SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sulfasalazine 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of sulfasalazine

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

Yellow-brown, round, normal convex tablets engraved with RL logo on one side, with a breakline and A333 on the other side.

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
Sulfasalazine 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 eight 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.

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

Sulfasalazine suspension may provide a more flexible dosage form.

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 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

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 the 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.

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.

Sodium
This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially `sodium-free´.

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 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.

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 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 foetal 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.

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

None reported.

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). 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.

System Organ Class / Frequency	***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 anaemia, haemolytic anaemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy, macrocytosis, megaloblastic anaemia, methaemoglobinaemina, neutropenia, pancytopenia, pseudomononucleosis**
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
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*, hepatitis fulminant *, hepatitis**, hepatitis cholestatic*, cholestasis*
Skin and Subcutaneous Tissue Disorders:	

Common	Pruritus, purpura**
Uncommon	Alopecia, urticaria
Not known	Epidermal necrolysis (Lyell's syndrome)**, Stevens-Johnson syndrome**, drug rash with eosinophilia and systemic symptoms (DRESS)**, angioedema*, toxic pustuloderma, erythema, exanthema, exfoliative dermatitis**, lichen planus, photosensitivity
Musculoskeletal, 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, nephrolithiasis*, 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

* ADR identified post-marketing
**See Section 4.4 Special Warnings and precautions for use

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

Pharmacotherapeutic group: Intestinal anti-inflammatory agents – aminosalicylic acid and similar agents.

ATC code: A07E C01

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 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/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 tomesalazine, 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/mm 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

Iron oxide, yellow (E172)
Povidone
Magnesium stearate
Sodium starch glycollate (Type A)

6.2 Incompatibilities

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

6.3 Shelf life

3 years in containers as packaged for sale.
2 years in blister packs as packaged for sale.

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original package in order to protect from light and moisture.

6.5 Nature and Contents of Container

1) Opaque plastic containers composed of PP tubes and PE made tamper evident closures in pack sizes of 28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000 tablets.

2) Opaque plastic containers (HDPP or HDPE) with a tamper-evident or child-resistant tamper-evident closure (HDPE) with a packing inclusion of standard polyether foam or PE or PP made filler in pack sizes 28, 42, 50, 56, 84, 100, 112, 250, 500 and 1000 tablets.

3) Aluminium / opaque PVC blister packs in pack sizes of 28, 42, 56, 84 and 112 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited

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Sarum Hill

Basingstoke

RG21 8SR

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 20416/0156

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/03/2009

10 DATE OF REVISION OF THE TEXT

11/11/2025