

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Asacolon 800mg Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro resistant tablet contains: 800mg mesalazine

Excipient with known effect: 152.8mg lactose, see section 4.4.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

The tablets are reddish to brownish and oblong-shaped.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Asacolon is indicated in adults, children above 6 years and adolescents:

For the treatment of mild to moderate acute ulcerative colitis. For the maintenance of remission of ulcerative colitis.

For the maintenance of surgically-induced remission of Crohn's Disease.

4.2 Posology and method of administration

Posology

Adults:

Ulcerative colitis:

Induction of remission:

2.4 g (3 tablets) per day once daily or in divided doses. If required the dose may be increased to 4.8 g (6 tablets) per day in divided doses. Above 2.4 g daily in divided doses only.

The dosage can be adjusted in accordance with the response to the treatment.

Maintenance of remission:

1.6 to 2.4 g (2 to 3 tablets) per day once daily or in divided doses.

Crohn's disease :

Maintenance of remission:

2.4 g (3 tablets) per day once daily or in divided doses.

Older people

The normal adult dose can be taken unless liver or renal function is severely impaired (see section 4.3 and 4.4). No studies have been carried out in older people.

Paediatric population

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 30-50 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.

Method 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.

4.3 Contraindications

- Hypersensitivity to salicylates.
- Hypersensitivity to the active substance or to any of the excipients (see section 6.1).
- Severe renal impairment (GFR less than 30 mL/min/1.73 m²).
- Severe liver impairment.
- Children under the age of 2 years.

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

Asacolon should not be used in patients with impaired renal function. 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.

Treatment with Asacolon should be stopped immediately if there is evidence of renal impairment and patients should seek immediate medical advice.

Nephrolithiasis

Cases of nephrolithiasis have been reported with the use of mesalazine including stones with a 100% mesalazine content. It is recommended to 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.

Blood dyscrasia

Serious blood dyscrasia has very rarely been reported. Treatment with Asacolon should be stopped immediately if there is a suspicion or evidence of blood dyscrasia (signs of unexplained bleeding, haematoma, purpura, anaemia, persistent fever or sore throat) 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 recommended if Asacolon is administered to patients with liver impairment.

Cardiac hypersensitivity reactions

Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have rarely been reported with Asacolon. In case of a suspected mesalazine-induced cardiac hypersensitivity Asacolon must not be reintroduced. Caution should be taken in patients with previous myo- and 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 Asacolon.

Adverse drug reactions to Sulphasalazine

Patients with a history of adverse drug reactions to sulphasalazine therapy should be kept close under 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.

Tablets in stool

A limited number of reports of intact tablets in 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.

Intolerance to carbohydrates

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

Older patients

Use in older patients 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 4.3.

Paediatric population

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

Pharmaceutical excipients of special interest

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, i.e. is essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

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

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

As a result, life-threatening infection can occur.

Patients should be closely observed for signs of infection and myelosuppression. Haematological parameters, especially the leukocyte, 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 Asacolone in pregnant women. However, data from a limited number of exposed pregnancies indicate no adverse effect of mesalazine on the pregnancy or on the health of the fetus/newborn child. To date no other relevant epidemiologic data are available.

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

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

Asacolone 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, Asacolone 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

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

4.8 Undesirable effects

a) Summary of the safety profile

Asacolone 800 mg 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 another 141 patients treated with placebo. Treatment related undesirable effects in the Asacolone group with the highest reporting rate were worsening of ulcerative colitis (3.6%), haematuria (2.9%), and ketonuria (2.1%). All undesirable effects with Asacolone 800 mg GR Tablets were of mild to moderate severity. Discontinuations due to adverse reactions occurred in 8.6% of patients in the Asacolone 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.

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).

b) Tabulated summary of adverse reactions

Undesirable effects reported from clinical studies with patients treated with Asacolone 400 mg GR tablets and other sources are listed below.

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)	Frequency not known
Blood and lymphatic system disorders	--	eosinophilia (as part of an allergic reaction).	--	altered blood counts (aplastic anemia, agranulocytosis, pancytopenia, neutropenia, leucopenia,	--

				thrombocytopenia).	
Immune system disorders	--	--	--	hypersensitivity reactions such as allergic exanthema, drug fever, lupus erythematosus syndrome, pancolitis.	--
Nervous system disorders	--	paresthesia.	headache, dizziness.	peripheral neuropathy.	--
Cardiac disorders	--	--	myocarditis, pericarditis.	--	--
Respiratory, thoracic and mediastinal disorders	--	--	--	allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), interstitial pneumonia, eosinophilic pneumonia, lung disorder.	pleurisy
Gastrointestinal disorders	dyspepsia.	--	abdominal pain, diarrhoea, flatulence, nausea, vomiting.	acute pancreatitis	--
Hepato-biliary disorders	--	--	--	changes in liver function parameters (increase in transaminases and cholestasis parameters), hepatitis, cholestatic hepatitis.	--
Skin and subcutaneous tissue disorders	rash.	urticaria, pruritus.	photosensitivity* * see section c)	alopecia.	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal, connective tissue and bone disorders	--	--	--	myalgia, arthralgia.	lupus-like syndrome with pericarditis and pleuropericarditis as prominent symptoms as well as rash and arthralgia.
Renal and urinary disorders	--	--	--	impairment of renal function including acute and chronic interstitial nephritis and renal	Nephrolithiasis** ** see section 4.4 for further information

				insufficiency, nephrotic syndrome, renal failure which may be reversible on early withdrawal.	
Reproductive system and breast disorders	--	--	--	oligospermia (reversible).	--
General disorders and administration site conditions	--	pyrexia, chest pain.	--	--	intolerance to mesalazine with C-reactive protein increased and/or exacerbation of symptoms of underlying disease
Investigations	--	--	--	--	blood creatinine increased, weight decreased, creatinine clearance decreased, amylase increased, red blood cell sedimentation rate increased, lipase increased, BUN increased.

