AUSTRALIAN PRODUCT INFORMATION - ASACOL® (MESALAZINE)

1. NAME OF THE MEDICINE

Mesalazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ASACOL enteric coated tablets contain 400 mg, 800 mg or 1600 mg mesalazine as the active ingredient.

Excipient with known effect: sugars as lactose (400 mg and 800 mg tablets).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

ASACOL 400 mg and 800 mg

ASACOL enteric coated tablets are reddish to brownish oblong tablets with a glossy to matt finish (ASACOL 400 mg dimensions: 15 x 6 x 7 mm; ASACOL 800 mg dimensions: 17 x 8 x 8 mm).

ASACOL 1600 mg

ASACOL enteric coated tablets are film coated dark orange oblong tablets with a glossy to matte finish (ASACOL 1600 mg dimensions: 23 x 11 x 9 mm).

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ASACOL is indicated for the treatment of mild to moderate ulcerative colitis and maintenance of remission in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults

Acute disease: 2.4 g to 4.8 g per day taken once daily or in divided doses. The dosage can be adjusted in accordance with the response to treatment.

Maintenance therapy: 1.6 g to 2.4 g per day taken once daily or in divided doses.

Elderly population

The normal adult dose can be taken unless liver or renal function is severely impaired, see sections 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE. No studies have been carried out in the elderly population.

Method of administration

The tablets must be swallowed whole preferably with some liquid.

The tablets must not be chewed, crushed or broken before swallowing. The tablets can be taken with or without food. If one or more doses have been missed, the next dose should be taken as usual.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 LIST OF EXCIPIENTS
- Known hypersensitivity to salicylates
- Severe liver impairment
- Severe renal impairment (GFR < 30 mL/min/1.73 m^2).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified 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 physician. As a guideline, follow-up tests are recommended 14 days after commencement of treatment, then a further two to three tests at intervals of 4 weeks.

If the findings are normal, follow-up tests should be carried out every 3 months. If additional symptoms occur, these tests should be performed immediately.

Blood dyscrasia

Serious blood dyscrasias have been very rarely reported. ASACOL therapy should be stopped immediately if there is a suspicion or evidence of blood dyscrasia (signs of unexplained bleeding, bruising, purpura, anaemia, persistent fever or sore throat), and the patient should be advised to seek immediate medical advice.

Cardiac hypersensitivity reactions

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

Pulmonary disease

Patients with pulmonary disease, in particular asthma, should be carefully monitored during treatment with ASACOL.

Adverse drug reactions to sulfasalazine

Patients with a history of adverse drug reactions to sulfasalazine therapy should be kept under close medical supervision. Treatment must be stopped immediately if acute symptoms of

intolerance occur such as abdominal cramps, acute abdominal pain, fever, severe headache and rash.

Gastric and duodenal ulcers

Caution is recommended when treating patients with existing gastric or duodenal ulcer.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalazine, including stones with mesalazine content. Ensure adequate fluid intake during treatment.

Discolouration of urine after contact with sodium hypochlorite

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g. in toilets cleaned with sodium hypochlorite contained in certain bleaches).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.

Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

ASACOL 400 mg and 800 mg

Tablets in stool

A limited number of reports of intact 400 mg and 800 mg tablets in the stool have been received. What appear to be intact tablets may in some cases represent largely empty shells of the coated tablets. If intact tablets are observed in the stool repeatedly, the patient should consult his/her physician.

Tablets contain lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take ASACOL 400 mg and 800 mg.

Use in hepatic 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.

Use in renal impairment

It is recommended that the renal function is monitored prior to and repeatedly whilst on mesalazine therapy. Caution should be exercised when initiating treatment in patients with raised serum creatinine or proteinuria.

Mesalazine-induced renal toxicity should be suspected if the renal function deteriorates during treatment and the treatment should be stopped immediately.

Short monitoring intervals for monitoring of renal function early after the start of ASACOL therapy will discover rare acute renal reactions. In the absence of an acute renal reaction, monitoring intervals can be extended to every 3 months and then annually after 5 years.

Use in the elderly

Mesalazine should be administered with caution in the elderly.

