Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salazopyrin® EN Tabs 500 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of sulfasalazine

Excipient with known effect:
Salazopyrin En-Tabs 500mg contains 5 mg propylene glycol in each tablet.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Orange/Yellow, oval-shaped tablets with 'KPh' imprinted on one side and '102' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Salazopyrin EN-Tabs 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 of the drug, as detailed below.

(a) Ulcerative Colitis

Adults and the elderly
Severe attacks: 2 to 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 the effect of the drug.

The night-time interval between doses should not exceed 8 hours.

Moderate attacks: 2 to 4 tablets, four times per day may be given in conjunction with steroids.

Mild attacks: 2 tablets, four times per day, may be taken 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 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.

Salazopyrin Suspension may provide a more flexible dosage form for children.

(b) Crohn's Disease
In active Crohn's Disease, Salazopyrin Tablets 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 Salazopyrin EN-Tabs are recommended, as follows: -

The patient should start with one tablet daily, increasing the dosage by one tablet a day each week until one tablet four times a day, or two tablets three times a day, is reached, according to tolerance and response. A reduction in ESR and C-reative protein should accompany an improvement in joint mobility. NSAIDs may be taken concurrently with sulfasalazine.

4.3 Contraindications

Use in infants under the age of two years.

Use in patients where there is a known hypersensitivity to either sulfasalazine, its metabolites or any excipients as well as sulfonamides or salicylates.

Use in patients with jaundice or 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, red cell and platelet counts 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 as 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.

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.

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

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 the administration of folic acid or folinic acid (leucovorin).

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
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 (see section 4.8).

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.

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.

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

Because sulfasalazine causes crystalluria and kidney stone formation, adequate fluidintake 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.

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

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 500mg 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 500mg tablets administered to an adult weighing 70 kg would result in a propylene glycol exposure of 1.14 mg/kg/day.
- 2 Salazopyrin En 500mg 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

Use of sulfonamides with folic-acid antagonists or hypoglycaemics may increase the effects of these agents.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproduction studies in rats and rabbits have revealed no evidence of harm to the foetus. Oral sulfasalazine inhibits the absorption and metabolism of folic acid and may cause folic acid deficiency (see section 4.4). 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. Caution should be used, particularly if breastfeeding premature infants or those deficient in glucose 6 phosphate dehydrogenase. 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

The effect of sulfasalazine on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable effects

The following events have been reported in patients receiving sulfasalazine:

MedDRA System Organ Class	**Frequency**	**Adverse Drug Reaction**
Infections and infestations	Not known	aseptic meningitis, pseudomembranous colitis, parotitis
Blood and lymphatic system disorders	Common	leukopenia
	Uncommon	thrombocytopenia†
	Not known	pancytopenia, agranulocytosis, aplastic anaemia, pseudomononucleosis*†, haemolytic anaemia, macrocytosis, megaloblastic anaemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy, methaemoglobinaemina, neutropenia, pancytopenia
Immune system disorders	Not known	anaphylaxis*, serum sickness, polyarteritis nodosa
Metabolism and nutrition system disorders	Common	loss of appetite
	Not known	folate deficiency*†
Psychiatric disorders	Uncommon	depression, hallucinations, insomnia
Nervous system disorders	Common	dizziness, headache, taste disorders
	Not known	encephalopathy, peripheral neuropathy, smell disorders, ataxia, convulsions
Ear and labyrinth disorders	Common	tinnitus
	Not known	vertigo
Eye disorders	Not known	conjuctivial and scleral infection
Cardiac disorders	Not known	allergic myocarditis*†, pericarditis, cyanosis

