SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SULAZINE EC
Sulfasalazine 500 mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500.00 mg Sulfasalazine
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant Tablets
Oval-shaped, orange, bi-convex tablets engraved ‘SULAZINE EC’

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Induction and maintenance of remission of ulcerative colitis; treatment of active Crohn’s disease
2. Treatment of rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs (NSAIDs)

4.2 Posology and method of administration

Gastro-resistant tablets 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.
1. Ulcerative colitis:

Adults :

- *Severe attacks:*

2-4 tablets four times a day, which 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 attacks:*

  2-4 tablets four times a day may be given in conjunction with steroids

- *Mild attacks:*

  2 tablets four times a day with or without steroids

- *Maintenance therapy:*

  With induction of remission gradually reduce dose to 4 tablets per day. The dosage should be continued indefinitely to avoid relapse, since discontinuation even several years after an acute attack is associated with a four-fold increase in risk of relapse.

Paediatric population (Children):
The dose is reduced in proportion to body weight.

- Acute attack or relapse: 40-60 mg/kg per day
- Maintenance therapy: 20-30 mg/kg per day

Sulfasalazine suspension may provide a more flexible dosage form.
2. Crohn's disease

In active Crohn's disease, sulfasalazine should be administered as in attacks of ulcerative colitis (see above)
3. Rheumatoid arthritis:

Patients with rheumatoid arthritis, and those treated over a long period with NSAIDs, may have sensitive stomachs and for this reason gastro-resistant sulfasalazine tablets are recommended for this disease, as follows:
The patient should start with one tablet daily for one week, thereafter increasing the dose by one tablet 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. NSAIDs may be taken concurrently with sulfasalazine.
Route of administration: Oral

4.3 Contraindications

Sulfasalazine is contraindicated in;

- patients with a known hypersensitivity to sulfasalazine, its metabolites or any of the excipients, as well as salicylate and sulfonamide hypersensitivity;
- children 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, 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 at monthly intervals for a minimum of the first three months of treatment. 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 should be performed as clinically indicated, especially in the early months of treatment. Treatment should be discontinued if renal function deteriorates.
Patients should be counselled to report immediately any development of sore throat, fever, malaise, pallor, purpura, jaundice, or non-specific illness, this may indicate myelosuppression, haemolysis or hepatoxicity; a Patient Information Leaflet should also be supplied to warn patients of this requirement, and of the risks of serious blood dyscrasias. Treatment should be stopped immediately while awaiting the results of blood tests. Please see Section 4.4 “Interference with laboratory testing” **for 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.
Patients with severe allergy or bronchial asthma should be treated with caution.
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.
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.
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 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.
Patients with glucose-6-phosphate dehydrogenase deficiency should be closely observed for signs of haemolytic anaemia (Heinz body anaemia).
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.

4.5 Interaction with other medicinal products and other forms of interaction

Reduce absorption of digoxin resulting in non-therapeutic serum levels, has been reported when use concomitantly with oral sulfasalazine.
Sulfonamides bear certain chemical similarities to some oral hypoglycaemic agents. Hypoglycaemia has occurred in patients receiving sulfonamides. Patients receiving sulfasalazine and hypoglycaemic agents should be closely monitored.
Due to inhibition of thiopurine methyltransferase by sulfasalazine, bone marrow suppression and leukopenia have been reported when the thiopurine 6-mercaptopurine or its pro-drug, 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.

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. 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 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 or diarrhoea in infants who were breastfed by 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 adverse effects due 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.

Infections and infestations:

Not known: Aseptic meningitis, Pseudomembranous colitis

Blood and the lymphatic system disorders:

Common: Leukopenia

Uncommon: Thrombocytopenia**

Not known: Agranulocytosis, aplastic anaemia, haemolytic anaemia, Heinz body anaemia, hypoprothrombinaemia, lymphadenopathy, macrocytosis, megaloblastic anaemia, methaemoglobinaemia, 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

Hepato-biliary disorders:

Not known: Hepatic failure*, fulminant hepatitis*, hepatitis**

Skin and subcutaneous tissue disorders:

Common: Pruritis

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**, Angioedema*, periorbital oedema, lichen planus, photosensitivity

Musculoskeletal, connective tissue and bone disorders:

Common: Arthralgia

Not known: Systemic lupus erythematosus, Sjogren's syndrome

Renal and urinary disorders:

Common: Proteinuria

Not known: Crystalluria**, haematuria, interstitial nephritis, nephrotic syndrome

Reproductive system and breast disorders:

Not known: Reversible oligospermia**

General disorders and administrative site disorders:

Common: Fever

Uncommon: Facial oedema

Not known: Yellow discolouration of skin and body fluids*

Investigations:

Uncommon: Elevation of liver enzymes

Not known: Induction of autoantibodies

*ADR identified post-marketing

**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 website 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.

5.1 Pharmacodynamic properties

ATC code: A07EC01: Aminosalicylic acid and similar agents

Pharmacological particulars: around 90% of a dose reaches the colon where bacteria split the drug into Sulfapyridine and mesalazine, and the unsplit sulfasalazine is also active on a variety of symptoms. 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. In rheumatoid arthritis a disease modifying effect is evident in 1-3 months, with characteristics falls in CRP and other indicators of inflammation. Mesalazine 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 gastro-resistant tablets show no statistically significant differences in main parameters compared with an equivalent dose of sulfasalazine 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 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 sulfapyridine 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 only acetyl-mesalazine (not free mesalazine) was demonstrable, the acetylation probably largely achieved in the colon mucosa. After a 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 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 heptocellular adenoma or carcinoma. The mechanism of induction of heptocellular neoplasia has been investigated and attributed to species-species 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 L5178Y 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 epidemiololgy studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K25
Maize Starch
Magnesium Stearate
Stearic Acid
Crospovidone
Methacrylic Acid Copolymer Type C
Triethyl Citrate
Glycerol Monostearate 40-50

6.2 Incompatibilities

None known other than those stated in 4.4 & 4.5

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C in a dry place in well closed containers.

6.5 Nature and contents of container

High-density polyethylene containers with polythene closures fitted with desiccant capsule insert within lid and sealed with a thick paper membrane.

Polypropylene or high-density polyethylene with polythene closures and polyurethane wads or polythene inserts.

Pack sizes: 28, 56, 84, 100, 112, 224 500

PVC/aluminium foils blister packs. (250 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade). 20-micron hard-tempered aluminium foil coated on the dull side with 6-7 gsm heat seal lacquer and printed on the bright side.)
Pack sizes: 28, 56, 84, 100, 112, 224, 500

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Hualan Pharmaceuticals Limited
16/17 College Green
Dublin
D02 V078
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

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