ASACOL should only be used in elderly patients with normal or non-severe hepatic and renal impairment (see section 4.3 CONTRAINDICATIONS, Use in hepatic impairment and Use in renal impairment).

Paediatric use

ASACOL 400 mg and 800 mg

As there is only limited documentation for an effect in children (age 6-18 years), administration in this age group is not recommended.

ASACOL 1600 mg

The safety and efficacy of ASACOL in children and adolescents aged younger than 18 years of age has not been established.

Effects on laboratory tests

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine causing false-positive test result have been observed in patients exposed to sulfasalazine or its metabolite, mesalazine.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin.

Caution is recommended for the concomitant use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine as these may increase the risk of renal adverse reactions.

A possible increase in the myelosuppressive effects of azathioprine, 6-mercaptopurine or thioguanine in patients who are concomitantly treated with any of these preparations, should be taken into account. Life-threatening infection can occur. Patients should be closely observed for signs of infection and myelosuppression. Haematological parameters, especially the leucocyte, thrombocyte and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy (see section 4.4 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No effects on fertility or reproductive performance were observed in male or female rats at oral doses of mesalazine of up to 480 mg/kg/day (similar to the maximal recommended human dose of ASACOL on a body surface area basis).

Use in pregnancy (Category C)

Mesalazine is known to cross the placental barrier, but available data are insufficient to assess the risk of adverse effects on either pregnancy or the health of the foetus/neonate. Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with nonsteroidal anti-inflammatory drugs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.

There are no adequate data on the use of ASACOL in pregnant women. However, data on a limited number (n = 627) of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on the health of the foetus/newborn child. To date no other relevant epidemiological data are available.

In one single case after long-term use of a high dose of mesalazine (2-4 g, orally) during pregnancy, renal failure in a neonate was reported.

Oral administration of mesalazine to rats and rabbits during the period of organogenesis at doses up to 480 mg/kg/day (about one to two times the maximum recommended clinical dose of ASACOL on a body surface area basis) did not cause embryofetal toxicity or teratogenicity in the presence of maternotoxicity.

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

Use in lactation

N-acetyl-5-aminosalicylic acid and to a lesser degree mesalazine are excreted in breast milk. The clinical significance of this has not been determined. Only limited experience during lactation in women is available to date. Hypersensitivity reactions such as diarrhoea in the infant cannot be excluded. Therefore, ASACOL should only be used during breast-feeding, if the potential benefit outweighs the possible risk. If the infant develops diarrhoea, breast-feeding should be discontinued.

In rats, oral administration of mesalazine from late gestation to weaning at doses of 480 mg/kg/day (similar to the maximal recommended clinical dose of ASACOL on a body surface area basis) was associated with toxicity to dams and offspring. A dose of 120 mg/kg/day was devoid of toxicity in either generation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

ASACOL has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

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

Treatment must be stopped immediately if acute symptoms of intolerance occur such as abdominal cramps, acute abdominal pain, fever, severe headache and rash.

Severe cutaneous adverse reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Tabulated summary of adverse reactions

Undesirable effects reported from clinical studies and other sources are listed in Table 1.

The following definitions apply to the incidence of undesirable effects: common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. Adverse drug reactions by frequency and system organ class

System Organ Class	Frequency	Reaction
Blood and lymphatic system disorders	Uncommon	Eosinophilia (as part of an allergic reaction)
	Very rare	Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia), blood dyscrasia
Immune system disorders	Very rare	Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis
Nervous system disorders	Uncommon	Paresthesia
	Rare	Headache, dizziness
	Very rare	Peripheral neuropathy
Cardiac disorders	Rare	Myocarditis, pericarditis
Respiratory, thoracic and mediastinal disorders	Very rare	Allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), interstitial pneumonia, eosinophilic pneumonia, lung disorder
	Non known	Pleurisy
Gastrointestinal disorders	Common	Dyspepsia
	Rare	Abdominal pain, diarrhoea, flatulence, nausea, vomiting
	Very rare	Acute pancreatitis
Hepatobiliary disorders	Very rare	Changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis

