SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulfasalazine 250mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sulfasalazine 250mg/5ml

Excipient(s) with known effect:
Sodium Benzoate 5mg/5ml

For excipients see section 6.1

3 PHARMACEUTICAL FORM

Oral suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction and maintenance of remission of ulcerative colitis and 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 of the drug, as detailed below.

A) Ulcerative colitis

Adults and the Elderly

Severe attacks: 20 to 40 ml four times a day may be given in conjunction with steroids as part of an intensive management regime. Rapid passage of the suspension may reduce the effect of the drug.

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

Moderate attacks: 20 ml four times a day may be taken with or without steroids.

Maintenance therapy: With induction of remission, reduce the dose gradually to 40 ml 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: 0.8 - 1.2 ml/kg/day.

Maintenance dosage: 0.4 - 0.6 ml/kg/day.

B) Crohn's Disease

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

4.3 Contraindications

Sulfasalazine is contraindicated in:

- Infants under the age of two years.
- Patients with a known hypersensitivity to sulfasalazine, its metabolites or any of the excipients as well as sulfonamides, salicylates or the sodium benzoate preservative.
- 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 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 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 glucose-6-phosphate dehydrogenase 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.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported very rarely in association with the use of sulfasalazine. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is 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 aetiology for the signs or symptoms cannot be established. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of sulfasalazine, sulfasalazine must not be re-started in this patient at any time.

Sulfasalazine may colour the urine orange-yellow.

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 warnings

- This medicine contains 5 mg sodium benzoate in each 5ml.
- This medicine contains less than 1 mmol sodium (23 mg) per 5ml, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Certain types of extended wear soft contact lenses may be permanently stained during therapy.
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 its prodrug, azathioprine, and oral sulfasalazine were used concomitantly.

Co-administration 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. 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.

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 of 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 three months of treatment and over 90% by six months. Some unwanted 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 (≥1/10,000 to <1/1000); very rare (<1/10,000); 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 list below.

Body System	**Adverse drug reactions**
Infections and infestations	
Not known	Aseptic meningitis, 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, pseudomononucleosis, methaemoglobinaemina, neutropenia, pancytopenia
Immune System Disorders:	
Not known	Anaphylaxis, polyarteritis nodosa, serum sickness
Metabolism and Nutrition Disorders:	
Common	Loss of appetite
Not known	Folate deficiency*

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
Not known	Pallor*

Respiratory, Thoracic and Mediastinal Disorders:

Common	Cough
Uncommon	Dyspnoea
Not known	Fibrosing alveolitis, eosinophilic infiltration, interstitial lung disease, oropharyngeal pain*

Gastrointestinal Disorders:

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

Hepato-biliary Disorders:

Uncommon	Jaundice*
Not known	Hepatic failure, fulminant hepatitis, hepatitis cholestatic, cholestasis*, hepatitis*

Skin and Subcutaneous Tissue Disorders:

Common	Pruritus, purpura
Uncommon	Alopecia, urticaria
Not known	Drug rash with eosinophilia and systemic symptoms (DRESS), epidermal necrolysis (Lyell's syndrome), Stevens-Johnson Syndrome, toxic pustuloderma, erythema, exanthema, exfoliative dermatitis, periorbital oedema, lichen planus, photosensitivity, angioedema

Musculoskeletal and Connective Tissue Disorders:

Common	Arthralgia
Not known	Systemic lupus erythematosus, Sjogren's syndrome

Renal and Urinary Disorders:

Common	Proteinuria
Not known	Nephrotic syndrome, interstitial nephritis, crystalluria*, haematuria, nephrolithiasis

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 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

Sulfasalazine has beneficial effects in the treatment of ulcerative colitis and maintenance of remission, and in the treatment of acute Crohn's disease. Around 90% of a dose reaches the colon where bacteria split the drug into

sulpyapyridine and mesalazine. These are active, and the unsplit sulfasalazine is also active on a variety of systems. Most Sulfapyridine is absorbed, hydroxylated or glucuronidated and a mix of unchanged and metabolised sulfapyridine appears in the urine.

Some mesalazine is taken up and acetylated in the colon wall, such that renal excretion is mainly acetyl-mesalazine. Sulfasalazine 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 sulfasalazine 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 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 sulfapyridine over about 50µg/ml are associated with a substantial risk of ADRs, especially in slow acetylators.
For sulfasalazine given as a single 3g oral dose, peak serum levels of sulfasalazine 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 sulfasalazine was 7.3 ±1.7ml/min, for sulfapyridine 9.9 ±1.9 and acetyl-mesalazine 100 ±20. Free sulfasalazine 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. For mesalazine, only acetyl-mesalazine (not free mesalazine) was demonstrable, the acetylation probably largely achieved in the colon mucosa. After 3g sulfasalazine dose lag time was 6.1 ±2.3 hours and plasma levels kept below 2µg/ml. total mesalazine. 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. Studies in volunteers suggest that sulfasalazine is handled in a similar manner whether given as suspension or tablets.

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.

6.1 List of excipients

Citric acid monohydrate (E330)
Sodium citrate (E331)
Sodium benzoate (E211)
Acesulfame K (E950)
Polysorbate 80
Dispersible cellulose
Xanthan gum (E415)
Terpeneless lemon oil
Purified water

6.2 Incompatibilities

None relevant.

6.3 Shelf life

24 months

1 month once open

6.4 Special precautions for storage

Do not store at above 25°C.

6.5 Nature and contents of container

Bottle: Amber (Type III) glass
Closure: HDPE, EPE wadded, tamper evident, child resistant closure
Pack: 1 bottle containing 500ml of liquid

6.6 Special precautions for disposal

Take the suspension with food.

7 MARKETING AUTHORISATION HOLDER

Rosemont Pharmaceuticals Ltd,
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8 MARKETING AUTHORISATION NUMBER(S)

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