**ASACOL™**

*Mesalazine (5-aminosalicylic acid) ASACOL 400mg enteric coated/gastro-resistant tablets*

*Mesalazine (5-aminosalicylic acid) ASACOL 800mg enteric coated/gastro-resistant tablets*

*Mesalazine (5-aminosalicylic acid) ASACOL 500mg (16.67% w/w) suppositories*

**QUALITATIVE & QUANTITATIVE COMPOSITION**

**ASACOL 400mg enteric coated/gastro-resistant Tablets**

Each gastro-resistant tablet contains 400mg mesalazine. Excipient with known effect: 76.4mg lactose, see *Clinical Particulars/Special Warnings and Precautions for Use*. For the full list of excipients, see *Pharmaceutical Particulars/List of Excipients*.

**ASACOL 800mg enteric coated/gastro-resistant Tablets**

Each gastro-resistant tablet contains 800mg mesalazine. Excipient with known effect: 152.8mg lactose, see *Clinical Particulars/Special Warnings and Precautions for Use*. For the full list of excipients, see *Pharmaceutical Particulars/List of Excipients*.

**ASACOL 500mg (16.67% w/w) Suppositories**

Each suppository contains 500mg mesalazine. For the full list of excipients, see *Pharmaceutical Particulars/List of Excipients*.

**PHARMACEUTICAL FORM**

Enteric coated tablets OR gastro-resistant (GR) tablets - coated red/brown oblong tablets.

Suppositories – light grey-brown, torpedo-shaped suppositories.
CLINICAL PARTICULARS

Therapeutic Indications

Gastro-resistant 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.

POSOLOGY & METHOD OF ADMINISTRATION

Gastro-resistant Tablets

**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.

Older People: The normal adult dose can be taken unless liver or renal function is severely impaired (see Clinical Particulars/Contraindications and Special Warnings and Precautions for Use). No studies have been carried out in older people.

Paediatric Population: Asacol 400mg and 800mg Tablets:

There is 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 4.0 g/day.
• **Maintenance treatment**: To be determined individually, starting with 15-30mg/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.

Asacol 500mg Suppositories:

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

**Route of administration**: oral.

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.

**Suppositories**

**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.

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

**Elderly Patients**: The normal adult dose can be used unless liver or renal function is severely impaired (see Clinical Particulars/Contraindications and Special Warnings and Precautions for Use). No studies have been carried out in the elderly.

**Paediatric Population**: There is little experience and only limited documentation for an effect in children.

**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.
CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Pharmaceutical Particulars/List of Excipients).
- Known hypersensitivity to salicylates.
- Severe liver impairment.
- Severe renal impairment (GRF < 30mL per minute/1.73m²).
- Children under 2 years of age.

SPECIAL WARNINGS & SPECIAL PRECAUTIONS FOR USE

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.

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.

**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.

**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 very carefully monitored during treatment with ASACOL.

**Adverse 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, on gastro-resistant tablets, with rare hereditary problems of galactose intolerance, the 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.

Older People

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 Clinical Particulars/Contraindications).

Paediatric Population

There is only limited documentation for an effect in children (age 6 – 18 years) (see Clinical Particulars/Posology and Method of Administration).

INTERACTION WITH OTHER MEDICINAL PRODUCTS & 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 Clinical Particulars/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.

FERTILITY, PREGNANCY & LACTATION

Pregnancy

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 the 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 – 4g, orally) during pregnancy, renal failure in a neonate was reported.

Animal studies on oral mesalazine 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.

**Effects on Ability to Drive & Use Machines**

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

**UNDESIRABLE EFFECTS**

**A1) Summary of the Safety Profile – Gastro-resistant Tablets**

ASACOL 800mg GR 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 undesirable 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 undesirable effects that occurred at a frequency of ≥1% in the ASACOL and placebo treated groups. All undesirable effects with ASACOL 800mg GR Tablets were of mild to moderate severity. Discontinuations due to adverse reactions 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 reactions that led to study drug discontinuation were related to worsening of ulcerative colitis.
| Table 1: Undesirable effects related to study drug at a frequency of ≥1% from ASACOL 800mg GR Tablets in mild to moderate active of UC versus placebo. |
|---------------------------------|---------------------------------|---------------------------------|
| Adverse events                  | % from 140 patients on ASACOL 800mg GR 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 clitis  | 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 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.

**A2) Summary of the Safety Profile - Suppositories**

The ASACOL clinical trial database includes 246 patients treated with ASACOL 500mg suppositories. The mesalazine doses were in the range of 1.0g/day to 1.5g/day, the treatment duration varied between four weeks and twelve months.

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 500mg suppositories monotherapy, but were observed with oral mesalazine 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.
B1) Tabulated Summary of Adverse Reactions – Gastro-resistant Tablets

In addition to the undesirable effects reported above in a clinical trial with ASACOL 800mg GR Tablets, undesirable effects relevant for the labelling reported from eight (8) double-blind and five (5) open label clinical studies with 739 patients treated with ASACOL 400mg GR tablets and information from spontaneous reporting, the literature and the EU Mesalazine Core Safety Profile of 07 April 2011 is listed below. The frequency of some reactions cannot be reliably estimated due to the limitation of the reporting sources.