System Organ Class	Frequency	Reaction
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Urticaria, pruritus
	Rare	Photosensitivity
	Very rare	Alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue disorders	Very rare	Myalgia, arthralgia
	Not known	Lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia
Renal and urinary disorders	Very rare	Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency, nephrotic syndrome, renal failure which may be reversible on early withdrawal.
	Not known	Nephrolithiasis
Reproductive system and breast disorders	Very rare	Oligospermia (reversible)
General disorders and administration site conditions	Uncommon	Pyrexia, chest pain
	Not known	Intolerance to mesalazine with C-reactive protein increased and/or exacerbation of symptoms underlying disease
Investigations	Not known	Blood creatinine increased, weight decreased, creatinine clearance decreased, amylase increased, red blood cell sedimentation rate increased, lipase increased, BUN increased

Description of selected adverse reactions

An unknown number of the above-mentioned adverse effects are probably associated to the underlying inflammatory bowel disease rather than ASACOL/mesalazine medication. This holds true especially for gastrointestinal adverse effects, arthralgia and alopecia.

To avoid blood dyscrasia resulting from developing bone marrow depression patients should be monitored with care (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Under co-administration of mesalazine with immunosuppressive drugs such as azathioprine or 6-mercaptopurine or thioguanine, life-threatening infection can occur (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 no 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).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is little data on overdose (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote and treatment is symptomatic and supportive.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Intestinal anti-inflammatory agents, ATC code: A07EC02.

Mechanism of Action

ASACOL contains mesalazine, also known as 5-aminosalicylic acid, which has a topical anti-inflammatory effect on the colonic mucosal cells through a mechanism that has not yet been fully clarified.

Mesalazine has been shown to inhibit LTB4-stimulated migration of intestinal macrophages by restricting migration of macrophages to inflamed areas. The production of pro-inflammatory leukotrienes (LTB4 and 5-HETE) in macrophages of the intestinal wall is thereby inhibited. Mesalazine has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses.

Under trial conditions mesalazine inhibited the cyclooxygenase and thus, the release of thromboxane B_2 and prostaglandin E_2, but the clinical meaning of this effect is still unclear.

Mesalazine inhibits the formation of 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.

Clinical trials

Induction of remission in mild-moderate ulcerative colitis

ASACOL 400 mg

A phase 3, multicentre, randomised, double-blind, double-dummy, placebo controlled study conducted in 53 centres across Japan between 2005 and 2007, compared the efficacy and safety of two doses of ASACOL 400 mg tablets (2.4 g/ day and 3.6 g/day, given in 3 equally divided doses) versus Pentasa® 250 mg tablets (2.25 g/day, given in 3 equally divided doses) and placebo, for the induction of remission in patients with mild to moderate active UC. Two hundred and twenty-nine (229) patients aged 16 to 64 years were enrolled with initial UC Disease Activity Index (UC-DAI) of 3 to 8.

The primary efficacy endpoint was the reduction of the UC-DAI score from baseline to week 8 or at discontinuation. Secondary endpoints of remission rate and efficacy rates were assessed.

Table 2. Efficacy for the induction of remission in patients with mild to moderate active ulcerative colitis

Treatment	**ASACOL 400 mg**		**Pentasa**	**Placebo**
Dose	2.4 g/day	3.6 g/day	2.25 g/day	
n	66	65	65	33
UC-DAI reduction at 8 weeks	1.5	2.9	1.3	0.3
Remission rate	30.3%	45.3%	28.6%	9.4%
Efficacy rates	45.5%	64.1%	49.2%	28.1%

Reductions in UC-DAI score verified the superiority of the 3.6 g/day ASACOL group to the Pentasa group, and non-inferiority of the 2.4 g/day ASACOL group compared to the Pentasa group. The three active groups were also compared to placebo, but only the 3.6 g/day ASACOL group demonstrated a statistically significant difference; group difference 2.7 (95% CI: 1.4, 3.9).

The remission rates were 30.3% in the 2.4 g/day ASACOL group, 45.3% in the 3.6 g/day ASACOL group, 28.6% in the 2.25 g/day Pentasa group, and 9.4% in the placebo group. The efficacy rates were 45.5% in the 2.4 g/day ASACOL group, 64.1% in the 3.6 g/day ASACOL group, 49.2% in the 2.25 g/day Pentasa group, and 28.1% in the placebo group.

