

Data Sheet

ASACOL™

Mesalazine (5-aminosalicylic acid) 400 mg Gastro-resistant Tablets

Mesalazine (5-aminosalicylic acid) 500 mg Suppositories

QUALITATIVE AND QUANTITATIVE COMPOSITION

ASACOL 400 mg Gastro-resistant Tablets

Each gastro-resistant tablet contains Mesalazine (5-aminosalicylic acid) 400 mg.

Also contains 76.4 mg lactose, see *Special Warnings and Precautions for Use*.

For full list of excipients, see *Pharmaceutical Particulars/List of Excipients*.

ASACOL 500 mg Suppositories

Each suppository contains mesalazine (5-aminosalicylic acid) 500 mg.

For full list of excipients, see *Pharmaceutical Particulars/List of Excipients*.

PHARMACEUTICAL FORM

Gastro-resistant (GR) tablets. Coated red/brown oblong tablets.

Suppositories - light grey-brown, torpedo-shaped suppositories.

CLINICAL PARTICULARS

Therapeutic indications

Gastro-resistant Tablets

Ulcerative Colitis: Induction of remission of mild to moderate episodes.
Maintenance of remission.

Crohn's ileo-colitis: Maintenance of remission.

Suppositories

Treatment of mild to moderate distal (proctitis and proctosigmoiditis) ulcerative colitis and maintenance of remission of distal ulcerative colitis.

Posology and Method of Administration

Gastro-resistant Tablets

Route of administration: oral.

The tablets should be swallowed whole with a glass of water one hour before food intake. They must not be chewed, crushed or broken before swallowing. If one or more doses have been missed, the next dose is to be taken as usual.

Ulcerative colitis

Induction of remission: 2.4 to 4.8 g (6 to 12 tablets) in divided doses (three times a day). The dosage can be adjusted in accordance with the response to the treatment.

Maintenance of remission: 1.2 to 2.4 g (3 to 6 tablets) in divided doses (three times a day).

Crohn's ileo-colitis

Maintenance of remission: 2.4 g (6 tablets) in divided doses (three times a day).

The elderly: The normal adult dose can be used unless renal function is impaired (see *Contraindications* and *Special Warnings and Precautions for Use*). No studies have been carried out in the elderly.

Children: There is no dose recommendation for children (see *Contraindications*).

Suppositories

Route of administration: rectal.

The suppositories are for rectal use and must not be swallowed.

Adult dose in proctitis and proctosigmoiditis 1 to 2 suppositories to be inserted up to three times daily (tid), after defecation. The dosage is dependent upon the severity of the disease and it may be possible to reduce the dosage as the condition improves. In severe generalised ulcerative colitis affecting the rectum or rectosigmoid and in cases slow to respond to oral therapy one to two suppositories used morning and evening (bid) may be used as an adjunct to oral therapy.

The elderly: The normal adult dose can be used unless renal function is impaired (see *Contraindications* and *Special Warnings and Precautions for Use*). No studies have been carried out in the elderly.

Children: There is no dose recommendation for children (see *Contraindications*).

Contraindications

- Hypersensitivity to mesalazine or to any other ingredient (see *Pharmaceutical Particulars/List of Excipients*).
- Known allergy to salicylates.
- Severe liver impairment.
- Severe renal impairment (GRF less than 30 mL per minute).
- Children under 2 years of age.

Special warnings and special precautions for use

Renal Impairment

Not recommended for use in patients with renal impairment. Caution should be exercised in patients with raised blood urea or proteinuria. The possibility of mesalazine-induced nephrotoxicity should be suspected in patients developing impairment of renal function during treatment.

It is recommended that all patients have an evaluation of their renal function prior to initiation of ASACOL therapy and annually while on ASACOL therapy.

Such a test is generally recommended within 14 days of initiation of therapy and then every 4 weeks for the following 12 weeks. Short monitoring intervals early after the start of ASACOL therapy will discover rare acute allergic impairment of renal function. In the absence of an acute allergic renal response monitoring intervals can be extended to every 6 months and then annually after 5 years. In case additional signs of illness appear, further control tests are necessary. Treatment with ASACOL should be stopped **immediately** if there is evidence of renal impairment and patients should seek immediate medical advice.

