# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Asacolon 500 mg Suppositories

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains: 500mg mesalazine.

Excipient(s) with known effect:
Each suppository contains 2.5g hard fat containing lecithin derived from soya, see section 4.4.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Suppository.
Torpedo-shaped suppositories with a light grey-brown colour.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

This medication is indicated in adults for:
For thetreatment of mild to moderate proctitis and proctosigmoiditis.

As an adjunct to oral therapy in severe generalised ulcerative colitis affecting the rectum or rectosigmoid colon.

### 4.2 Posology and method of administration

Posology
Adults:
One suppository to be inserted up to three times daily, after defaecation. 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 suppository may be used morning and evening, as an adjunct to oral therapy.

Older people:
The normal adult dose can be used 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 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.

### 4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Known hypersensitivity to salicylates.
- Known allergy to peanut or soya oil.
- Severe renal impairment (GFR less than 30 mL/min/1.73 $m^2$).
- Severe liver impairment.

- 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
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. Asacolon therapy should be stopped immediately if there is a suspicion or evidence of blood dyscrasia (signs of unexplained bleeding, bruising, purpura, anemia, 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. 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 been rarely reported with Asacolon. In case of previous 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 a course of treatment with Asacolon.

Adverse drug 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.

Older people
Use inolder 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 little experience and only limited documentation for an effect in children.

**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 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 Asacolon in pregnant women. However, data from 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 (2-4 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/foetal 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*
The Asacolon clinical trial database includes 246 patients treated with Asacolon 500 mg Suppositories. The mesalazine doses were in the range of 1.0 g/day to 1.5 g/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 Asacolon 500 mg 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.

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 relevant for the labelling reported from four double-blind clinical studies and one open label clinical trial, 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.

| **System Organ Class** | **Rare (≥ 1/10,000 to < 1/1,000)** | **Very rare (< 1/10,000)** | **Frequency not known** |
|---|---|---|---|
| **Blood and lymphatic system disorders** | -- | 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** | 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). | pleurisy |
| **Gastrointestinal disorders** | 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** | photosensitivity* * See section c) | alopecia. | Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) |
| **Musculoskeletal, connective tissue and bone disorders** | -- | myalgia, arthralgia. | |
| **Renal and urinary disorders** | -- | impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency. | Nephrolithiasis**--<br>** see section 4.4 for further information |
| **Reproductive system and breast disorders** | -- | oligospermia (reversible). | |
| **General disorders and administration site conditions** | | | 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 associated to the underlying IBD rather than Asacolon/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 section 4.4.

Under co-administration of 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 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 HPRA 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
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
*Clinical studies in patients with mild to moderate proctitis and proctosigmoiditis.*
Two prospective, double-blind, placebo controlled studies including 156 patients provided evidence of clinical efficacy for Asacolon 500 mg Suppositories for the induction of remission of mild to moderate proctitis and proctosigmoiditis.
In one study, 94 patients with mild to moderate distal proctosigmoiditis (<20 cm) were enrolled. The primary endpoint included clinical, endoscopic and histologic remission rates at one month. Clinical remission was achieved in 22 of 32 (69%) in the 1 g Asacolon group, in 23 of 31 (74%) in the 1.5 g Asacolon group versus 7 of 31 (39%) with placebo.
A second study included 62 patients with mild to moderate ulcerative colitis localized at the distal rectosigmoid region. The primary endpoint included clinical, endoscopic and histologic remission rates at one month.
The clinical outcome of either remission or improvement was achieved in 28 of 32 (88%) in the 500 mg t.i.d Asacolon group versus 10 of 30 (33%) with placebo.

*Clinical study in patients with quiescent ulcerative proctitis.*
A prospective, double-blind, multicentre trial studied the efficacy and tolerability of Asacolon 500 mg Suppositories in 111 patients with quiescent ulcerative proctitis limited to the rectum (≤ 15 cm from anus) for one year. Clinical outcome assessment was based on cumulative relapse rates at 12 months which were: 3 of 32 (10%) in the 1.0 g/day Asacolon group, 11 of 35 (32%) in the 0.5 g/day Asacolon group and 14 of 29 (47%) in the placebo group.

**5.2 Pharmacokinetic properties**

Absorption
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 Asacolon 500 mg Suppositories in healthy volunteers the mean Cmax and Tmax were 211 ng/mL and 2.0 hours for mesalazine and 443 ng/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
Low concentrations of mesalazine and its N-acetyl metabolite 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.

Elimination
The elimination of mesalazine is essentially faecal and urinary in the form of mesalazine and its N-acetyl metabolite. 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 Asacolon 500 mg Suppositories in healthy volunteers.

Linearity/non-linearity
No specific studies have been performed.

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

Hard Fat.
Lecithin, derived from soya oil.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Store in a dry place protected from direct heat. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

PVC/polyethylene laminate foil strips of 5 suppositories packed in an outer cardboard carton containing 20 suppositories.

### 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 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 Rheinfelden
Germany

## 8 MARKETING AUTHORISATION NUMBER

PA2018/001/003

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 June 1995

Date of last renewal: 26 June 2010

## 10 DATE OF REVISION OF THE TEXT

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