Salazopyrin® EN-tabs
(Sulfasalazine)

1. TRADE NAME OF THE MEDICINAL PRODUCT

Salazopyrin® EN Tab 0.5 g Enteric Coated

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric-coated tablet contains: Sulfasalazine USP 0.5 g.

Excipient with known effect:
Salazopyrin EN-Tabs 0.5 g contains 5 mg propylene glycol in each tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow-orange, elliptical, convex, enteric-coated tablets, with the letters "KPh" on one face, and the product code "102" on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Ulcerative colitis
In the treatment of mild to moderate ulcerative colitis and as adjunctive therapy in severe ulcerative colitis. For maintenance of remission in ulcerative colitis.

Crohn's disease
In the treatment of active Crohn's disease, especially in patients with colonic involvement.

Rheumatoid arthritis

4.2. Posology and Method of Administration

The dosage should be adjusted according to the patient's response to treatment and tolerance to the drug. The tablets should be taken at regular intervals during the day, preferably in connection with meals. Patients not previously treated with Salazopyrin EN-tabs are recommended to increase the dose gradually during the first few weeks. The use of enteric coated tablets will reduce the incidence of gastrointestinal side effects.

The enteric coated tablets should not be crushed or broken.

Inflammatory bowel diseases
Acute attacks:

Adults

Severe attacks:	2-4 tablets 3-4 times a day may be given in conjunction with steroids as part of an intensive management regime.
Moderate and mild attacks:	2 tablets 3-4 times a day.

Children
40-60 mg/kg body weight per day, divided into 3-6 doses.

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

Children
20-30 mg/kg body weight per day, divided into 3-6 doses.

Rheumatoid Arthritis
Experience has shown that the clinical effect appears within 1-2 months' treatment.

Concurrent treatment with analgesics and/or non-steroidal anti-inflammatory agents is recommended at least until the disease-modifying effect of Salazopyrin EN-tabs is apparent. Salazopyrin EN-tabs has been shown effective and well tolerated in long term treatment.

Adults
Two enteric coated tablets twice a day, i.e. 2 grams a day. The enteric coated tablets should not be crushed or broken. When starting therapy, it is advisable to increase the daily dose according to the following schedule: (Salazopyrin EN-tabs)

	Morning	Evening
1st week		1 tablet
2nd week	1 tablet	1 tablet
3rd week	1 tablet	2 tablets
4th week and after	2 tablets	2 tablets

If no response has been seen after 2 months' treatment, the dose may be increased to 3 g per day.

Children
At present, no recommendation regarding treatment with Salazopyrin EN-tabs in juvenile chronic arthritis can be given.

4.3. Contraindications

Sulfasalazine is contraindicated in:

Infants under the age of 2 years.

Patients with a known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sulfonamides or salicylates.

Patients with porphyria.

4.4. Special warnings and special precautions for use

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. The patient should also be counselled to report immediately with any sore throat, fever, malaise, pallor, purpura, jaundice or unexpected non-specific illness during sulfasalazine treatment, this may indicate myelosuppression, haemolysis or hepatoxicity. 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 or renal 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.

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.

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

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

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 should be ensured during treatment.

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.

<u>Excipient information</u>
Salazopyrin EN 0.5 g tablets 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 0.5 g tablets administered to an adult weighing 70 kg would result in a propylene glycol exposure of 1.14 mg/kg/day.

- 2 Salazopyrin EN 0.5 g tablets 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. Interactions

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 by salazopyrin, bone marrow suppression and leucopenia have been reported when the thiopurine 6-mercaptopurine or it's 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.

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

4.7. Effects on ability to drive and use machines

No specific effects.

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 (⩾1/10); common (⩾1/100 to< 1/10); uncommon (⩾1/1000 to < 1/100). 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 list below.

Body System	**Adverse drug reactions**
Infections and Infestations	
Not known	*Pseudomembranous colitis*
Blood and Lymphatic System Disorders	
Common	*Leukopenia*
Uncommon	*Thrombocytopenia**
Not known	*Agranulocytosis, aplastic anemia, haemolytic anemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy, macrocytosis, megaloblastic anemia, methaemoglobinaemia, neutropenia, pancytopenia*
Immune System Disorders:	
Not known	*Anaphylaxis, polyarteritis nodosa, serum sickness*
Metabolism and Nutrition Disorders:	
Not known	*Loss of appetite*
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*
Eye Disorders:	
Common	*Conjunctival and scleral injection*
Cardiac Disorders:	
Not known	*Allergic myocarditis, cyanosis, pericarditis*
Vascular Disorders:	
Uncommon	*Vasculitis*
Respiratory, Thoracic and Mediastinal Disorders:	
Common	*Cough*
Uncommon	*Dyspnoea*
Not known	*Fibrosing alveolitis, eosinophilic infiltration, interstitial lung disease*
Gastrointestinal Disorders:	
Very common	*Gastric distress, nausea*
Common	*Abdominal pain, diarrhoea, vomiting, stomatitis*
Not known	*Aggravation of ulcerative colitis, pancreatitis, parotitis*
Hepato-biliary Disorders:	
Not known	*Hepatic failure, fulminant hepatitis, hepatitis**
Skin and Subcutaneous Tissue Disorders:	
Common	*Pruritus*
Uncommon	*Alopecia, urticaria*
Not known	*Epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), toxic pustuloderma, erythema, exanthema, exfoliative dermatitis, periorbital oedema, lichen planus, photosensitivity*
Musculoskeletal and Connective Tissue Disorders:	
Common	*Arthralgia*
Not known	*Systemic lupus erythematosus*
Renal and Urinary Disorders:	
Common	*Proteinuria*

Not known	*Nephrotic syndrome, interstitial nephritis, crystalluria*, haematuria*
Reproductive System and Breast Disorders:	
Not known	*Reversible oligospermia**
General Disorders and Administration Site Conditions:	
Common	*Fever*
Uncommon	*Facial oedema*
Not known	*Yellow discoloration of skin and body fluids*
Investigations:	
Uncommon	*Elevation of liver enzymes*
Not known	*Induction of autoantibodies*

* See Section 4.4 for further information

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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

5.1. Pharmacodynamic Properties

Pharmacological particulars: around 90% of a dose reaches the colon where bacteria split the drug into sulfapyridine (SP) and mesalazine (ME). These are also 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. 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.

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

Pharmacokinetic particulars: 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 50 μg/ml are associated with a substantial risk of ADRS, especially in slow acetylators.

For SASP given as a single 3 g 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 3 g SASP dose lag time was 6.1±2.3 hours and plasma levels kept below 2 μg/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

Povidone, maize starch, magnesium stearate, colloidal silicon dioxide, cellulose acetate phthalate, propylene glycol (E1520), traces of beeswax, carnauba wax, glyceryl monosterate, talc.

6.2. Incompatibilities

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

6.3. Shelf Life

Please refer to the outer carton for the expiry date.

6.4. Special Precautions for Storage

Please refer to the outer carton for the storage condition.

6.5. Special precautions for disposal and other handling

Take the tablets whole: Do not break

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

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