

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ASACOL 400 mg enteric coated tablet

ASACOL 800 mg enteric coated tablet

ASACOL 16.67% w/w suppository

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Enteric coated tablets

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

Excipient with known effect: lactose monohydrate 76.4 mg or 152.8 mg.

Suppositories

ASACOL suppositories contain 16.67% w/w (500 mg) mesalazine as the active ingredient.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Enteric coated 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Enteric coated tablets

Dosage for adults

Ulcerative colitis

Induction of remission: 2.4 to 4.8 g (6 to 12 of the 400 mg tablets, or 3 to 6 of the 800 mg tablets) a day in divided doses. 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 of the 400 mg tablets, or up to 3 of the 800 mg tablets) a day taken once daily or in divided doses.

Crohn's ileo-colitis

Maintenance of remission: 2.4 g (6 of the 400 mg tablets, or 3 of the 800 mg tablets) in divided doses.

Elderly patients

Except in cases of severely impaired hepatic and renal function, the dosage stated for adults can be administered, see sections 4.3 and 4.4. No studies have been performed with elderly patients.

Dosage for paediatrics/children

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

Children 6 years of age and older

Active disease: To be determined individually, starting with 30 - 50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4.0 g/day.

Maintenance treatment: To be determined individually, starting with 15 - 30 mg/kg/day in divided doses. The total dose should not exceed 2.0 g/day. It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

Method of administration

The enteric coated tablets are for oral treatment and must be taken whole. The enteric coated tablets must not be chewed, crushed or broken under any circumstances. If possible, tablets should be taken before a meal with a glass of liquid.

If one or several doses are omitted, the next dose should be taken as normal.

Suppositories

Dosage for adults

Induction of remission (proctitis and proctosigmoiditis): 1 to 2 suppositories three times per day, 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.

Maintenance of remission (distal ulcerative colitis): 1 suppository two times per day, after defecation.

Elderly patients

Except in cases of severely impaired hepatic and renal function, the dosage stated for adults can be administered (see section 4.3 and section 4.4). No studies have been performed with elderly patients.

Dosage for paediatrics/children

There is little experience and only limited documentation for an effect in children.

Method of administration

The suppositories are for rectal use and must not be swallowed. The suppositories should be inserted deep into the anus after defecation.

If one or more doses have been missed, the next dose is to be taken as usual.

4.3 CONTRAINDICATIONS

- Hypersensitivity to mesalazine or to any of the excipients listed in section 6.1
- Known hypersensitivity to salicylates
- Severe liver impairment
- Severe renal impairment (GFR < 30 mL/min/1.73 m²)
- Children under 2 years of age.

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 and then every 4 weeks for the following 12 weeks, 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 enteric coated tablets

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.

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, Use in hepatic impairment and Use in renal impairment).

Paediatric population

There is only limited documentation for an effect in children (age 6-18 years) (see section 4.2).

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 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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).

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

Pregnancy

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.

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

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

Breast-feeding

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.

Fertility

No effects on fertility have been observed.

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 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 in association with oral or combined oral and rectal mesalazine administration.

Most of these undesirable effects have not been reported following ASACOL suppository monotherapy, but were observed with oral administration. However, it cannot be excluded that these events can also occur with rectal mesalazine use alone.

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).

Tabulated summary of adverse reactions

Enteric coated tablets

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 ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 for ASACOL tablets

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)
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
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)

System Organ Class	Frequency	Reaction
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

Suppositories

Undesirable effects reported from clinical studies and other sources are listed in [Table 2](#).

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

Table 2. Adverse drug reactions by frequency and system organ class for ASACOL suppositories

System Organ Class	Frequency	Reaction
Blood and lymphatic system disorders	Very rare	Altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia)
Immune system disorders	Very rare	Hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis
Nervous system disorders	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)
	Non known	Pleurisy
Gastrointestinal disorders	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	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
Renal and urinary disorders	Very rare	Impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency
	Not known	Nephrolithiasis
Reproductive system and breast disorders	Very rare	Oligospermia (reversible)
General disorders and administration site conditions	Not known	Intolerance to mesalazine with C-reactive protein increased and/or exacerbation of symptoms underlying disease, local reaction

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).