ASACOL 800 mg

A multi-national, multicentre, randomised, placebo-controlled, double-blind phase 3 study was conducted by Tillotts Pharma in 26 study centres in the Ukraine, Belarus, India, and Turkey to determine the efficacy of ASACOL 4.8 g/day (3 x 800 mg tablets, given twice a day) to induce remission after 6 weeks of treatment compared to placebo in patients with mild to moderate UC.

The initial primary efficacy endpoint (as per FDA Guidelines) of the proportion of patients achieving clinical and endoscopic remission at week 6 was modified prior to the unblinding of treatment allocation in order to be consistent with the European Guideline which defined clinical remission (UC-DAI; score of 0 for stool frequency and rectal bleeding and absence of urgency) at week 6 as the only primary efficacy endpoint for the analysis. Endoscopic remission (sigmoidoscopic score of ≤1 at week 6) was added as a new secondary endpoint.

For the ITT population clinical remission (primary endpoint) at week 6 was achieved in 42 (30.0%) of the subjects who received ASACOL 800 mg tablets and 29 (20.68%) of the subjects who received placebo ($p = 0.069$; 95% CI of the between group difference = [-0.7%, 19.43%]). The difference between ASACOL 800 mg and placebo did not meet the pre-set significance level of $p < 0.05$ for clinical remission, however, all pre-specified secondary endpoints were met.

For the ITT population week 6 endoscopic remission was achieved in 64 (45.7%) of the subjects who received ASACOL 800 mg tablets and 35 (24.8%) of the subjects who received placebo ($p < 0.001$; 95% CI: 9.7%, 31.3%). Endoscopic remission at week 10 was achieved in 73 (52.1%) of the subjects who received ASACOL 800 mg tablets and 52 (36.9%) of placebo-treated subjects ($p = 0.010$; CI: 3.6%, 26.3%). Clinical remission at week 10 was achieved in 57 (40.7%) of the subjects who received ASACOL 800 mg and 30 (21.3%) of placebo-treated subjects ($p < 0.001$; 95% CI: 8.6%, 29.6%).

A secondary post-hoc analysis was also conducted, in which data form India (identified as the outlier country) were excluded. This reanalysis showed a statistically significant result ($p = 0.02$) for the primary endpoint; clinical remission at week 6. All secondary endpoints apart from the modified UC-DAI score at week 6 were statistically significant. The results of the secondary endpoints were similar to what was observed with the ITT population, where all secondary endpoints were statistically significant.

ASACOL 1600 mg

This indication was investigated in a randomised, active-controlled, double-blind, multi-centre, non-inferiority induction trial study with 817 patients receiving 3.2 g mesalazine daily for 8 weeks.

At week 8, 22.4% of the Per-Protocol patients treated with ASACOL 1600 mg tablets and 24.6% of those treated with ASACOL 400 mg tablets achieved clinical and endoscopic remission. The unadjusted between group difference was 2.2% (95% confidence interval: -8.1% up to 3.8%). Once daily ASACOL 1600 mg were considered to be non-inferior to twice daily ASACOL 400 mg in inducing clinical and endoscopic remission.

A total of 10.3% of patients treated with ASACOL 1600 mg and 9.8% of patients receiving ASACOL 400 mg reported treatment related adverse events. The incidence of subjects with serious adverse events (SAEs) in both treatment groups was 2.0% versus 1.7%.

Maintenance of remission in mild-moderate ulcerative colitis

ASACOL 400 mg tablets

A multi-centre, randomised, double-blind study was conducted to verify the non-inferiority of ASACOL 400 mg (2.4 g/day, given in 3 equally divided doses) to Pentasa 250 mg tablets (2.25 g/day, given in 3 equally divided doses) for the maintenance of remission in patients with mild to moderate UC. The primary endpoint was the proportion of patients without bloody stools.

One hundred and thirty-one (131) outpatients aged 16 to 64 years with quiescent UC (UC-DAI ≤ 2) 2 and a bloody stool score of 0 were included. Over a period of 48 weeks, the two groups were administered either ASACOL 2.4 g/day (n=65) or Pentasa™ 2.25 g/day (n=66). A total of 34 patients withdrew from the study. The most frequent reason for withdrawal was relapse of UC based on the discontinuation criteria of a bloody stool score of 1 or more and

UC-DAI of 3 or more (ASACOL, 10; Pentasa, 13), and the second most common reason was the occurrence of AEs (ASACOL, 1; Pentasa, 3).

