1 ASACOL

Asacol 400mg enteric coated tablet

Asacol 800mg enteric coated tablet

Asacol 16.67% w/w suppository

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient

Asacol 400mg enteric coated tablet:
Mesalazine (5-aminosalicylic acid, 5-ASA) 400mg in each enteric coated (gastro-resistant) tablet.
Excipient with known effect: 76.4mg lactose, see section 4.4.

Asacol 800mg enteric coated tablet:
Mesalazine (5-aminosalicylic acid, 5-ASA) 800mg in each enteric coated (gastro-resistant) tablet.
Excipient with known effect: 152.8mg lactose, see section 4.4.

Asacol 16.67% w/w (500mg) suppository:
Mesalazine (5-aminosalicylic acid, 5-ASA) 16.67% w/w (500mg) in each suppository.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Enteric coated tablets (gastro-resistant [GR]) tablets – coated red/brown oblong tablets.

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

Crohn's ileo-colitis
Maintenance of remission: 2.4g (6 of the 400mg tablets, or 3 of the 800mg 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 – 50mg/kg/day in divided doses. Maximum dose: 75mg/kg/day in divided doses. The total dose should not exceed 4.0g/day.
- *Maintenance treatment:* To be determined individually, starting with 15 – 30mg/kg/day in divided doses. The total dose should not exceed 2.0g/day. It is generally recommended that half the adult dose may be given to children up to a body weight of 40kg; and the normal adult dose to those above 40kg.

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, they 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 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.

Administration
Method of administration: rectal. The suppositories are for rectal use and must not be swallowed. If one or more doses have been missed, the next dose is to be taken as usual.

The suppositories should be inserted deep into the anus after defecation.

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 (GRF < 30mL per minute/1.73m^2).
- Children under 2 years of age.

4.4 Special warnings and precautions for use

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. If the findings are normal, follow-up tests should be carried out every three months. If additional signs appear, these tests should be performed immediately.

Renal impairment

Caution should be exercised in patients with raised serum creatinine or proteinuria. The possibility of mesalazine-induced nephrotoxicity must be considered in patients developing renal impairment during treatment.

Treatment with Asacol should be stopped *immediately* at the onset of renal impairment and patients should seek *immediate* medical advice.

Blood dyscrasia

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

Hepatic impairment

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

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myocarditis and pericarditis) have rarely been reported with Asacol. In cases of known, previous mesalazine-induced cardiac hypersensitivity Asacol must not be administered. Caution should be exercised in patients with previous myocarditis or pericarditis of allergic origin regardless of its cause.

Pulmonary disease

Patients with pulmonary disease, especially asthma, should be monitored with particular care during treatment with Asacol.

Hypersensitivity to products containing sulphasalazine

In patients with known hypersensitivity to sulphasalazine, treatment with Asacol should be initiated only under careful medical supervision. Treatment must be stopped *immediately* if acute symptoms of intolerance occur, such as cramps, abdominal pain, fever, severe headache or rash.

Gastric and duodenal ulcers

On theoretical grounds, treatment should commence with caution in case of existing gastric or duodenal ulcers.

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

Tablets in stool
There have been a limited number of reports of intact tablets in the stool. These seemingly intact tablets may, in some cases, represent largely empty shells from the coated tablets. If tablets are observed in the stool repeatedly, the patient should consult his/her physician.

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

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs), including 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.

Use in elderly
In elderly patients, Asacol is recommended for use only when renal and hepatic function is normal and should generally proceed with caution, see section 4.3.

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

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.

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 sections 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
Fertility
No effects on fertility have been observed.

Pregnancy
There are no adequate data from the use of Asacol in pregnant women. However, in a limited number of pregnant women exposed to mesalazine (627), no negative effects were found with regard to pregnancy or foetal/neonatal health. No other relevant epidemiological data are currently available. In one isolated case during long-term use of a high mesalazine dose (2 – 4g, oral) during pregnancy, renal failure was observed in one newborn infant.

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 when the expected benefit outweighs the potential risk.

Lactation
Low concentrations of mesalazine and its N-acetyl metabolite have been detected in human breast milk. The clinical significance of this is not known. To date, there is only limited experience during breastfeeding in women. Hypersensitivity reactions such as infant diarrhoea cannot be excluded. Therefore, Asacol should only be used during breastfeeding when the expected benefit outweighs the potential risk. If the infant develops diarrhoea, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines
No relevant studies have been carried out. No relevant effects on the ability to drive and use machines are anticipated.

