SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Salazopyrin® En-Tabs 500 mg gastro-resistant tablets
Sulfasalazine 500 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulfasalazine 500 mg

Excipient with known effect:
Each tablet contains 5 mg propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.
Yellow film-coated, ovoid gastro-resistant tablets embossed “Kph” on one side and “102” on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

b) Treatment of rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs).

4.2 Posology and method of administration

This medicine should be used where there is gastro-intestinal intolerance of plain tablets. They should not be crushed or broken.

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 Attack: 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.

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.

Paediatric population
The dose is reduced in proportion to body weight.
Acute Attack or relapse: 40- 60 mg/kg per day
Maintenance Dosage: 20 – 30 mg/kg per day

Suspension may provide a more flexible dosage form.

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

c) Rheumatoid Arthritis
Patients with rheumatoid arthritis, and those treated over a long period with NSAIDs, may have sensitive stomachs and for this reason enteric-coated sulfasalazine gastro-resistant tablets are recommended for this disease, as follows:

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. $NSAID_S$ may be taken concurrently with sulfasalazine.

4.3 Contraindications

Sulfasalazine is contraindicated in:

Hypersensitivity to sulfasalazine, its metabolites or sulfonamides or salicylates or to any of the excipients listed in section 6.1.

Infants under the age of 2 years.

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 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 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 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.

Excipient information
This medicine contains propylene glycol (see section 2).

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

- 16 sulfasalazine 500 mg gastro-resistant tablets administered to an adult weighing 70 kg would result in a propylene glycol exposure of 1.14 mg/kg/day.
- 2 sulfasalazine 500 mg gastro-resistant 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 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 sulfasalazine, bone marrow suppression and leucopenia have been reported when the thiopurine 6-mercaptopurine or it's prodrug, azathioprine, and oral sulfasalazine 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 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

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥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**
Infections and Infestations	Not known	Aseptic meningitis, Pseudomembranous colitis
Blood and lymphatic system disorders	Common	Leukopenia
	Uncommon	Thrombocytopenia**
	Not known	Agranulocytosis, Aplastic anaemia, Haemolytic anaemia, Heinz body anaemia, Hypoprothrombinaemia, Lymphadenopathy, Macrocytosis, Megaloblastic anaemia, Methaemoglobinaemina, Neutropenia, Pancytopenia,
Immune system disorders	Not known	Anaphylaxis*, Polyarteritis nodosa, Serum sickness
Metabolism and nutrition system disorders	Common	Loss of appetite
Psychiatric disorders	Common	Insomnia
	Uncommon	Depression
	Not known	Hallucinations
Nervous system disorders	Common	Dizziness, Headache, Taste disorders
	Uncommon	Convulsions
	Not known	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
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
Hepatobiliary disorders	Not known	Hepatic failure*, Hepatitis fulminant*, Hepatitis**
Skin and subcutaneous tissue disorders	Common	Pruritus
	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, Photosensitvity, 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, Haematuria, Crystalluria**
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
* 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. 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

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

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 metablites exert immunimodulatory 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 sulfasalazine gastro-resistant tablets 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 sulfasalazine 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

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±1.7ml/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 125ml/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), macrogol 20,000, 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

5 years

6.4 Special precautions for storage

Store in a dry place

6.5 Nature and contents of container

Polyolefin Square pot with screw cap. To contain 112 tablets

6.6 Special precautions for disposal

Take the tablets whole: do not break.

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent

CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00057/1041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 September 2002

10 DATE OF REVISION OF THE TEXT

24/05/2024