Blood dyscrasia

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. Such tests are generally recommended within 14 days of initiation of therapy and then every 4 weeks for the following 12 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 sore throat. Treatment with ASACOL should be stopped **immediately** if there is a suspicion or evidence of blood dyscrasia and patients should seek immediate medical advice.

Liver impairment

There have been reports of increased liver enzyme levels in patients taking preparations containing mesalazine. Caution is recommended if ASACOL is administered to patients with liver impairment.

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported rarely with ASACOL. In case of previous mesalazine-induced cardiac hypersensitivity ASACOL must not be reintroduced. Caution should be used in patients with previous myo- or pericarditis of allergic background regardless of its origin.

Hypersensitivity to Sulphasalazine

In patients with a history of hypersensitivity 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.

Gastric and duodenal ulcers

In case of existing gastric or duodenal ulcers treatment should begin with caution based on theoretical grounds.

Intolerance to carbohydrates

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tablets in stool

A limited number of reports of intact tablets in the stool have been received. What appear to be intact tablets may in some cases represent largely empty shells of the tablet coating. ASACOL 400 mg GR Tablets release their content even if fragments of the coating remain. Once pH 7.0 is reached, cracks in the coating are sufficient for the release of mesalazine from the tablets. This process is irreversible from here on and mesalazine will therefore be released continuously, independent of intestinal pH. If tablets are observed in the stool repeatedly, the patient should consult his/her physician.

The elderly

Use in the elderly should be handled with caution and the product should only be prescribed to patients having a normal renal function.

Children

Safety and effectiveness of ASACOL in children patients have not been established.

Concomitant use of lactulose or similar preparations should be avoided.

Interaction with other medicaments and other forms of interaction

Sulphasalazine decreases the absorption of digoxin. There are no data on interaction of digoxin with mesalazine.

There have been isolated reports of supposedly altered INR when taken with warfarin.

Mesalazine can increase the immunosuppressive effects of azathioprine and 6-mercaptopurine. Life-threatening infection can occur. Patients should be closely observed for signs of infection and immunosuppression. Haematological parameters, especially the leucocyte and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy (see *Special Warnings and Precautions for Use*). If white blood cells are stable after 1 month, testing every 4 weeks for the following 12 weeks followed by 3 monthly monitoring intervals appears to be justified.

The concurrent use of known nephrotoxic agents, such as NSAIDs, azathioprine or methotrexate, may increase the risk of renal reactions. However, no adverse events proving such interactions have been reported.

Pregnancy and lactation

Pregnancy

Data on a limited number (627) of pregnant women exposed to mesalazine do not indicate an increased risk of congenital malformations. However, some studies have shown an increased incidence of premature births and reduced birth weight in babies born to mothers treated with mesalazine during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, parturition or postnatal development (see *Pharmacological Properties/Preclinical Safety Data*). Caution should be exercised when prescribing to pregnant women.

Lactation

Low concentrations of mesalazine and its N-acetyl metabolite have been detected in human breast milk. The clinical significance of this has not been determined. Caution should be exercised when mesalazine is administered to nursing mothers.

Effects on ability to drive and use machines

ASACOL tablets and suppositories have no influence on the ability to drive and use machines.

Undesirable effects

Gastro-resistant Tablets

The ASACOL clinical trial database includes 651 patients treated with ASACOL 400 mg GR Tablets. The mesalazine doses were in the range of 0.8 g/day to 4.8 g/day, the average treatment duration varied between four weeks and four years.

Undesirable effects reported from nine double-blind and six open clinical studies for which an association with mesalazine use is suspected or cannot be ruled out, are presented by system organ class.

The only very common undesirable effect was headache, which occurred in approximately 17.8% of patients. The following common undesirable effects were reported: nausea (8.4%), dyspepsia (7.5%), abdominal pain (4.3%), dizziness (4.0%), rash (2.8%), vomiting (2.5%), arthralgia (2.3%), diarrhea (1.8%) and drug fever (1.7%).

Organ specific allergic reactions affecting the heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue have been reported.