4.8 Undesirable effects
A1) Summary of the safety profile – enteric coated tablets
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 Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

A2) Summary of the safety profile - suppositories
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 500 mg suppositories 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 Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

B1) Tabulated Summary of Adverse Reactions – enteric coated tablets
The following frequencies are used for the evaluation of adverse reactions:

Very common: ≥ 1/10; common: ≥ 1/100 and < 1/10, uncommon: ≥ 1/1,000 and < 1/100, rare: ≥ 1/10,000 and < 1/1,000, very rare: < 1/10,000, not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Uncommon:	eosinophilia (as part of an allergic reaction)
Very rare:	abnormal blood count (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, 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.
Not known: pleurisy.

Gastrointestinal disorders

Common: dyspepsia
Rare: abdominal pain, diarrhoea, flatulence, nausea, vomiting
Very rare: acute pancreatitis.

Hepatobiliary disorders

Very rare: change 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: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone 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 discontinuation of treatment.
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 and/or exacerbation of symptoms of underlying disease.

Investigations

Not known: elevated blood creatinine levels, weight loss, creatinine clearance decreased, amylase increased, erythrocyte sedimentation rate increased, lipase increased, blood urea nitrogen (BUN) increased.

B2) Tabulated summary of adverse reactions – suppositories

The following frequencies are used for the evaluation of adverse reactions:

Very common: ≥ 1/10; common: ≥ 1/100 and < 1/10, uncommon: ≥ 1/1,000 and < 1/100, rare: ≥ 1/10,000 and < 1/1,000, very rare: < 1/10,000, not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very rare: altered blood counts (aplastic anaemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, 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).

Not known: pleurisy.

Gastrointestinal disorders

Rare: abdominal pain, diarrhoea, flatulence, nausea, vomiting.

Very rare: acute pancreatitis.

Hepato-biliary disorders

Very rare: changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis.

Skin and subcutaneous tissue disorders

Rare: photosensitivity

Very rare: alopecia.

Not known: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone 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 of underlying disease, local reaction.

C) Description of selected adverse reactions
An unknown number of the above undesirable effects are probably related to the underlying chronic inflammatory bowel disease rather than to treatment with **Asacol**. This is particularly valid for adverse gastrointestinal effects.

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-MP 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.

D) Paediatric population
There is only limited safety experience with the use of **Asacol** tablets or **Asacol** 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 are few data with regard to overdose (e.g. intended suicide with high oral doses of mesalazine), which do not indicate renal or hepatic toxicity. There is no specific antidote. Treatment is symptomatic and supportive.

For advice on the management of overdose please contact the National Poisons Centre (New Zealand) on: 0800 POISON [0800 764 766] or (Australia) phone 131126.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group:	*ATC Code:*
Intestinal anti-inflammatory agents	A07EC02

Mechanism of action
Asacol tablets and suppositories contain mesalazine (5-aminosalicylic acid), which has anti-inflammatory properties through a mechanism of action that has not yet been fully clarified. Mesalazine has been shown to inhibit LTB_4-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 (LTB_4 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.

Pharmacodynamic effects
Under trial conditionsmesalazine inhibited the cyclooxygenase and thus, the release of thromboxane B_2 and prostaglandin E_2but 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 800mg enteric coated 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.

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 400mg enteric coated tablets. 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 ranging 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 UC at daily doses of 2.4 – 4.8g 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 400mg enteric coated tablets. 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 – 4.4g 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 – 2.4g 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 400mg enteric coated tablets. 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 2.4g mesalazine.

Clinical efficacy and safety – suppositories
Induction of remission of mild to moderate proctitis and proctosigmoiditis.
Maintenance of remission of mild to moderate proctitis.
The clinical development of Asacol 16.67% w/w (500mg) 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

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 IBD. After any initial disruption of the coating mesalazine will continue to be released irrespective of the pH. Asacol tablets Asacol been designed to minimize absorption in the digestive tract.

400mg GR tablets

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

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 60h.

Following concomitant food intake in the same study a single dose of 2.4g of mesalazine resulted in quantifiable amounts of mesalazine after 9.0h (median t_{lag}). The geometric mean C_{max}–value of mesalazine was 1725.93ng/mL with a median t_{max} of about 22.0h, whereas that of N-acetyl mesalazine was 2235.32ng/mL with a median t_{max} of 24.0h.

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

Following concomitant food intake the C_{max}-values of mesalazine increased 2.39-fold, and the extent of exposure ($AUC_{0\text{-}t\ last}$) increased 1.57-fold. Concerning 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.

800mg GR tablets

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

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 60h.

Following concomitant food intake in the same study, a single dose of 2.4g of mesalazine resulted in quantifiable amounts of mesalazine after 14.5h (median t_{lag}). The geometric mean C_{max}-value of mesalazine was 653.56ng/mL with a median t_{max} of about 30.0h, whereas that of N-acetyl mesalazine was 1245.46ng/mL with a median t_{max} of 30.0h.