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).

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 or suppositories 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphv.otago.ac.nz/reporting/>.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

ASACOL tablets and suppositories contain 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.

Pharmacodynamic effects

Under trial conditions mesalazine 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). Mesalazine is also an antioxidant; it has been shown to decrease formation of reactive oxygen products and to capture free radicals.

Epidemiological data indicate that continued long-term mesalazine maintenance treatment may reduce the risk of colon cancer.

Clinical efficacy and safety

Enteric coated tablets

Mild to moderate acute ulcerative colitis

ASACOL 800 mg has 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.

This indication was also investigated in seven controlled and three open clinical trials. A total of 787 patients were enrolled, of whom 559 received ASACOL 400 mg. Three studies were placebo-controlled, one of which also compared the efficacy of ASACOL to another proprietary oral mesalazine product. Five studies were performed without comparator. The studies included

dose ranges of ASACOL. One study compared the efficacy of mesalazine versus sulfasalazine. The studies included dose ranging of ASACOL from 1.2-4.8 g/day. One study used computerised morphometry to assess the efficacy of ASACOL compared with a prednisolone enema. These studies established the safety and efficacy of ASACOL for the treatment of mild to moderate acute ulcerative colitis (UC) at daily doses of 2.4-4.8 g mesalazine.

Maintenance of remission of ulcerative colitis

This indication was studied in five controlled and two open label clinical trials involving 667 patients, of whom 406 received ASACOL 400 mg. ASACOL treatment was compared to sulfasalazine in three studies, to another proprietary oral mesalazine product in one study, and to placebo in one study. The dosage varied from 0.8-4.4 g mesalazine per day. These studies established the safety and efficacy of ASACOL for the maintenance of remission of UC at daily doses of 1.6-2.4 g mesalazine.

Maintenance of remission of Crohn's ileo-colitis

This indication was studied in one double blind, one retrospective and two open label clinical studies involving 336 patients, of whom 159 received ASACOL 400 mg. ASACOL treatment was compared to sulfasalazine in one study and to placebo or no specific treatment in three studies. Two studies confirmed efficacy in preventing post-operative recurrence of Crohn's disease. These studies support the safety and efficacy of ASACOL in the treatment of quiescent Crohn's disease of the terminal ileum and colon including post-operative patients at a daily dose of 2.4 g mesalazine.

Suppositories

The clinical development of ASACOL 16.67% w/w (500 mg) suppositories included one comparative bioavailability study, one small scale tolerability and four double-blind clinical studies. The bioavailability study showed an acceptable profile in comparison to another licensed mesalazine suppository. The tolerability and clinical studies provided data supporting the safe and efficacious use. Evidence of clinical efficacy showed a statistically significant improvement in clinical, sigmoidoscopic and histological indices of disease.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Enteric coated tablets

ASACOL tablets are coated with a pH-responsive polymer which enables the release of mesalazine only at a pH above 7 (i.e. within the terminal ileum and colon) which are the main sites of inflammation in inflammatory bowel disease (IBD). After any initial disruption of the coating mesalazine will continue to be released irrespective of the pH. ASACOL tablets have been designed to minimise absorption in the digestive tract.

ASACOL 400 mg

After a single dose of 2.4 g of mesalazine (6 x ASACOL 400 mg) in 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 oral administration under fasting conditions, approximately 25% of the dose (more than 95% as metabolite) was excreted renally within 60 h.

Following concomitant food intake in the same study a single dose of 2.4 g of mesalazine 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 oral administration under fed conditions, approximately 30% of the dose (about 90% as metabolite) was excreted renally within 60 h.

Following concomitant food intake the C_{max} values of mesalazine increased 2.39-fold, and the extent of exposure ($AUC_{0-t_{last}}$) increased 1.57-fold. *N*-acetyl mesalazine after concomitant food intake the C_{max} values increased 1.55-fold, whereas its extent of exposure increased about 1.1-fold only.