The proportion of patients without bloody stools after the 48-week treatment period was 76.9% in the ASACOL group and 69.2% in the Pentasa group. The difference between the two groups was 7.7% (95% CI: -7.4, 22.8), and the lower limit of CI was more than "-10.0%", the critical value for demonstration of predetermined non-inferiority. The hazard ratio for time to bloody stools was 0.690 (95% CI: 0.353, 1.350). There was no significant difference in the results of the log-rank test between the two groups (p = 0.27), but the time to bloody stools (secondary endpoint) tended to be longer in the ASACOL group in comparison with the Pentasa group.

The proportion of patients without relapse was 80.0% in the ASACOL group and 79.7% in the Pentasa group. The time to relapse was prolonged in the ASACOL group compared to the Pentasa group, but the difference was not statistically significant (p = 0.79). The decrease in UC-DAI at the final assessment was -0.8 in the ASACOL group and -0.9 in the Pentasa group, respectively, and the difference between the two groups was not significant.

ASACOL 1600 mg

727 patients participated in an open label extension (OLE) of the induction study.

The daily dose of ASACOL in the maintenance phase was allocated depending on the 8 or 12-week induction results.

- Patients in clinical remission (202) at week 12 on either formulation had a dose reduction to 1.6 g/day with 70.3% (142/202) maintaining remission to week 38.
- Patients with a clinical response (274) at week 12 on either formulation continued to receive 3.2 g/day and a further 33.9% (93/274) of them went into remission.
- Initial non-responders on either formulation (243) at week 8 who responded after a further 8 weeks on 4.8 g/day plus another 8 non responders at week 12 on 3.2 g/day (total 199), remained on 4.8 g/day for another 22 weeks in the study. Of those up dosed to 4.8 g/day 26.8% (61/228) achieved a later clinical remission.

The incidence of treatment related adverse events was 13.9% (28/202), 8.8% (24/274) and 10.7% (26/243) of patients in the 1.6, 3.2 and 4.8 g/day dose groups respectively.

The incidence of SAEs in the OLE was low and independent of daily dose, with 5.0% (10/202), 4.4% (12/274) and 1.6% (4/243) of patients in the 1.6, 3.2 and 4.8 g/day dose groups affected.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

ASACOL 400 mg and 800 mg tablets consists of a tablet core which is coated with a copolymer providing the tablet a pH-dependent disintegration behaviour. Therefore ASACOL tablets resist the acidic environment of the stomach and small intestine, whereas disintegration and drug release occurs from pH 7 onwards to ensure start of drug delivery at the target site (i.e. from the terminal ileum onwards).ASACOL 1600 mg tablets contain a core of mesalazine covered by a multi-layer coating system. This system consists of a layer of methacrylic acid copolymer combined with starch particles on top of a middle alkaline buffer layer (which accelerates drug release). The coating is designed to delay release of mesalazine until intestinal fluids reach a pH of 7. The starch can be digested by colonic bacteria which also provides a second trigger for release of mesalazine from the coated tablet.

Systemic bioavailability/plasma concentrations of mesalazine are of no relevance for therapeutic efficacy, but rather a criterion for safety.

ASACOL 400 mg

After administration of a single dose of 2.4 g mesalazine (6 x ASACOL 400 mg tablets) to healthy volunteers under fasting conditions, quantifiable amounts (> 2.00 ng/mL) of mesalazine were observed in plasma after 4.5 h (median T_{lag}). The geometric mean C_{max} value of mesalazine was 722.11 ng/mL with a median T_{max} of about 9.5 h, whereas that of *N*-acetyl mesalazine was 1437.90 ng/mL with a median T_{max} of 12.0 h.

The same study showed that when administered with concomitant food intake, quantifiable amounts of mesalazine were observed after 9.0 h (median t_{lag}). The geometric mean C_{max} value of mesalazine was 1725.93 ng/mL with a median T_{max} of about 22.0 h, whereas that of *N*-acetyl mesalazine was 2235.32 ng/mL with a median T_{max} of 24.0 h.