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

Following concomitant food intake the C_{max}-values of mesalazine increased 1.69-fold, and the extent of exposure ($AUC_{0\text{-}t\ last}$) increased 1.23-fold. Concerning 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 (500mg) suppositories in healthy volunteers the mean C_{max} and T_{max} were 211ng/mL and 2.0 hours for mesalazine and 443ng/mL and 3.0 hours for N-acetylmesalazine, respectively. About 43% of mesalazine and about 78% of N-acetyl mesalazine are bound to plasma proteins.

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.

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

800mg GR Tablets
The mean apparent volume of distribution per kg of body weight (Vdw) was 147.73L/kg (geometric mean: 76.06L/kg) after a single dose of 2.40g of mesalazine (3 enteric coated tablets of Asacol 800mg) in healthy volunteers under fasting conditions. Based upon the absorption of 23.2% of the administered dose, this parameter is equal to 34.27L/kg(geometric mean: 17.65L/kg).

All presentations of Asacol, low concentrations of mesalazine and N-acetyl mesalazine have been detected in human breast milk. The clinical significance of this has not been determined.

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

400mg GR Tablets
At least 90% of the drug recovered in the urine after oral administration is found as the main metabolite N-acetyl-mesalazine.

800mg GR Tablets
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.

400mg GR Tablets
The geometric mean of total apparent clearance of mesalazine after administration of 2.40g of mesalazine (6 enteric coated tablets of Asacol 400mg) in healthy volunteers under fasting conditions was about 135L/h (geometric mean, CV% = 61.43%, intersubject). The median elimination half-life was 20h ranging from 5 to 77h.

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

800mg GR 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 2.40g of mesalazine (3 enteric coated tablets of Asacol 800mg) in healthy volunteers under fasting conditions was about 318L/h (geometric mean, CV% = 137.67%, intersubject). The median elimination half-life was 17h ranging from 10 to 50h.

About 23% of the total dose administered was recovered in the urine within 60h 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 hours and 8.32 hours, respectively, following the use of Asacol 16.67% w/w (500mg) suppositories in healthy volunteers.

Linearity/non-linearity
In a cross-over design with 3 test periods and 3 ascending oral doses of Asacol 400mg enteric coated tablets administered 6 hourly over 4 consecutive doses (total daily dose of mesalazine: 3200, 4800, 6400mg) 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}'s and the combined plasma AUC's, there was a linear dose response for the 3 Asacol tablet doses. The clinical performance of Asacol enteric coated tablets should be similar for the range of doses evaluated in this study.

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: 76.4 or 152.8mg lactose monohydrate, sodium starch glycolate (type A), magnesium stearate (vegetable) E 572, talc E553b, povidone.

Film-coating: methacrylic acid - methyl methacrylate copolymer (1 : 2), 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.

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

Asacol must be kept out of the reach of children.

6.5 Nature and contents of container
Asacol 400mg enteric coated tablets are available in PVC/aluminium blister strips, each containing ten tablets. The blister strips are packed in cartons containing 100 tablets (10 strips).

Asacol 800mg enteric coated tablets are available in PVC/aluminium blister strips, each containing ten tablets. The blister strips are packed in cartons containing 90 or 180 tablets (9 or 18 strips).

Asacol 16.67% w/w (500mg) suppositories are available in white opaque PVC/PE laminate foil strips each containing five suppositories. The laminate foil strips are packed in cartons containing 20 suppositories (4 laminate foil strips).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
There are no special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

7 MEDICINE SCHEDULE
Prescription Only Medicine.

8 SPONSOR
Asacol is distributed in New Zealand by:

Chiesi New Zealand Ltd
58 Richard Pearse Drive
Airport Oaks Mangere 2022
New Zealand
Email: medicalaffairs.au@chiesi.com

9 DATE OF FIRST APPROVAL

Asacol *400mg enteric coated/gastro-resistant Tablets: TT50-4507*
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
24 February 1994.

Asacol *800mg enteric coated/gastro-resistant Tablets: TT50-4507b*
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
19 September 2013.

Asacol 16.67% w/w (500mg) suppositories: TT50-4507/1
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
7 February 1997.

10 DATE OF REVISION OF THE TEXT

14 April 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
8	Change in sponsor name

Based on ASACOL 400mg enteric coated tablets, ASACOL 800mg enteric coated tablets & ASACOL 16.67% w/w (500mg) suppositories *SPC revised November 2016.*

*Please refer to the Medsafe website (*www.medsafe.govt.nz*) for most recent data sheet.*

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