# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Mesren MR 400 mg tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Mesalazine 400 mg per tablet.

For excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Modified-Release Tablets

Red-brown, oblong, modified-release tablets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Ulcerative Colitis:*

For the treatment of mild to moderate acute exacerbations. For the maintenance of remission.

*Crohn's ileo-colitis*

For the maintenance of remission.

### 4.2 Posology and method of administration

Route of administration: Oral

Swallow whole with a glass of water. Do not chew, crush or break tablets before swallowing.

ADULTS

*Acute disease:* Six tablets a day in divided doses, with concomitant corticosteroid therapy where clinically indicated.

*Maintenance therapy:* Three to six tablets a day in divided doses.

ELDERLY

The normal adult dosage may be used unless renal function is impaired (see section 4.4)

CHILDREN

There is only limited documentation for an effect in children (age 6-18 years).

Children 6 years of age and older

- Active disease: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).
- Maintenance treatment: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

## 4.3 Contraindications

Use in patients with a history of allergy to salicylates, or hypersensitivity to any ingredient. Severe renal impairment (GFR less than 20 ml/min).

Severe hepatic impairment. Gastric or duodenal ulcer, haemorrhagic tendency.

## 4.4 Special warnings and precautions for use

Patients on oral forms of mesalazine should have renal function monitored, with serum creatinine levels measured prior to the start of treatment, every three months for the first year, then six monthly for the next four years and annually thereafter.

Treatment with mesalazine should be discontinued if renal function deteriorates.

Renal disorder: Mesalazine is excreted rapidly by the kidney, mainly as its metabolite, N-acetyl-5-aminosalicyclic acid. Mesren MR 400 mg tablets are best avoided in patients with mild to moderate renal impairment but, if necessary, should be used with extreme caution.

If dehydration develops, normal electrolyte levels and fluid balance should be restored as soon as possible.

In case of lung function impairment, especially asthma, patients need to be very closely monitored.

In patients with a history of sensitivity to sulphasalazine, therapy should be initiated only under close medical supervision. Treatment must be stopped immediately if acute symptoms of intolerance occur such as cramps, abdominal pain, fever, severe headache, or rash.

Very rarely serious blood dyscrasia has been reported. Haematological investigations including a complete blood count should be performed prior to initiation and whilst on therapy according to the physician's judgement. Such tests are generally recommended within 14 days of initiation of therapy with 2-3-repeat tests each after another 4 weeks. If the results are normal, tests are recommended quarterly. In case additional signs of illness appear, further control tests are necessary. This procedure is to be followed especially, if a patient develops signs and symptoms suggestive of blood dyscrasia during treatment, such as unexplained bleeding, haematoma, purpura, anaemia, persistent fever, or a sore throat. Treatment with Mesren MR 400 mg tablets should be stopped immediately if there is a suspicion or evidence of blood dyscrasia and patients should seek immediate medical advice.

Use in the elderly should be cautious and subject to patients having normal renal function.

With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

The concurrent use of known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions (see Section 4.4).

Mesalazine decreases the absorption of digoxin.

Mesalazine can increase the immunosuppressive effects of azathioprine and 6-mercaptopurine. A blood count, especially the leukocyte cell count should be monitored repeatedly, especially at initiation of such combination therapy.

The uricosuric activity of probenecid and sulfinpyrazone, the diuretic effect of furosemide and the activity of spironolactone can be reduced.

Gastrointestinal side-effects of glucocorticoids can be increased.

## 4.6 Pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the foetus/new born child. To date, no other relevant epidemiological data are available. In one single case, after long-term use of high dose mesalazine (2-4-g, orally) during pregnancy, renal failure in a neonate was reported.

Animal studies on oral mesalazine do not indicate direct or indirect harmful effects, with respect to pregnancy embryonic/foetal development, parturition or postnatal development.

Mesalazine should only be used during pregnancy if the potential benefit outweighs the possible risk.

Lactation

N-acetyl-mesalazine and, to a lesser degree, mesalazine are excreted in breast milk. Only limited experience during lactation in woman is available to date. Hypersensitivity reactions like diarrhoea cannot be excluded. Therefore, mesalazine should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the suckling neonate develops diarrhoea, the breast-feeding should be discontinued.

## 4.7 Effects on ability to drive and use machines

Mesalazine has no, or negligible, influence on ability to drive and use machines.

## 4.8 Undesirable effects

Side-effects are rare (1/1000; incidence/treatment years) and are predominately gastrointestinal; diarrhoea, abdominal pain, bloating, alopecia, fever.