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: altered blood counts (aplastic anemia, 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.

Gastrointestinal disorders
Common: dyspepsia.
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
Common: rash.
Uncommon: urticaria, pruritus.
Very rare: alopecia.

Musculoskeletal, connective tissue and bone disorders
Very rare: myalgia, arthralgia.
Not known: lupus-like syndrome with pericarditis and pleuroperticarditis 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.

Reproductive system and breast disorders
Very rare: oligospermia (reversible).

General disorders and administration site conditions

Investigations
Not known: blood creatinine increased, weight decreased, creatinine clearance decreased, amylase increased, red blood cell sedimentation rate increased, lipase increased, BUN increased.

B2) Tabulated Summary of Adverse Reactions – Suppositories

Undesirable effects relevant for the labelling reported from four double-blind clinical studies and one open clinical trial, from spontaneous reporting, the literature and the EU Mesalazine Core Safety Profile (7 April 2011) is listed below. The frequency of some reactions cannot be reliably estimated due to the limitation of the reporting sources.

Common: $\geq 1/100$ and $< 1/10$, uncommon: $\geq 1/1,000$ and $< 1/100$, rare: $\geq 1/10,000$ to $< 1/1000$, very rare: $< 1/10,000$

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
- Rare: allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis).
- Very rare: allergic and fibrinotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis).

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
- Very rare: alopecia.

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.

Reproductive system and breast disorders
- Very rare: oligospermia (reversible).

C) Description of Selected Adverse Reactions

An unknown number of the above mentioned undesirable effects are probably associated to the underlying IBD rather than ASACOL/mesalazine medication. This holds true especially for gastrointestinal undesirable effects.

To avoid blood dyscrasia resulting from developing bone marrow depression patients should be monitored with care, see Clinical Particulars/Special Warnings & Precautions for Use.

Under co-administration of mesalazine with immunosuppressive drugs such as azathioprine, or 6-MP, or thioguanine life-threatening infection can occur, see Clinical Particulars/Interactions with Other Medicinal Products and Other Forms of Interaction.
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 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 via the national reporting system.

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.

PHARMACOLOGICAL PROPERTIES

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 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.

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 – gastro-resistant tablets

Mild to moderate acute ulcerative colitis

ASACOL 800mg GR 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 GR 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 GR 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 – 2.4 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 400mg GR 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 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.
Pharmacokinetic Properties - Gastro-resistant Tablets

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 have been designed to minimize absorption in the digestive tract.

400mg GR tablets
After a single dose of 2.4g of mesalazine (6 ASACOL 400mg GR 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-t \text{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 GR 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-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 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-acetyl mesalazine, 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 (V_{dw}) was 59.07L/kg (geometric mean: 48.86L/kg) after a single dose of 2.40g of mesalazine (6 GR 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 (V_{dw}) was 147.73L/kg (geometric mean: 76.06L/kg) after a single dose of 2.40g of mesalazine (3 GR 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 GR 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 GR 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 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 GR 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 % 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 \( C_{\text{max}} \)'s and the combined plasma AUC’s, there was a linear dose response for the 3 ASACOL tablet doses. The clinical performance of ASACOL GR 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.

**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.

**PHARMACEUTICAL PARTICULARS**

**List of Excipients**

**ASACOL gastro-resistant tablets**
*Tablet core:* lactose monohydrate, sodium starch glycolate (type A), magnesium stearate (vegetable origin) E 572, talc E553b, povidone.

*Film-coating:* methacrylic acid - methyl methacrylate copolymer (1 : 2), triethylcitrate, ferric oxide yellow (E172), ferric oxide red (E172) and, macrogol 6000.

**ASACOL suppositories**
Hard fat.

**Incompatibilities**
Not applicable.

**Shelf life**
ASACOL suppositories and tablets: 3 years.

**Special Storage Precautions**
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.

**Nature and Contents of Container**

ASACOL 400mg GR 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 GR tablets are available in PVC/aluminium blister strips, each containing ten tablets. The blister strips are packed in cartons containing 60, 90 or 180 tablets (6, 9 or 18 strips).

ASACOL 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.

**Directions for Use/Handling**

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

**Special Precautions for Disposal**

Tablets and Suppositories: No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**MEDICINE CLASSIFICATION**

Prescription Medicine.

**NAME & ADDRESS**

**New Zealand**

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MARKETING AUTHORISATION NUMBERS

ASACOL 400mg enteric coated/gastro-resistant Tablets: TT50-4507
ASACOL 800mg enteric coated/gastro-resistant Tablets: TT50-4507b
ASACOL 500mg (16.67% w/w) Suppositories: TT50-4507/1

DATE OF PREPARATION

22 May 2014

Based on ASACOL 400mg tablets, ASACOL 800mg tablets & ASACOL 500mg suppositories SPC revised February 2014.

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

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