AUSTRALIAN PRODUCT INFORMATION - ASACOL® (MESALAZINE)

1 NAME OF THE MEDICINE

Mesalazine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ASACOL enteric coated tablets contain 400 mg or 800 mg mesalazine as the active ingredient as well as the following inactive excipients: lactose, sodium starch glycollate type A, magnesium stearate, purified talc, povidone, methacrylic acid copolymer, triethyl citrate, iron oxide yellow, iron oxide red, macrogol 6000.

3 PHARMACEUTICAL FORM

ASACOL enteric coated tablets are reddish to brownish oblong tablets. ASACOL 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.

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

Ulcerative Colitis

Acute disease: 2.4 g per day taken once daily or in divided doses to 4.8 g per day taken 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 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients of ASACOL
- 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

Blood dyscrasia

Serious blood dyscrasia has very rarely been 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 patients should seek immediate medical advice. It is recommended that haematological investigations (differential blood count) are performed prior to initiation of ASACOL and whilst on therapy, 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.

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myo- 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 myo- 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 Sulphasalazine

Patients with a history of adverse drug reactions to sulphasalazine 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

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, 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 coated tablets. If intact tablets are observed in the stool repeatedly, the patient should consult his/her physician.

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. Blood tests (liver function parameters such as ALT or AST) should be performed 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.

Use in renal impairment

Urinary status (dip sticks) should be determined prior to and during treatment, at the discretion of the treating physician. Caution should be exercised in patients with raised serum creatinine 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 repeatedly whilst on therapy. As a guideline, follow-up tests are recommended 14 days after commencement of treatment and then every 4 weeks for the following 12 weeks. Short monitoring intervals 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. If additional laboratory or clinical signs of renal impairment appear, these tests should be performed immediately. Treatment with ASACOL should be stopped immediately if there is evidence of renal impairment and patients should seek immediate medical advice.

Use in the elderly

Use in older people should be handled with caution and the product should only be prescribed to patients having a normal or non-severely impaired liver and renal function, see section “4.3 CONTRAINDICATIONS”.

Paediatric use

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

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.

In patients who are concomitantly treated with azathioprine, or 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, or 6-mercaptopurine or thioguanine should be taken into account. As a result, 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.

Caution should be exercised when mesalazine is used concomitantly with other known nephrotoxic agents such as NSAIDs and azathioprine, because increased risk of renal adverse effects may occur.

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 (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 epidemiologic 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)

ASACOL 800 mg tablets have been evaluated in 140 patients with mild to moderate active ulcerative colitis in one controlled study lasting for 10 weeks comparing safety and efficacy versus placebo. Treatment related adverse effects in the ASACOL group with the highest reporting rate were worsening of ulcerative colitis (3.6%), haematuria (2.9%), and ketonuria (2.1%). Table 1 enumerates treatment related adverse effects that occurred at a frequency of ≥1% in the ASACOL and placebo treated groups. All adverse effects with ASACOL 800 mg tablets were of mild to moderate severity. Discontinuations due to adverse effects occurred in 8.6% of patients in the ASACOL group and in 21.3% of patients in the placebo group. Most of the drug related adverse effects that led to study drug discontinuation were related to worsening of ulcerative colitis.

Table 1: Adverse effects related to study drug at a frequency of ≥1% from ASACOL 800 mg tablets in mild to moderate active of UC versus placebo

Adverse effects	**% from 140 patients on ASACOL 800 mg tablets**	**% from 141 patients on placebo**
Blood and lymphatic system disorders		
Anaemia	1.4	0.7
Eosinophilia	1.4	0.0
Leukocytosis	1.4	0.0
Macrocytosis	1.4	0.0

Monocytopenia	1.4	2.8
Gastrointestinal disorders		
Worsening of ulcerative colitis	3.6	8.5
Haemorrhoids	1.4	0.0
Hepatobiliary disorders		
Hyperbilirubinaemia	1.4	1.4
Nervous system disorders		
Headache	1.4	0.7
Renal and urinary disorders		
Haematuria	2.9	2.1
Ketonuria	2.1	0.7

Organ specific adverse effects 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.

The following table represents the frequency of adverse effects based on clinical trials and reports from international post-marketing surveillance for all preparations of ASACOL, including tablets, suppositories and enemas. The frequency of some adverse effects cannot be reliably estimated due to the limitation of the reporting sources.