Based on the recovery of unchanged mesalazine and the main metabolite *N*-acetyl mesalazine in collected urine after oral administration under fed conditions approximately 30% of the dose (about 90% as metabolite) was excreted renally within 60 h.

Mesalazine C_{max} values increased 2.39-fold under fed conditions, and the extent of exposure ($AUC_{0\text{-}tlast}$) increased 1.57-fold. Under the same conditions, *N*-acetyl mesalazine C_{max}-values increased 1.55-fold, whereas the extent of exposure only increased by about 1.1-fold.

ASACOL 800 mg

After administration of a single dose of 2.4 g mesalazine (3 x ASACOL 800 mg tablets) to healthy volunteers under fasting conditions, quantifiable amounts (> 2.00 ng/mL) of mesalazine were observed in plasma after 4.5 h (median T_{lag}). The geometric mean C_{max} value of mesalazine was 387.86 ng/mL with a median T_{max} of 14.0 h, whereas that of *N*-acetyl mesalazine was 971.09 ng/mL with an identical median T_{max} (i.e. 14.0 h).

The same study showed that when administered with concomitant food intake, quantifiable amounts of mesalazine were observed after 14.5 h (median t_{lag}). The geometric mean C_{max}-value of mesalazine was 653.56 ng/mL with a median t_{max} of about 30.0 h, whereas that of *N*-acetyl mesalazine was 1245.46 ng/mL with a median t_{max} of 30.0 h.

Based on the recovery of unchanged mesalazine and the main metabolite *N*-acetyl mesalazine in collected urine after oral administration under fed conditions, approximately 23% of the dose (more than 95% as metabolite) was excreted renally within 60 h.

Mesalazine C_{max}-values increased 1.69-fold, and the extent of exposure ($AUC_{0\text{-}tlast}$) increased 1.23-fold. Under the same conditions, *N*-acetyl mesalazine C_{max}-values increased 1.28-fold, whereas the extent of exposure remained practically unchanged.

ASACOL 1600 mg

A single dose of a ASACOL 1600 mg in healthy volunteers in the fasted state resulted in a 1.5-fold increase of mesalazine C_{max} and a 1.4-fold increase of AUC compared to fed state.

Distribution

About 43% mesalazine and about 78% *N*-acetyl mesalazine are bound to plasma proteins.

ASACOL 400 mg

Approximately 75% of the administered dose remains in the gut lumen and the mucosal tissue.

The mean apparent volume of distribution per kg of body weight (Vd_w) was 59.07 L/kg (geometric mean: 48.86 L/kg) after a single dose of 2.40 g of mesalazine (6 x ASACOL 400 mg tablets) in healthy volunteers under fasting conditions. Based upon the absorption of 24.8% of the administered dose, this parameter is equal to 14.65 L/kg (geometric mean: 12.12 L/kg).

ASACOL 800 mg

Approximately 77% of the administered dose remains in the gut lumen and the mucosal tissue. The mean apparent volume of distribution per kg of body weight (Vd_w) was 147.73 L/kg (geometric mean: 76.06 L/kg) after a single dose of 2.40 g of mesalazine (3 x ASACOL 800 mg tablets) in healthy volunteers under fasting conditions. Based upon the absorption of 23.2% of the administered dose, this parameter is equal to 34.27 L/kg (geometric mean: 17.65 L/kg).

ASACOL 1600 mg

The mean apparent volume of distribution (V_{dw}) was 25 L/kg.

Metabolism

Mesalazine is metabolised both by the intestinal mucosa and the liver to the inactive metabolite *N*-acetyl mesalazine. At least 90% of the drug recovered in the urine after oral administration is found as the main metabolite *N*-acetyl-mesalazine.

Excretion

ASACOL 400 mg

The elimination of mesalazine is essentially urinary and faecal in the form of mesalazine and its *N*-acetyl metabolite. The geometric mean of total apparent clearance of mesalazine after administration of 2.40 g of mesalazine (6 x ASACOL 400 mg tablets) in healthy volunteers under fasting conditions was about 135 L/h (geometric mean, CV% = 61.43%, inter-subject). The median elimination half-life was 20 h ranging from 5 to 77 h.