In patients with a history of hypersensitivity to sulphasalazine, treatment must be stopped immediately if acute symptoms of intolerance occur such as cramps, abdominal pain, fever, severe headache or rash (see *Special Warnings and Precautions for Use*).

Very common: $\geq 1/10$, common: $\geq 1/100$ and $< 1/10$,

uncommon: $\geq 1/1,000$ and $< 1/100$, rare: $\geq 1/10,000$ and $< 1/1,000$,

very rare: $< 1/10,000$, not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Uncommon : anemia.

Nervous system disorders

Very common : headache.

Common : dizziness.

Uncommon : paresthesia, tinnitus.

Gastrointestinal disorders

Common : abdominal pain, vomiting, nausea, diarrhoea, dyspepsia.

Uncommon : flatulence.

Skin and subcutaneous tissue disorders

Common : rash.

Uncommon : urticaria, pruritus.

Musculoskeletal, connective tissue and bone disorders

Common : arthralgia.

Uncommon : myalgia.

General disorders and administration site conditions

Common : drug fever.

Uncommon : drug ineffective.

Suppositories

The ASACOL clinical trial database includes 246 patients treated with ASACOL 500 mg Suppositories. The mesalazine doses were in the range of 1.0 g/day to 1.5 g/day, the treatment duration varied between four weeks and twelve months.

Undesirable effects reported from four double-blind and one open clinical study for which an association with mesalazine use is suspected or cannot be ruled out, are presented by system organ class.

The only common undesirable effect was abdominal pain (1.2%).

Gastrointestinal disorders

Common : abdominal pain.

Uncommon : vomiting, nausea, diarrhoea.

General disorders and administration site conditions

Uncommon : drug fever, drug ineffective.

Gastro-resistant Tablets and Suppositories

The following undesirable effects were noticed from spontaneous reporting or the literature. The incidence rate is not known.

Blood and lymphatic system disorders

: agranulocytosis, pancytopenia, aplastic anemia, bone marrow depression, leucopenia, neutropenia, thrombocytopenia, eosinophilia, blood disorder.

Cardiac disorders

: myocarditis, pericarditis.

Respiratory, thoracic and mediastinal disorders

: dyspnoea, pneumonia, interstitial pneumonia, eosinophilic pneumonia, chest pain, lung disorder, cough.

Gastrointestinal disorders

: acute pancreatitis, exacerbation of the symptoms of colitis.

Hepato-biliary disorders

: hepatitis, liver function test abnormal.

Skin and subcutaneous tissue disorders

: alopecia.

Musculoskeletal, connective tissue and bone disorders

: lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia.

Renal and urinary disorders

: nephrotic syndrome, interstitial nephritis, renal failure which may be reversible on withdrawal.

Investigations

: Blood creatinine increased, weight decreased, creatinine clearance decreased, amylase increased, red blood cell sedimentation rate increased, lipase increased, BUN increased.

An unknown number of the above undesirable effects are probably associated to the underlying IBD rather than ASACOL/mesalazine medication. This holds true especially for gastrointestinal undesirable effects and arthralgia.

Mesalazine-induced nephrotoxicity, which may be reversible on withdrawal, should be suspected in patients developing renal dysfunction during treatment (see *Special Warnings and Precautions for Use*).

To avoid blood dyscrasia resulting from developing bone marrow depression patients should be monitored with care (see *Special Warnings and Precautions for Use*).

Co-administration of immunosuppressive drugs such as azathioprine or 6-MP can precipitate leucopenia (see *Interaction with Other Medicinal products and Other Forms of Interaction*).

Concurrent use of NSAIDs, azathioprine or methotrexate may increase the risk of renal reactions (see *Interaction with Other Medicinal products and Other Forms of Interaction*).

