

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Salazopyrin Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulfasalazine EP 500 mg

3 PHARMACEUTICAL FORM

Yellow round tablets embossed “KPh” on one side and “101” and a score line on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction and maintenance of remission of ulcerative colitis; treatment of active Crohn's Disease.

4.2 Posology and method of administration

The dose is adjusted according to the severity of the disease and the patient's tolerance to the drug, as detailed below.

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.

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

Salazopyrin Suspension may provide a more flexible dosage form.

B) Crohn's Disease

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

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 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 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 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.

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.

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 by Salazopyrin, 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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in rats and rabbits have revealed no evidence of harm to the fetus. Published data regarding use of sulfasalazine in pregnant women have revealed no evidence of teratogenic hazards. If sulfasalazine is used during pregnancy, the possibility of fetal harm appears remote. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency. Because the possibility of harm cannot be completely ruled out, sulfasalazine should be used during pregnancy only if clearly needed.

Lactation

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 Data Held

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 $< 1/100$). 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:

<i>Common</i>	<i>Dizziness, headache, taste disorders</i>
<i>Uncommon</i>	<i>Convulsions</i>
<i>Not known</i>	<i>Aseptic meningitis, ataxia, encephalopathy, peripheral neuropathy, smell disorders</i>

Ear and Labyrinth Disorders:

<i>Common</i>	<i>Tinnitus</i>
<i>Uncommon</i>	<i>Vertigo</i>

Eye Disorders:

<i>Common</i>	<i>Conjunctival and scleral injection</i>
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Cardiac Disorders:

<i>Not known</i>	<i>Allergic myocarditis, cyanosis, pericarditis</i>
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vascular Disorders:

<i>Uncommon</i>	<i>Vasculitis</i>
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Respiratory, Thoracic and Mediastinal Disorders:

<i>Common</i>	<i>Cough</i>
<i>Uncommon</i>	<i>Dyspnoea</i>
<i>Not known</i>	<i>Fibrosing alveolitis, eosinophilic infiltration, interstitial lung disease</i>

Gastrointestinal Disorders:

<i>Very Common</i>	<i>Gastric distress, nausea</i>
<i>Common</i>	<i>Abdominal pain, diarrhoea, vomiting, stomatitis</i>
<i>Not known</i>	<i>Aggravation of ulcerative colitis, pancreatitis, parotitis</i>

Hepato-biliary Disorders:

<i>Not known</i>	<i>Hepatic failure, fulminant hepatitis, hepatitis*</i>
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Skin and Subcutaneous Tissue Disorders:

<i>Common</i>	<i>Pruritus</i>
<i>Uncommon</i>	<i>Alopecia, urticaria</i>
<i>Not known</i>	<i>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</i>

Musculoskeletal and Connective Tissue Disorders:

<i>Common</i>	<i>Arthralgia</i>
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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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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 is registered for the treatment of rheumatoid arthritis, where the effect resembles penicillamine or gold.

5.2 Pharmacokinetic properties

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 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 ± 1.7ml/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.

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 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.

6.2 Incompatibilities

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

6.3 Shelf life

The tablets are stable for 5 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Square or rectangular HDPE jar with easy to open tamper-evident polypropylene screw-cap. To contain 112 tablets.

6.6 Special precautions for disposal

Take with water.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2 April 2002

10 DATE OF REVISION OF THE TEXT

09/10/2019