Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Asacolon 400mg Gastro-Resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains: Mesalazine 400mg.

Excipient with known effect: 76.4 mg 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 (6 tablets) per day once daily or in divided doses. If required the dose may be increased to 4.8 g (12 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:
1.2 to 2.4 g (3 to 6 tablets) per day once daily or in divided doses.

Crohn's disease:
Maintenance of remission:
2.4 g (6 tablets) per day once daily or in divided doses.

Older people
As for adults above unless liver or renal function is severely impaired (see section 4.3 and 4.4). No studies have been carried out 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 mesalazine or any of the excipients (see section 6.1).
- Severe renal impairment (GFR less than 30 mL/min/1.73 m^2).
- 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.

Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g. in toilets cleaned with sodium hypochlorite contained in certain bleaches).

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.

Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

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, such as 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 been reported rarely 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.

Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

Pulmonary disease
Patients with pulmonary disease, in particular asthma, should be very carefully monitored during treatment with Asacolon.

Hypersensitivity 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.

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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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 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 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 Asacolon 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.
Asacolon 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, Asacolon 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

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

4.8 Undesirable effects

a) Summary of the safety profile
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 Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

b) Tabulated summary of adverse reactions
Undesirable effects reported from clinical studies with patients treated with Asacolon 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.	Idiopathic intracranial hypertension (see section 4.4)
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	--
Hepatobiliary 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.	Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
Musculoskeletal and connective tissue 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 insufficiency, nephrotic syndrome, renal failure which may be reversible on early withdrawal.	Nephrolithiasis** ** see section 4.4 for further information
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 Asacolon/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 Asacolon 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 HPRA Pharmacovigilance, Website: www.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
Asacolon 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. 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 B_2 and prostaglandin E_2, 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

This indication was investigated in a double blind, randomised study with 229 patients. In the full analysis set (n=225), the UC-DAI reductions calculated between initiation and end of therapy after 8 weeks treatment were 1.5 in the 2.4 g/day Asacolon 400 group, 2.9 in the 3.6 g/day Asacolon 400 group, 1.3 in the 2.25 g/day active comparator group and 0.3 in the placebo group. Treatment with 3.6 g/day Asacolon 400 was superior to 2.25 g/day mesalazine comparator drug (P=0.003). No significant differences were seen in the safety profiles of all treatments.

Maintenance of remission of ulcerative colitis

The efficacy of Asacolon 400 was investigated in a double-blind randomised placebo-controlled study including 264 patients. Treatment success in the two Asacolon 400 groups (0.8 g/day and 1.6 g/day) was compared by endoscopic evaluation at the 6-month endpoint 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). Asacolon 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 Asacolon 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 (±0.12) (±S.E.M.) and 0.85 (±0.07), respectively. The cumulative proportions of severe recurrence was also significantly lower in the Asacolon 400 group 0.17 (±0.09) vs. 0.38 (±0.09); P=0.021. The results of the study indicate that Asacolon 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
Asacolon 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. Asacolon tablets have been designed to minimise absorption in the digestive tract.

After a single dose of 2.4 g of mesalazine (6 Asacolon 400 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 722.11 ng/mL with a median t_{max} of about 9.5 h, whereas that of N-acetyl mesalazine was 1437.90 ng/mL with a median t_{max} of 12.0 h.

Based on the recovery of unchanged mesalazine and the main metabolite N-acetyl mesalazine in collected urine after fasted oral administration approximately 25% of the dose (more than 95 % as metabolite) was excreted renally within 60 h.
Following concomitant food intake in the same study a single dose of 2.4 g of mesalazine resulted in quantifiable amounts of mesalazine after 9.0 h (median t_{lag}). The geometric mean C_{max} –value of mesalazine was 1725.93 ng/mL with a median t_{max} of about 22.0 h, whereas that of N-acetyl mesalazine was 2235.32 ng/mL with a median t_{max} of 24.0 h.

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

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

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

Approximately 75 % of the administered dose remains in the gut lumen and the mucosal tissue.

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

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. At least 90% 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 (6 GR tablets of Asacolon 400 mg) in healthy volunteers under fasting conditions was about 135 L/h (geometric mean, CV% = 61.43%, intersubject). The median elimination half-life was 20 h ranging from 5 to 77 h.

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

Linearity/non-linearity
In a cross-over design with 3 test periods and 3 ascending oral doses of Asacolon 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 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 Asacolon tablet doses. The clinical performance of Asacolon 400 should be similar for the range of doses evaluated in this study.

Pharmacokinetic/pharmacodynamics 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 (Type A)
Magnesium stearate
Talc (E553b)
Povidone (E1201)

Film Coating
Methacrylic acid-methylmethacrylate copolymer (1:2)
Talc (E553b)
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 25ºC. 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 contained within an outer cardboard carton, containing 100 tablets.

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

7 MARKETING AUTHORISATION HOLDER

Tillotts Pharma GmbH
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DE- 79618 Rheinfelden
Germany

8 MARKETING AUTHORISATION NUMBER

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