PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

ASACOL TABLETS

ASACOL 800 Tablets

COMPOSITION

Per **ASACOL TABLETS** (400 mg tablet): Mesalazine (5-aminosalicylic acid) 400 mg

Per **ASACOL 800** mg tablet: Mesalazine (5-aminosalicylic acid) 800 mg

Excipients:

The 400 mg and 800 mg tablets contain 76,4 mg and 152,8 mg of lactose monohydrate respectively. Other excipients are magnesium stearate, povidone, sodium starch glycolate (Type A) and talc.

Film-coating contains:

Macrogol 6000, methacrylic acid-methylmethacrylatecopolymer, talc, triethyl citrate, red pigment (ferric oxide) and yellow pigment (ferric oxide).

Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION

A 11.10 Medicines acting on gastrointestinal tract, other.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The acrylic based resin coating, which is pH-dependent (pH=7), delays the release of mesalazine (5-aminosalicylic acid) until the tablet reaches the distal ileum and colon. There it acts locally, probably

involving the inhibition of prostaglandin and leukotriene synthesis.

Pharmacokinetic properties

Mesalazine is mostly excreted in the faeces either as 5-aminosalicylic acid (5-ASA) or N-acetyl-5-ASA. About 20 per cent of the 5-ASA released in the colon is absorbed and rapidly acetylated to N-acetyl-5-ASA which is excreted in the urine. The acetylated metabolite (active ingredient) has a half-life of approximately 10 hours and that of the parent compound approximately one hour.

INDICATIONS

Ulcerative Colitis:

ASACOL is used for the treatment and maintenance of remission in ulcerative colitis.

CONTRAINDICATIONS

Hypersensitivity to mesalazine or to any of the other ingredients of **ASACOL** tablets

Sensitivity to salicylates

Severe renal impairment (GFR less than 30 mℓ per minute)

Severe liver impairment

Gastric and duodenal ulcers

Bleeding tendency

WARNINGS AND SPECIAL PRECAUTIONS

Blood tests (differential blood count, liver function parameters such as ALT or AST; serum creatinine) and urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating medical practitioner. As a guideline, follow-up tests are recommended 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. If the findings are normal, follow-up tests should be carried out every three months. If additional signs appear, these tests should be performed immediately.

Renal impairment

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

Treatment with **ASACOL** should be stopped immediately if there is evidence of renal impairment and patients should seek immediate medical advice.

Liver impairment

There have been reports of increased liver enzyme levels in patients taking **ASACOL**. Caution is advised if **ASACOL** is given to patients with liver impairment (see CONTRAINDICATIONS).

Blood dyscrasia

Serious blood dyscrasia has been reported. Treatment with **ASACOL** should be stopped immediately if a blood dyscrasia (signs of unexplained bleeding, haematoma, purpura, anaemia, persistent fever or sore throat) is suspected or present and patients should seek immediate medical advice (see SIDE EFFECTS).

Pulmonary disease

Patients with pulmonary disease, in particular asthma, should be very carefully monitored during a course of treatment with **ASACOL** tablets.

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have been reported 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.

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** tablets release their content in the lower gut even if the coating does not dissolve entirely. 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 medical practitioner.

Elderly patients

Use in elderly patients should be handled with caution and **ASACOL** should only be prescribed to patients having a normal renal and hepatic function (see CONTRAINDICATIONS).

Paediatric patients

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

Gastric and duodenal ulcers

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

Co-administration of immunosuppressive agents such as azathioprine or 6-MP can precipitate leucopenia (see INTERACTIONS).

Concurrent use of NSAIDs or azathioprine may increase the risk of renal reactions (see INTERACTIONS).

Effects on ability to drive and use machines

ASACOL tablets may influence the ability to drive and use machines.

The tablets contain lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance, e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take **ASACOL**.

INTERACTIONS

ASACOL should not be given with preparations which lower stool pH, e.g. lactulose, and which prevent release of the active ingredient.

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

There is weak evidence that **ASACOL** might decrease the anticoagulant effect of warfarin, frequent INR monitoring is advisable.

ASACOL can increase the immunosuppressive effects of azathioprine, 6-mercaptopurine or thioguanine. Life-threatening infection can occur. Patients should be closely observed for signs of infection and immunosuppression. Haematological parameters, such as leukocyte and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy (see WARNINGS AND SPECIAL PRECAUTIONS). 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 medicines, such as NSAIDs or azathioprine, may increase the risk of renal reactions. However, no adverse events proving such interactions have been reported (see WARNINGS AND SPECIAL PRECAUTIONS).

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

HUMAN REPRODUCTION

Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

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.

ADULTS:

Ulcerative Colitis:

ASACOL 400 mg:

Induction of remission: 2,4 g (six tablets) once daily or divided in 2 - 3 times daily. If required, the dose may be increased to 4,8 g (twelve tablets) divided in 2 - 3 times daily. 2,4 g may be taken once daily or in divided doses. Above 2,4 g should be taken in divided doses.

Maintenance of remission: 1,6 to 2,4 g (4 to 6 tablets) once daily or divided in 2 - 3 times daily.