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, 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-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 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 HPRC Pharmacovigilance; Earlsfort Terrace IRL-Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Asacol contains mesalazine, also known as 5-aminosalicylic acid, which has 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. Recently 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.

Clinical efficacy and safety

Mild to moderate acute ulcerative colitis

One placebo controlled, double-blind trial has been conducted with Asacolone 800 mg GR Tablets including 281 patients with mild to moderate UC. The primary outcome was clinical remission (UCDAI, stool frequency and bleeding scores of 0, and no fecal urgency) at week 6. Due to misclassification of some of the sigmoidoscopy readings at recruitment, a post hoc analysis was performed restricting analysis to UC patients with the endoscopically active disease confirmed by an independent reader.

Overall, 35.1% of patients (40 of 114) in the Asacolone 800 group and 20.9% of patients (23 of 110) in the placebo group showed clinical remission resulting in an absolute difference in remission rate of 14.2% (P = .018; 95% CI of the between-group difference, 2.4%–25.4%).

Maintenance of remission of ulcerative colitis

The efficacy of Asacolone 400 was investigated in a double blind randomized placebo-controlled study including 264 patients. Treatment success Asacolone 400 (0.8 g/day and 1.6 g/day) was compared by endoscopic evaluation at the 6-month endpoint with the placebo group by using the Fischer exact test. In the intention-to-treat analysis of all patients, 42 of 87 patients (48.3%) in the placebo group had treatment success compared to 57 of the 90 patients (63.3% [CI, 52.8% to 73.8%]) in the group receiving 0.8 g/day (P= 0.050) and 61 of the 87 patients (70.1% [CI, 59.9% to 80.3%]) in the group receiving 1.6 g/day (P= 0.005). Asacolone 400 mg GR Tablets were safe and effective in maintaining remission in quiescent ulcerative colitis.

Maintenance of surgically-induced remission of Crohn's Disease

One open-label study in 15 collaborating centres enrolled 110 CD patients operated for Crohn's disease by first intestinal resection, of which 47 evaluable patients treated with Asacolone 400 (2.4 g/day) were compared to 48 patients given no treatment. The cumulative proportion of recurrence at 6, 12 and 24 months was significantly lower in the mesalazine group than in the untreated group (P=0.002). At 24 months the cumulative proportions of endoscopic recurrence were 0.52 (\pm 0.12) (\pm S.E.M.) and 0.85 (\pm 0.07), respectively. The cumulative proportions of severe recurrence was also significantly lower in the Asacolone 400 group 0.17 (\pm 0.09) vs. 0.38 (\pm 0.09); P=0.021. The results of the study indicate that Asacolone 400 mg GR Tablets are safe and delay the recurrence and lessens the severity of the disease at 2 years.

5.2 Pharmacokinetic properties

Absorption

Asacolone 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. Asacolone tablets have been designed to minimize the absorption of mesalazine from the digestive tract.

After a single dose of 2.4 g of mesalazine (3 Asacolone 800 mg GR Tablets) 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 387.86ng/mL with a median t_{max} of 14.0 h, whereas that of N-acetyl mesalazine was 971.09 ng/mL with an identical median t_{max}, i.e. 14.0 h.

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

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 fed administration, 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. Concerning N-acetyl mesalazine after concomitant food intake the C_{max} -values increased 1.28-fold, whereas its extent of exposure remained practically unchanged.

Distribution

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

The mean apparent volume of distribution per kg of body weight ($V_{d,w}$) was 147.73 L/kg (geometric mean: 76.06 L/kg) after a single dose of 2.40 g of mesalazine (3 GR tablets of Asacol 800 mg) in healthy volunteers under fasting conditions. Based upon the absorption of 23.2% of the administered dose, this parameter is equal to 34.27 L/kg (geometric mean: 17.65 L/kg). Low concentrations of mesalazine and N-acetyl mesalazine have been detected in human breast milk. The clinical significance of this has not been determined.

Biotransformation

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

The geometric mean of total apparent clearance of mesalazine after administration of 2.40 g of mesalazine (3 GR tablets of Asacol 800 mg) 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%).

Linearity/non-linearity

In a cross-over design with 3 test periods and 3 ascending oral doses of Asacol 400 mg GR Tablets administered 6 hourly over 4 consecutive doses (total daily dose of mesalazine: 3200, 4800, 6400 mg) it was shown that the absorption and elimination kinetics for mesalazine are dose independent for the 3 doses evaluated.

For each dose, about $\frac{3}{4}$ 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} 's and the combined plasma AUC's, there was a linear dose response for the 3 Asacol tablet doses. The clinical performance of Asacol should be similar for the range of doses evaluated in this study.

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

Lactose monohydrate
Sodium starch glycolate
Magnesium stearate (E572)
Talc (E553b)
Povidone

Film Coating

Methacrylic acid-methyl methacrylate copolymer (1:2)

Talc

Triethyl citrate

Yellow pigment (ferric oxide) (E172)

Macrogol 6000

Red pigment (ferric oxide) (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister strips of aluminium foil and PVC, and outer cardboard carton containing 90 tablets per pack.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillotts Pharma GmbH
Warmbacher Strasse 80
DE- 79618 Rheinfeldern
Germany

8 MARKETING AUTHORISATION NUMBER

PA2018/001/002

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