Side effects which occur very rarely (<1/10,000; incidence/treatment years), are listed by body system:

| | |
|---|---|
| Blood and lymphatic[(1)] | Blood dyscrasia[(1)], thrombocytopenia, leucopenia, neutropenia, pancytopenia, anaemia, aplastic anaemia, agranulocytosis, bone marrow depression. |
| Nervous | Headache, peripheral neuropathy, vertigo. |
| Cardiac | Myocarditis, pericarditis |
| Respiratory | Allergic lung reactions, bronchospasm, eosinophilic pneumonia. |
| Gastro-intestinal | Pancreatitis, nausea, vomiting, exacerbation of the symptoms of colitis. |
| Hepatobiliary | Abnormalities of hepatic function/transitory abnormal liver function tests, hepatitis. |
| Skin and subcutaneous tissue | Rash, urticaria, bulbous skin reactions, erythema multiforme, Stevens Johnson syndrome. |
| Musculoskeletal, connective tissue and bone | Mesalazine-induced lupus-erythematosus-like syndrome with peridarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia, myalgia, arthralgia. |
| Renal and urinary[(2)] | Renal failure, which may be reversible on withdrawal, interstitial nephritis, nephritic syndrome. |

[(1)]The frequency of blood dyscrasia appears smaller than the number of reported changes in individual white blood count, because reporting health professional may have labelled several cases of blood dyscrasia not in this category

[(2)]Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment

## 4.9 Overdose

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis wit normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults and children over the age of 4 years. In children aged 4 years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis my increase salicylate transfer across the blood brain barrier.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Management

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients under 10 years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Mesalazine belongs to the group known as intestinal anti-inflammatory agents;

ATC code: A07E C02

Mesren MR 400 mg tablets contain mesalazine, or 5-aminosalicylic acid, which has an anti-inflammatory effect through a mechanism that has not yet been fully clarified. Mesalazine inhibits the migration of polymorphonuclear leucocytes and the lipooxygenase of the cells with the concentrations that are reached in the large intestine during treatment. The production of proinflammatory leukotrienes ($LTB_4$ and 5-HETE) in the macrophages of the intestinal wall is then inhibited. Mesalazine has inhibited, in trial conditions, also cyclo-oxygenase and thus, the release of thromboxane $B_2$ and prostaglandin $E_2$, but the clinical meaning of this effect is still unclear. Mesalazine also inhibits formation of the platelet activating factor (PAF). Mesalazine is also an antioxidant; it has been shown to decrease formation of reactive oxygen products and to capture free radicals. Furthermore, mesalazine inhibits secretion of water and chloride and increases the reabsorption of sodium in the intestine in experimental colitis in test animals.

## 5.2 Pharmacokinetic properties

Mesren MR 400 mg tablets are coated with a Eudragit S-based film. This copolymer allows the active principle to be released when the intraluminal pH is greater than 7, that is within the terminal ileum and colon, which are the true sites of inflammation. Mesren MR 400 mg tablets have been designed to be weakly absorbed in the

digestive tract. Absorption by the oral route is approximately 24%. Consequently, 76% of the administered dose remains within the terminal ileum and colon, being available to exert a topical anti-inflammatory effect. Mesalazine is metabolised both by the liver and the intestinal mucosa into an inactive derivative, N-actyl-5-5aminosalicylic acid. Studies show that mesalazine has an elimination half-life of less than one hour. The elimination of mesalazine is essentially urinary and faecal, in the form of mesalazine and its N-acetyl metabolite. Following repeated administration for seven days, the quantities of mesalazine absorbed and eliminated by the urinary route in unchanged form and as the N-acetyl metabolite were 21.2% and 20.9% respectively.

Mesren MR 400 mg Tablets contain, in a single tablet, an equivalent quantity of mesalazine to that theoretically available from the complete azoreduction of 1 g of sulfasalazine.

### 5.3 Preclinical safety data

Preclinical data with mesalazine reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity or toxicity to reproduction.

Renal toxicity (renal capillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose monohydrate

Sodium starch glycolate (Type A)

Magnesium stearate

Talc E553b

Povidone E1201

Methacrylic acid – methyl methacrylate copolymer (1:2)

Dibutyl phthalate

Iron oxides E172

Macrogol 6000

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

### 6.5 Nature and contents of container

Mesren MR 400 mg tablets are available in PVC/aluminium blister strips, each containing ten tablets. The blister strips are packed in cartons containing either 90 or 120 tablets (9 or 12 strips).

### 6.6 Special precautions for disposal

Not applicable.

## 7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
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Eastbourne
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BN22 9AG

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1644

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 November 2003

## 10 DATE OF REVISION OF THE TEXT

24/05/2011