The dose can be adjusted in accordance with the response to the treatment.

ASACOL 800 mg:

- *Mild acute disease*: 2,4 g (three tablets) once daily or divided in 2 - 3 times daily, with concomitant corticosteroid therapy where clinically indicated.
- *Moderate acute disease*: 2,4 g to 4,8 g (three to six tablets) divided in 2 - 3 times daily, with concomitant corticosteroid therapy where clinically indicated. 2,4 g may be taken once daily or in divided doses. Above 2,4 g should be taken in divided doses.
- *Maintenance therapy*: 1,6 g to 2,4 g (two to three tablets) taken once daily or in divided doses.

The maximum adult dose should not exceed six tablets a day and not exceed 3 tablets taken together at any one time.

ELDERLY:

The normal adult dosage may be used unless renal or liver function is severely impaired (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS

Side effects are presented by system organ class according to the following frequencies:

Very common: ≥ 10 % patients

Common: ≥ 1 % and < 10 % patients

Uncommon: ≥ 0,1 % and < 1 % patients

Rare: ≥ 0,01 % and < 0,1 % patients

The only very common side effect was headache, which occurred in approximately 17,8 % of patients. The following common side 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 %), diarrhoea (1,8 %) and fever (1,7 %).

Tabulated summary of side effects:

System Organ Class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Frequency not known**
Blood and the lymphatic system disorders		anaemia eosinophilia (as part of an allergic reaction)		altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia)	bone marrow depression, blood disorder
Immune system disorders				hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis	
Nervous system disorders		paraesthesia tinnitus	headache, dizziness	peripheral neuropathy	vertigo
Cardiac disorders			myocarditis, pericarditis		

Respiratory, thoracic and mediastinal disorders				allergic and fibrotic lung reactions (including dyspnoea, cough bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), interstitial pneumonia, eosinophilic pneumonia, lung disorder	pleurisy pneumonia, chest pain
Gastrointestinal disorders	dyspepsia		abdominal pain, diarrhoea, flatulence, nausea, vomiting	acute pancreatitis	exacerbation of the symptoms of colitis
Hepato-biliary disorders				changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis	hepatic function abnormal/ abnormal liver function tests, increased blood bilirubin
Skin and subcutaneous tissue disorders	rash	pruritus, urticaria	photo= sensitivity*	alopecia	Stevens Johnson syndrome, erythema multiforme, bulbous skin reactions

Musculoskeletal, connective tissue and bone disorders				myalgia, arthralgia	lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia
Renal and urinary disorders				impairment of renal function including acute and chronic interstitial nephritis, renal insufficiency, nephrotic syndrome and renal failure which may be reversible on early withdrawal	
Reproductive system and breast disorders				oligospermia (reversible)	
General disorders and administrative site conditions		pyrexia, chest pain			intolerance to mesalazine with C-reactive protein increased and/or exacerbation of symptoms of underlying disease
Investigations					increased blood creatinine, amylase, red blood cell sedimentation rate, lipase and BUN decreased weight and creatinine

					clearance

Description of selected adverse reactions

An unknown number of the above mentioned undesirable effects are probably associated to the underlying IBD rather than **ASACOL** medicine. This holds true especially for gastrointestinal undesirable effects, arthralgia, and alopecia.

To avoid blood dyscrasia resulting from developing bone marrow depression patients should be monitored with care (see WARNINGS AND SPECIAL PRECAUTIONS).

Under co-administration of mesalazine contained in **ASACOL** with myelosuppressive drugs, such as azathioprine, or 6-MP, or thioguanine, life-threatening infection can occur (see INTERACTIONS).

**Photosensitivity*

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

Paediatric population

There is only limited safety experience with the use of **ASACOL** tablets in the paediatric population. It is expected that the target organs of possible adverse reactions in the paediatric population are the same as for adults (heart, lungs, liver, kidneys, pancreas, skin and subcutaneous tissue).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms of overdosage include that of salicylism: mixed acidosis-alkalosis, hyperventilation, pulmonary oedema, dehydration as a result of sweating and vomiting, and hypoglycaemia.

There is no specific antidote. Treatment is symptomatic and supportive.

IDENTIFICATION

ASACOL TABLETS: An oblong, red-brown enteric-coated tablet.

ASACOL 800: Coated, reddish to brownish oblong tablet with a glossy to matt finish; length 17 mm, width and height 8 mm.

PRESENTATION

ASACOL TABLETS: 90's in clear colourless PVC/aluminium blister packs.

ASACOL 800: 60 or 90 tablets in clear colourless PVC/aluminium blister strip.

Each blister contains 10 **ASACOL** gastro-resistant tablets. The blisters are packed in bundles of 6 or 9 depending on the pack size into cardboard boxes, a package insert is included.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ASACOL TABLETS: S/11.10/171

ASACOL 800: 37/11.10/0629

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of Registration:

ASACOL TABLETS: 21 November 1989

ASACOL 800: 01 December 2006

Date of latest revision of text: 18 December 2019

Namibia: NS2 ASACOL 400 mg: 90/11.10/00299 ASACOL 800 mg: 13/11.10/0268

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