Overdose

There is no clinical experience with overdose of ASACOL 400 mg GR Tablets or ASACOL 500 mg Suppositories. Mesalazine is not metabolized to salicylate. There is no specific antidote for mesalazine overdose and treatment is symptomatic and supportive. It may include intravenous infusion of appropriate electrolytes.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Gastro-resistant Tablets and Suppositories

ASACOL 400 mg GR Tablets and ASACOL 500 mg Suppositories contain mesalazine [ATC A07EC02], also known as 5-aminosalicylic acid, which has an anti-inflammatory effect through a mechanism that has not yet been fully clarified. Mesalazine inhibits the migration of polymorphnuclear leucocytes and the lipooxygenase of the cells at concentrations reached in the large intestine during treatment. The production of proinflammatory leukotrienes (LTB₄ and 5-HETE) in macrophages of the intestinal wall is then inhibited. Under trial conditions mesalazine has also inhibited the cyclooxygenase and thus, the release of thromboxane B₂ and prostaglandin E₂, but the clinical meaning of this effect is still unclear. Mesalazine inhibits the formation of platelet activating factor (PAF). Recently mesalazine has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses. Mesalazine is also an antioxidant; it has been shown to decrease formation of reactive oxygen products and to capture free radicals.

Pharmacokinetic properties

Gastro-resistant Tablets

ASACOL GR tablets are coated with a polymer [Eudragit® S] which allows mesalazine to be released when the intraluminal pH is above 7, i.e. within the terminal ileum and colon, which are the sites of inflammation in IBD. ASACOL tablets have been designed to minimise absorption of mesalazine in the digestive tract. Absorption by the oral route

is approximately 24%. Consequently, 76% of the administered dose remains in the gut lumen and the mucosal tissue. Mesalazine is metabolised both by the intestinal mucosa and the liver to the inactive metabolite N-acetyl mesalazine. The elimination of mesalazine is essentially faecal and urinary in the form of mesalazine and its N-acetyl metabolite.

After a single dose of 0.8 g mesalazine (two ASACOL 400 mg GR Tablets) in healthy volunteers the mean C_{max} and t_{max} were 720 ng/mL and 12.4 hours for mesalazine and 1000 ng/mL and 13.9 hours for N-acetyl mesalazine, respectively. Mesalazine has an elimination half-life between 9 hours (single dose) and 11 hours (steady state). A high inter-subject variability has been seen in clinical trials. About 43% mesalazine and about 78% N-acetyl mesalazine are bound to plasma proteins. Low concentrations of mesalazine and N-acetyl mesalazine have been detected in human breast milk. The clinical significance of this has not been determined.

Suppositories

As with the tablets, only a proportion of mesalazine contained in the suppositories is absorbed and available to the systemic circulation. The mode of action of mesalazine is local rather than systemic. Acetylation of mesalazine to N-acetyl mesalazine occurs in the gastrointestinal wall and in the liver. N-acetyl mesalazine is predominantly excreted in the urine. After a single dose of 500 mg Suppositories in healthy volunteers the mean C_{max} and t_{max} were 211 ng/mL and 2 hours for mesalazine and 443 ng/mL and 3 hours for N-acetyl mesalazine, respectively.

Mesalazine and the main metabolite N-acetyl mesalazine were reported to have biological half-lives of 4.97 hours and 8.32 hours, respectively.

Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of this data sheet.

PHARMACEUTICAL PARTICULARS

List of excipients

ASACOL gastro-resistant tablets

Tablet core: lactose monohydrate, sodium starch glycollate, magnesium stearate (vegetable origin), talc, povidone.

Film-coating: methacrylic acid - methyl methacrylate copolymer, talc, triethylcitrate, ferric oxide red and yellow (E172), macrogol 6000.

ASACOL suppositories

Hard fat.

Incompatibilities

Not applicable.

Special storage precautions

ASACOL tablets and suppositories should not be stored above 25°C, refrigerated or frozen. Store in the original package. Store in a dry place. The suppositories should be stored away from direct sunlight.

ASACOL must not be used past the expiry date marked on the packaging.

ASACOL must be kept out of the reach of children.

Nature and contents of container

ASACOL 400 mg GR tablets are available in PVC/aluminium blister strips, each containing ten tablets. The blister strips are packed in cartons containing 100 tablets (10 strips).

ASACOL 500 mg suppositories: are available in white opaque PVC/polyethylene laminate foil strips each containing five suppositories. The laminate foil strips are packed in an outer cardboard carton containing 20 suppositories (4 laminate foil strips).

Directions for use/handling

The suppositories are for rectal use and must not be swallowed.

Medicine classification

Prescription Medicine.

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22 October 2009.

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