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.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Product imported from the Italy:
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.

Children
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-reactive protein should accompany an improvement in joint mobility. NSAIDs may be taken concurrently with sulphasalazine.

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 of the excipients as well as sulphonamides or salicylates.

Use in patients with jaundice or porphyria.

4.4 Special warnings and precautions for use

Complete blood counts (including differential white cell, red cell and platelet counts) liver function tests and 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 Salazoprin treatment may indicate myelosuppression, haemolysis, or hepatotoxicity. Treatment should be stopped while awaiting the results of blood tests.

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 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, Pregnancy and lactation), potentially resulting in serious blood disorders (e.g. marcocytosis and pancytopenia). This can be normalized by administration of folic acid or folinic acid (leucovorin).

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 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.
As far as is known oligospermia has not occurred during therapy per rectum.

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

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.

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. 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. Caution should be used, particularly if breastfeeding premature infants or those deficient in G-6-PD.

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 have been reported to sulfasalazine given orally or rectally. The drug rectally is well tolerated. Overall, about 75% of adverse drug reactions occur within three months of starting therapy and over 90% by six 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 sulphapyridine and 5-amino salicylate so adverse drugs reactions to either sulphonamide or salicylate are possible. Patients with slow acetylator status are more likely to experience adverse drug reactions related to sulphapyridine. The most commonly encountered adverse drugs reactions 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	Aseptic meningitis, parotitis, 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, methaemoglobinaemina, neutropenia, pancytopenia The risk of sulfasalazine-associated blood disorders is substantially higher in patients treated for rheumatoid arthritis than it is in patients treated for inflammatory bowel disease.
Immune System Disorders:	
Not known	Anaphylaxis, polyarteritis nodosa, serum sickness
Metabolism and Nutrition Disorders:	
Not known	Loss of appetite
Psychiatric Disorders:	
Uncommon	Depression
Not known	Hallucinations, insomnia
Nervous System Disorders:	
Common	Dizziness, headache, taste disorders
Not known	Ataxia, convulsions, encephalopathy, peripheral neuropathy, smell disorders
Ear and Labyrinth Disorders:	
Common	Tinnitus
Not known	Vertigo
Eye Disorders:	
Not known	Conjuctivial and scleral infection
Cardiac Disorders:	
Not known	Allergic myocarditis, cyanosis, pericarditis
Vascular Disorders:	
Not known	Vasculitis
Congenital, familial and Genetic Disorders:	
Not known	Acute attack may be precipitated in patients with prophyria**

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
Uncommon	Abdominal pain, diarrhoea, vomiting
Not known	Aggravation of ulcerative colitis, pancreatitis, stomatitis
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, Sjögren's syndrome
Renal and Urinary Disorders:	
Common	Proteinuria
Not known	Crystalluria*, haematuria, Nephrotic syndrome, interstitial nephritis
Reproductive System and Breast Disorders:	
Not known	Reversible oligospermia*
General Disorders and Administration Site Conditions:	
Common	Fever
Uncommon	Facial oedema
Not known	Drug fever, yellow discoloration of skin and body fluids, generalised skin eruptions
Investigations:	
Uncommon	Elevation of liver enzymes
Not known	Induction of autoantibodies

* See Section 4.4 for further information
** See section 4.3 for further information

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: Aminosalicyclic acid and similar agents
ATC code: A07EC01.

Sulphasalazine is split by bacteria in the colon into sulfapyridine (SP) and mesalazine. All three compounds have pharmacological effects, principally immunomodulatory, antibacterial and alteration of the arachidonic acid cascade and the activity of certain enzymes.

5.2 Pharmacokinetic properties

Around 90% of a sulphasalazine (SU) dose reaches the colon where bacteria split the drug into sulfapyridine (SP) and mesalazine (ME). Most SP is absorbed, either hydroxylated 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 50 µg/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 2µg/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
Bees wax (trace)
Carnauba wax
Polyethylene glycol 20,000
Glyceryl monostearate
Talc
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the blister strip and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C. Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Qpaque blister packs of 10 tablets per blister. Pack size of 100 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 PARALLEL PRODUCT AUTHORISATION HOLDER

B & S Healthcare
Unit 4, Bradfield Road
Ruislip
Middlesex HA4 0NU
United Kingdom

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/129/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th January 2010

10 DATE OF REVISION OF THE TEXT