Common ≥ 1% to < 10%	**Gastrointestinal disorders**	Dyspepsia
	Skin and subcutaneous tissue disorders	Rash
Uncommon ≥ 0.1% to < 1%	**Blood and lymphatic system disorders**	Eosinophilia (as part of an allergic reaction)
	Skin and subcutaneous tissue disorders	Urticaria, pruritus
	Nervous system disorders	Paresthesia
	General disorders and administration site conditions	Pyrexia, chest pain
Rare ≥ 0.01% to < 0.1%	**Nervous system disorders**	Headache, dizziness
	Cardiac disorders	Myocarditis, pericarditis
	Gastrointestinal disorders	Abdominal pain, diarrhoea, flatulence, nausea, vomiting
	Skin and subcutaneous tissue disorders	Photosensitivity
Very rare < 0.01%	**Blood and lymphatic system disorders**	Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia)
	Immune system disorders	Hypersensitivity reactions such as allergic exanthema,

		drug fever, lupus erythematosus syndrome, pancolitis
	Nervous system disorders	Peripheral neuropathy
	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
	Gastrointestinal disorders	Acute pancreatitis
	Hepato-biliary disorders	Changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis
	Skin and subcutaneous tissue disorders	Alopecia
	Musculoskeletal, connective tissue and bone disorders	Myalgia, arthralgia
	Renal and urinary disorders	Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency, nephrotic syndrome, renal failure which may be reversible on early withdrawal
	Reproductive system and breast disorders	Oligospermia (reversible)
Not known cannot be estimated from the available data	**Respiratory, thoracic and mediastinal disorders**	Pleurisy
	Musculoskeletal, connective tissue and bone disorders	Lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia
	General disorders and administration site conditions	Intolerance to mesalazine with C-reactive protein increased and/or exacerbation of symptoms of underlying disease
	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-mentioned adverse effects are probably associated to the underlying IBD 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 azathioprine or 6-MP 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.

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 Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Mesalazine, also known as 5-aminosalicylic acid, has an anti-inflammatory effect through a mechanism that has not yet been fully clarified. Mesalazine has been shown to inhibit LTB4-stimulated migration of intestinal macrophages and thus may reduce intestinal inflammation 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 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. Mesalazine is also an antioxidant;

it has been shown to decrease formation of reactive oxygen compounds and to capture free radicals.

Clinical Trials

Induction of remission in mild-moderate ulcerative colitis

ASACOL 400 mg tablets

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.

Treatment	**ASACOL 400mg tablets**		**Pentasa**	**Placebo**
Dose	2.4g/day	3.6g/day	2.25g/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 tablets

A multi-national, multicentre, randomised, placebo-controlled, double-blind phase III 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 tablets 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 tablets 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.

Maintenance of remission in mild-moderate ulcerative colitis

A multi-centre, randomised, double-blind study was conducted to verify the non-inferiority of ASACOL 400 mg tablets (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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

ASACOL 400 mg tablets

After administration of a single dose of 2.4 g mesalazine (as 6 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.

Based on the recovery of unchanged mesalazine and the main metabolite *N*-acetyl mesalazine in collected urine after fasted oral administration approximately 25% of the dose (more than 95% as metabolite) was excreted renally within 60 h.

The same study showed that when administered with concomitant food intake, 6 ASACOL 400 mg tablets (2.4 g mesalazine as a single dose) resulted in quantifiable amounts of mesalazine 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 tablets:

After administration of a single dose of 2.4 g mesalazine (as 3 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.

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

The same study showed that when administered with concomitant food intake, 3 ASACOL 800 mg tablets (2.4 g mesalazine as a single dose) resulted in quantifiable amounts of mesalazine 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.

Distribution

ASACOL 400 mg tablets:

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

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

Low concentrations of mesalazine and *N*-acetyl mesalazine have been detected in human breast milk. The clinical significance of this has not been determined.

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 tablets:

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 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 tablets:

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 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%).

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 Cmax 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

Refer to section “2 QUALITATIVE AND QUANTITATIVE COMPOSITION”.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ASACOL 400 mg: Store below 25°C.
ASACOL 800 mg: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

ASACOL 400 mg / 800 mg tablets are available in PVC/aluminium blister strips, each containing ten tablets. ASACOL tablets are presented as coated, reddish to brown oblong tablets with a glossy to matt finish.

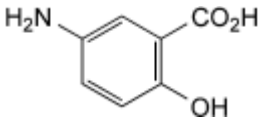
The blister strips are packed in cartons containing either 60, 90 or 180 tablets. Not all pack sizes may be marketed.

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)

S4

8 SPONSOR

Emerge Health Pty Ltd
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Hawthorn East, VIC. 3123
Australia
T: +61 3 9077 4468
E: customerservice@emergehealth.com.au

9 DATE OF FIRST APPROVAL

21st September 2016

ASACOL 400mg: *AUST R 261419*
ASACOL 800mg: *AUST R 261420*

10 DATE OF REVISION

5 March 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of photosensitivity following update to Global Company Core Data Sheet
6.3	Addition of shelf life information for consistency with the TGAs new format for PIs
8	Update of Sponsor address following office relocation