\geq 1/10$; Common $\geq 1/100$ to $< 1/10$; Uncommon $\geq 1/1000$ to $< 1/100$; Rare $\geq 1/10000$ to $< 1/1000$; Very rare $< 1/10000$; Not known (cannot be estimated from available data) * ADR identified post-marketing ** see section 4.4 Special warnings and precautions for use		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>.

4.9. Overdose

The drug has low acute per oral toxicity in the absence of hypersensitivity. There is no specific antidote and treatment should be supportive.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Aminosalicylic acid and similar agents, ATC code: A07EC01

5.1. Pharmacodynamic Properties

Around 90% of a dose reaches the colon where bacteria split the drug into sulfapyridine (SP) and mesalazine (ME). These are active, and the unsplit sulfasalazine (SASP) is also active on a variety of symptoms. Most SP is absorbed, hydroxylated or glucuronidated and a mix of unchanged and metabolised SP appears in the urine. Some ME is taken up and acetylated in the colon wall, such that renal excretion is mainly ac-me. SASP is excreted unchanged in the bile and urine. Overall, the drug and its metabolites exert immunomodulatory effects, antibacterial effects, effects on the arachidonic acid cascade and alteration of activity of certain enzymes. The net result clinically is a reduction in activity of the inflammatory bowel disease. The enteric coated SASP is registered for the treatment of rheumatoid arthritis, where the effect resembles penicillamine or gold.

In rheumatoid arthritis a disease modifying effect is evident in 1-3 months, with characteristics falls in CRP and other indicators of inflammation. ME is not believed to be responsible for this effect.

For EN-tabs, radiographic studies show marked reduction in progression (larsen or sharp index) compared with placebo or hydroxychloroquine over two years in early patients. If drug is stopped the benefit appears to be maintained.

5.2. Pharmacokinetic properties

Studies with En-tabs show no statistically significant differences in main parameters compared with an equivalent dose of SASP powder, and the figures produced below relate to ordinary tablets. With

regard to the use of salazopyrin in bowel disease there is no evidence that systemic levels are of any relevance other than with regard to ADR incidence. Here levels of SP over about 50µg/ml are associated with a substantial risk of ADRs, especially in slow acetylators.

For SASP given as a single 3g oral dose, peak serum levels of SASP occurred in 3-5 hours, elimination half life was 5.7 ± 0.7 hours, lag time 1.5 hours. During maintenance therapy renal clearance of SASP was 7.3 ± 1.7 ml/min, for SP 9.9 ± 1.9 and AC-ME 100 ± 20 . Free SP first appears in plasma in 4.3 hours after a single dose with an absorption half life of 2.7 hours. The elimination half life was calculated as 18 hours.

Turning to mesalazine, in urine only AC-ME (not free ME) was demonstrable, the acetylation probably largely achieved in the colon mucosa. After a 3g SASP dose lag time was 6.1 ± 2.3 hours and plasma levels kept below 2µg/ml total ME. Urinary excretion half-life was 6.0 ± 3.1 hours and absorption half life based on these figures 3.0 ± 1.5 hours. Renal clearance constant was 125 ml/min corresponding to the GFR.

With regard to rheumatoid arthritis there is no data which suggests any differences from those above.

5.3. Preclinical Safety Data

In two-year carcinogenicity studies in rats and mice, sulfasalazine showed some evidence of carcinogenicity. In rats, there was a small increase in the incidence of transitional cell papillomas in the urinary bladder and kidney. The tumours were judged to be induced mechanically by calculi formed in the urine rather than through a direct genotoxic mechanism. In the mouse study, there was a significant increase in the incidence of hepatocellular adenoma or carcinoma. The mechanism of induction of hepatocellular neoplasia has been investigated and attributed to species-specific effects of sulfasalazine that are not relevant to humans.

Sulfasalazine did not show mutagenicity in the bacterial reverse mutation assay (Ames test) or in the L51784 mouse lymphoma cell assay at the HGPRT gene. It did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, and in vivo mouse bone marrow chromosomal aberration tests were negative. However, sulfasalazine showed positive or equivocal mutagenic responses in rat and mouse micronucleus assays, and in human lymphocyte sister chromatid exchange, chromosomal aberration and micronucleus assays. The ability of sulfasalazine to induce chromosome damage has been attributed to perturbation of folic acid levels rather than to a direct genotoxic mechanism.

Based on information from non-clinical studies, sulfasalazine is judged to pose no carcinogenic risk to humans. Sulfasalazine use has not been associated with the development of neoplasia in human epidemiology studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Salazopyrin® tablets: starch pregelatinized, povidone, magnesium stearate, silica colloidal anhydrous.

Salazopyrin® EN tablets: starch pregelatinized; povidone, magnesium stearate; silica colloidal anhydrous; cellulose acetate phthalate; propylene glycol (E1520), talc, macrogol, carnauba wax, glyceryl monostearate, beeswax white.

6.2. Incompatibilities

Certain types of extended wear soft contact lenses may be permanently stained during therapy.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special Precautions for Storage

Store below 25°C.

Bottles: After first opening can be used for 6 months in room temperature under 25°C

6.5. Nature and Contents of Container

Available in HDPE bottles containing 100 or 300 tablets or in blisters inside cartons containing 30 or 100 tablets.

Not all pack sizes are marketed.

6.6. Special precautions for disposal and other handling

Salazopyrin[®] : Take with water

Salazopyrin[®] EN : Take the tablets whole. Do not break.

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

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd. 9 Shenkar st., Herzeliya 46725.

8. LICENSE NUMBERS

Salazopyrin[®]: 113-35-21579

Salazopyrin[®] EN : 113-34-20570

Revised in 10/2023 According to MOH's guideline.