ASACOL 800 mg

After a single dose of 2.4 g of mesalazine (3 x ASACOL 800 mg) in 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 administration in fasting conditions, approximately 23% of the dose (more than 95% as metabolite) was excreted renally within 60 h.

Following concomitant food intake in the same study, a single dose of 2.4 g of mesalazine 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.

Following concomitant food intake the C_{max} values of mesalazine increased 1.69-fold, and the extent of exposure ($AUC_{0-t_{last}}$) increased 1.23-fold. *N*-acetyl mesalazine after concomitant food intake the C_{max} values increased 1.28-fold, whereas its extent of exposure remained practically unchanged.

Suppositories

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. After a single dose of ASACOL 16.67% w/w (500 mg) suppositories in healthy volunteers the mean C_{max} and T_{max} were 211 ng/mL and 2.0 h for mesalazine and 443 ng/mL and 3.0 h for *N*-acetylmisalazine, respectively.

Distribution

About 43% mesalazine and about 78% *N*-acetyl mesalazine are bound to plasma proteins. Approximately 75-77% of the administered dose remains in the gut lumen and the mucosal tissue.

Enteric coated tablets

ASACOL 400 mg

The mean apparent volume of distribution per kg of body weight (V_{dw}) 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

The mean apparent volume of distribution per kg of body weight (V_{dw}) 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).

Biotransformation

Enteric coated tablets

Mesalazine is metabolised both by the intestinal mucosa and the liver to the inactive metabolite *N*-acetyl mesalazine.

ASACOL 400 mg

At least 90% of the drug recovered in the urine after oral administration is found as the main metabolite *N*-acetyl-mesalazine.

ASACOL 800 mg

About 96% of the drug recovered in the urine after oral administration is found as the main metabolite *N*-acetyl-mesalazine.

Elimination

The elimination of mesalazine is essentially urinary and faecal in the form of mesalazine and its *N*-acetyl metabolite.

Enteric coated tablets

ASACOL 400 mg

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%, intersubject). 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%).

Suppositories

Mesalazine and the main metabolite *N*-acetyl mesalazine were reported to have biological half-lives of 4.97 h and 8.32 h, respectively, following the use of ASACOL 16.67% w/w (500 mg) suppositories in healthy volunteers.

Linearity/non-linearity

Enteric coated tablets

In a cross-over design with 3 test periods and 3 ascending oral doses of ASACOL 400 mg 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 $\frac{3}{4}$ of the dose was available for the therapeutic activity for the colon. Only about $\frac{1}{4}$ 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.

Suppositories

No specific studies have been performed on ASACOL suppositories.

Pharmacokinetic/pharmacodynamic relationship(s)

No specific studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Enteric coated tablets

Tablet core: lactose monohydrate (76.4 mg or 152.8 mg), sodium starch glycollate type A, magnesium stearate (E572), purified talc (E553b) and povidone. Film-coating: methacrylic acid copolymer, triethyl citrate, iron oxide yellow (E172), iron oxide red (E172) and macrogol 6000.

Suppositories

Hard fat.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ASACOL tablets and suppositories should not be stored above 25°C. Store in the original package to protect from moisture.

ASACOL suppositories should also be stored away from direct sunlight.

6.5 NATURE AND CONTENTS OF CONTAINER

Enteric coated tablets

ASACOL 400 mg: PVC/aluminium blister strips packed in cartons containing 100 tablets.

ASACOL 800 mg: PVC/aluminium blister strips packed in cartons containing 90 or 180 tablets.

Suppositories

ASACOL 16.67% w/w: white opaque PVC/PE laminate foil strips in cartons containing 20 suppositories.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Chiesi New Zealand Limited t/a Emerge Health
58 Richard Pearse Drive
Mangere 2022
New Zealand

Phone number: 09 951 3003

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9. DATE OF FIRST APPROVAL

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10. DATE OF REVISION OF THE TEXT

30 May 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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