Vascular disorders	Not known	pallor*†, vasculitis
Congenital, familial and genetic disorders	Not known	acute attack may be precipitated in patients with porphyria
Respiratory, thoracic and mediastinal disorders	Common	cough
	Uncommon	dyspnoea
	Not known	interstitial lung disease* , eosinophilic infiltration, fibrosing alveolitis, oropharyngeal pain*†
Gastrointestinal disorders	Very common	gastric distress, nausea
	Common	abdominal pain, diarrhoea*, vomiting*
	Not known	aggravation of ulcerative colitis* , pancreatitis, stomatitis
Hepatobiliary disorders	Uncommon	jaundice*†
	Not known	hepatic failure*, hepatitis fulminant*, hepatitis†, hepatitis cholestatic*, cholestasis*
Skin and subcutaneous tissue disorders	Common	purpura*†, pruritus
	Uncommon	alopecia, urticaria
	Very rare	toxic epidermal necrolysis
	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, periorbital oedema
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*, 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*, drug fever, generalised skin eruptions
Investigations	Uncommon	elevation of liver enzymes

	Not known	induction of autoantibodies

Frequency categories: 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)
* 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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

The most common symptoms of overdose, similar to other sulfonamides, are nausea and vomiting. Patients with impaired renal function are at increased risk of serious toxicity. Treatment is symptomatic and should be supportive including alkalinisation of urine.
Patients should be observed for development of methemoglobinema or sulfaheamoglobinemia. If these occur treat appropriately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminosalicylic acid and similar agents
ATC Code: A07EC01

Sulfasalazine is split by bacteria in the colon into sulphapyridine and mesalazine. All three compounds have pharmacological effects, principally immunomodulatory, antibacterial and alteration of the arachidonic acid cascade and the activity of certain enzymes. The net result is a reduction of the activity of certain inflammatory diseases namely ulcerative colitis, Crohn's Disease and rheumatoid arthritis. In rheumatoid arthritis the effect is disease modifying, taking one to three months to develop. Mesalazine is not believed to cause this effect. Improvement in ESR and CRP, and progression (Larsen or Sharp Index) have been shown to be markedly reduced in early patients compared with placebo or hydroxychloroquine treatment over two years. The benefit appears to be maintained when the drug is stopped.

5.2 Pharmacokinetic properties

Around 90% of a sulfasalazine (SU) dose reaches the colon where bacteria split the drug into sulphapyridine (SP) and mesalazine (ME). Most SP is absorbed, either hydroxlylated or glucoronidated, 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 acetylated ME (Ac-ME). SU is excreted in the bile and urine.

Studies with Salazopyrin EN-Tabs show no statistically significant differences in the main parameters compared with an equivalent dose of SU powder, and the data below relate to ordinary tablets. In respect of the use of Salazopyrin in bowel disease, there is no evidence that systemic levels are of any special clinical relevance other than with regard to ADR incidence. Here, levels of SP over about 50mg/mL are associated with a substantial risk of ADRs, especially in slow acetylators. For SU given as a single 3g oral dose: peak plasma levels of SU occurred in 3-5 hours, elimination half-life was 5.7 $\pm$ 0.7 hours and lap time was 1.5 hours.

During maintenance therapy, renal clearance was: 7.2 $\pm$ 1.7 mL/min. for SU, 9.9 $\pm$ 1.9 mL/min. for SP and 100 $\pm$ 20 mL/min. for Ac-ME. Free SP first appears in plasma 4.3 hours after a single oral dose with an absorption half-life of 2.7 hours. The elimination half-life was calculated as 18 hours. As regards mesalazine, in urine only Mc-ME (not free ME) was demonstrable, the acetylation probably largely achieved in the colon mucosa.

After a 3g dose of SU the dose lag-time was 6.1 $\pm$ 2.3 hours and plasma levels were below 2mg/ml total ME. Urinary excretion half-life was 6.0 $\pm$ 3.1 hours and absorption half-life, based on these figures was 3.0 $\pm$ 1.5 hours. The renal clearance constant was 125 mL/min. corresponding to the GFR.

As regards rheumatoid arthritis, there are no data that suggest any differences to the above.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
maize starch
magnesium stearate
silica, colloidal anhydrous
cellulose acetate phthalate
macrogol
bees wax (trace)
carnauba wax
glyceryl monostearate
talc
propylene glycol (E1520)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Polylefin rectangular HDPE pot with orange knurled cap, designed for easy opening, and containing 112 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Take the tablet(s) whole with water. Do not break or crush.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0822/196/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1977

Date of last renewal: 1st April 2007

10 DATE OF REVISION OF THE TEXT

December 2024