SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

SULAZINE EC 500mg 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 Tablet
Oval-shaped 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

EC 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.

1. Ulcerative colitis:

Adults and Elderly:

- *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 the effect of the drug.

Night-time interval between doses should not exceed 8 hours.

When remission occurs maintenance therapy should be commenced.

- *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 the 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.

Children over 2 years:

Adjust the dose in proportion to bodyweight

- 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 enteric-coated sulfasalazine tablets are recommended for this disease. NSAIDs may be taken concurrently with sulfasalazine.

Adults and Elderly:

Commence treatment with 0.5 g daily (one tablet) 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, to a maximum of 3 g/day (six tablets). Should a patient experience nausea, the dose should be reduced to a previously tolerated dose for one week and then increased. 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.

Children:

Not recommended

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

Haematological and hepatic side effects may occur. 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. Thereafter, monitoring should be performed as clinically indicated. 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.

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.

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 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.

The drug may colour the urine orange yellow. Extended wear soft lenses have been reported as being permanently stained during Sulfasalazine treatment. Daily wear soft contact and glass permeable lenses should respond to standard cleaning.

Oligospermia and infertility may occur in men treated with sulfasalazine. Discontinuation of the drug appears to reverse these effects within 2 to 3 months.

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin and folate uptake may be reduced when used concomitantly with oral sulfasalazine, resulting in non-therapeutic serum levels.

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.

Concomitant antibiotic therapy may alter the patient's response to sulfasalazine.

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 the use of sulfasalazine in pregnant women has not revealed any teratogenic effects. 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.

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

None known

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.

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.

The following adverse reactions have been reported with the frequencies:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1000 to < 1/100)

Not known frequency cannot be estimated from the available data

Infections and infestations:

Not known: 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, methaemoglobinaemina, neutropenia, pancytopenia

The risk of sulfasalazine-associated blood disorders is substantially higher in patients treated for rheumatoid arthritis than it is for patients treated for inflammatory bowel disease.

Immune system disorders:

Not known: Anaphylaxis, polyarteritis nodosa, serum sickness

Metabolism and nutrition:

Not known: Loss of appetite

Psychiatric disorders:

Common: Insomnia

Uncommon: Mental depression

Not known: Hallucinations

Nervous system disorders:

Common: Dizziness, headache, taste disorders

Uncommon: Convulsions

Not known: Aseptic meningitis, ataxia, encephalopathy, peripheral neuropathy, smell disorders

Eye disorders:

Common: Conjunctival and scleral injection

Not known: Some soft contact lenses may be stained

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: Exacerbation of symptoms of colitis, acute pancreatitis, parotitis

Hepato-biliary disorders:

Not known: Hepatic failure, fulminant hepatitis, hepatitis*

Skin and subcutaneous tissue disorders:

Common: Pruritis

Uncommon: Alopecia, urticaria

Not known: Lupus erythematosus-like syndrome, 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, connective tissue and bone disorders:

Common: Arthralgia

Not known: Myalgia, systemic lupus erythematosus

Renal and urinary disorders:

Common: Proteinuria

Not known: Crystalluria*, haematuria, renal dysfunction (interstitial nephritis, nephrotic syndrome) and urine may be coloured orange

Reproductive system and breast disorders:

Not known: Oligospermia* (reversible on discontinuance of drug)

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

*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.

4.9 Overdose

The drug has low acute per oral toxicity in the absence of hypersensitivity. Gastric lavage, correction of any electrolyte imbalance and supportive treatment. There is no specific antidote. Severe crystalluria, if occurred, should be treated accordingly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A07EC01: Aminosalicylic acid and similar agents

Sulfasalazine is a chemical combination of Sulfapyridine and 5-amino salicylic acid (mesalazine). Activity resides in the mesalazine moiety; Sulfapyridine acts only as a carrier to the colonic site of action (in inflammatory bowel disease) where the di-azo bond linking the two moieties is broken by colonic bacteria. Around 90% of a dose reaches the colon. Sulfapyridine and mesalazine, and the unsplit sulfasalazine are all 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. The exact mechanism of action of the anti-inflammatory effect of mesalazine is unknown.

Sulfasalazine was initially introduced for the treatment of rheumatoid arthritis and 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

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.

Sulfasalazine is partly absorbed from the small intestine and may later enter the enterohepatic circulation; the majority of the dose passes to the colon where it is broken down by bacteria to Sulfapyridine and 5-aminosalicylic acid.

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.

Up to 10% of a dose of Sulfasalazine is excreted unchanged and about 60% as Sulfapyridine and its metabolites.

The majority of the 5-aminosalicylic acid is eliminated unchanged in the faeces but some appears in the blood; about 20% is excreted in urine unchanged and in the acetylated form. In urine 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.

Sulfasalazine has been claimed to be concentrated in connective tissue.

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 epidemiology studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Containers: Do not store above 25°C. Keep container tightly closed.
Blister packs: Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polypropylene or high density polystyrene with polythene closures and polyurethane wads or polythene inserts.
PVC/aluminum foil blister packs.
Pack sizes: 28, 56, 84, 100, 112, 224, 500

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

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/01/2009

10 DATE OF REVISION OF THE TEXT

08/07/2016