About 25% of the total dose administered was recovered in the urine within 60 h after fasted administration mainly as *N*-acetyl mesalazine and as the parent compound (about 1%).

ASACOL 800 mg

The elimination of mesalazine is essentially urinary and faecal in the form of mesalazine and its *N*-acetyl metabolite. The geometric mean of total apparent clearance of mesalazine after administration of 2.40 g of mesalazine (3 x ASACOL 800 mg tablets) in healthy volunteers under fasting conditions was about 318 L/h (geometric mean, CV% = 137.67%, inter-subject). The median elimination half-life was 17 h ranging from 10 to 50 h.

About 23% of the total dose administered was recovered in the urine within 60 h after fasted administration mainly as *N*-acetyl mesalazine and as the parent compound (about 1%).

ASACOL 1600 mg

The elimination of mesalazine is essentially urinary and faecal in the form of mesalazine and its *N*-acetyl metabolite. The median elimination half-life of mesalazine was 10 h range 4 to 23 h.

Linearity/non-linearity

In a cross-over design with 3 test periods and 3 ascending oral doses of ASACOL 400 mg tablets administered 6 hourly over 4 consecutive doses (total daily dose of mesalazine: 3200, 4800, 6400 mg) it was shown that the absorption and elimination kinetics for mesalazine are dose independent for the 3 doses evaluated. For each dose, about ¾ of the dose was available for the therapeutic activity for the colon. Only about ¼ of each dose was absorbed and excreted in the urine, primarily as the metabolite. Based on urine drug excretion, plasma drug C_{max} and the combined plasma AUC values, there was a linear dose response for the 3 ASACOL tablet doses. The clinical performance of ASACOL 400 mg tablets should be similar for the range of doses evaluated in this study.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of genotoxicity was observed with mesalazine in assays for bacterial gene mutation *in vitro*, mammalian cell sister chromatid exchange, chromosomal aberrations in Chinese hamster ovary cells *in vitro*, or chromosomal damage *in vivo*.

Carcinogenicity

There was no evidence of carcinogenicity in rats or mice treated with mesalazine in the diet for two years at respective doses up to 480 and 2000 mg/kg/day. In rats, estimated respective exposures (plasma AUC) of mesalazine and its metabolite *N*-acetyl-5- aminosalicyclic acid were about 4- and 2.5-fold the corresponding clinical exposures at the maximum recommended dose of ASACOL. In mice, the highest dose tested was about twice the maximum recommended human dose on a body surface area basis.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ASACOL 400 mg and 800 mg

The 400 mg and 800 mg tablet core contains: lactose monohydrate, sodium starch glycollate type A, magnesium stearate, purified talc and povidone. The film-coating contains: methacrylic acid copolymer, triethyl citrate, iron oxide yellow, iron oxide red and macrogol 6000.

ASACOL 1600 mg

The 1600 mg tablet core contains: microcrystalline cellulose, sodium starch glycollate type A, hypromellose, colloidal anhydrous silica and magnesium stearate. The film-coating contains: methacrylic acid copolymer, triethyl citrate, glycerol monostearate, maize starch, polysorbate 80, macrogol 6000, iron oxide yellow, iron oxide red, monobasic potassium phosphate and sodium hydroxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ASACOL 400 mg and 800 mg

PVC/aluminium blister strips packed in cartons containing either 30, 60, 90 or 180 tablets.

ASACOL 1600 mg

PVC/aluminium blister strips packed in cartons containing either 30, 60 or 90 tablets.

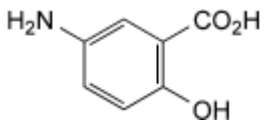
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure:



Formula: $C_7H_7NO_3$

Molecular weight: 153.1

CAS number: 89-57-6

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8. SPONSOR

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Australia
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9. DATE OF FIRST APPROVAL

21 September 2016

10. DATE OF REVISION

27 June 2023

Summary table of changes

Section changed	Summary of new information
4.4	Addition of urine discoloration after contact with sodium hypochlorite and drug reaction with eosinophilia and systemic symptoms (DRESS)
4.8	Addition of drug reaction with eosinophilia and systemic symptoms (DRESS)
All	Minor editorial changes

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