1. NAME OF THE MEDICINAL PRODUCT

ASACOL® 800 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric coated tablet contains:
Mesalazine (5-aminosalicylic acid) 800 mg

Excipient with known effect: 152.8 mg lactose, see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Enteric coated Tablet.
Reddish to brownish oblong tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative colitis:
For the treatment of mild to moderate acute exacerbations. For the maintenance of remission.

Crohn's disease:
For the treatment of acute episodes.

4.2 Posology and method of administration

Posology

Ulcerative colitis:

Mild acute disease: 2.4 g (three tablets) once daily or in divided doses, with concomitant corticosteroid therapy to be taken when clinically indicated.

Moderate acute disease: 2.4 g to 4.8 g (three to six tablets) a day in divided doses, with concomitant corticosteroid therapy where clinically indicated. 2.4 g may be taken once daily or in divided doses. Above 2.4 g daily should be taken in divided doses.

The maximum adult dose should not exceed six tablets a day and not exceed three tablets taken together at any one time.

Maintenance of remission:
1.2 to 2.4 g per day once daily or in divided doses.

Crohn's disease:
2.4 g per day in divided doses.

Elderly population
Use in the elderly should be handled with caution and only for patients having a normal renal function.

Pediatric population

There is no specific dose recommendation for children.

Method of administration
The tablets should be taken before meals and must be swallowed whole and preferably with some liquid. They must not be chewed, crushed or broken before swallowing.

4.3 Contra-indications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Known hypersensitivity to salicylates
- Severe liver impairment.
- Severe renal impairment (GFR less than 30 mL/min/1.73 m2).
- 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
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. Patients need to remain well hydrated whilst taking Asacol to reduce the risk of crystalluria and consequential kidney damage.

Treatment with Asacol 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. Asacol 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 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 carefully monitored during treatment with Asacol.

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.

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.

Elderly population
Use in the elderly 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
Safety and effectiveness of Asacol tablets have not been fully established in paediatric patients.

Pharmaceutical excipients of special interest
Intolerance to carbohydrates

With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicaments and other forms of interaction

No interaction studies have been performed.

There is weak evidence that mesalazine might decrease the anticoagulant effect of warfarin. In patients who are concomitantly treated with azathioprine, or 6-mercaptopurine or thioguanine, a possible increase in the myelosuppressive effects of azathioprine, or 6-mercaptopurine or thioguanine should be taken into account. As a result, life-threatening infection can occur. Patients should be closely observed for signs of infection and myelosuppression. Haematological parameters, especially the leucocyte, thrombocyte, and lymphocyte cell counts should be monitored regularly (weekly), especially at initiation of such combination therapy, see 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 Asacol in pregnant women. However, data on a limited number (627) of exposed pregnancies indicate no adverse effect of mesalazine on 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.

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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) Summary of the safety profile
Asacol 800 mg enteric coated Tablets have been evaluated in 140 patients with mild to moderate active ulcerative colitis in one controlled study lasting for 10 weeks comparing safety and efficacy versus another 141 patients treated with 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%). All undesirable effects with Asacol 800 mg enteric coated 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.
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

In addition to the undesirable effects reported above in a clinical trial with Asacol 800 mg enteric coated Tablets, undesirable effects relevant for the labeling reported from eight (8) double-blind and five (5) open clinical studies with 739 patients treated with Asacol 400 mg MR Tablets 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*	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	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, renal insufficiency, nephrotic syndrome and renal failure which may be reversible on early withdrawal	Nephrolithiasis**

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
*see section c) **see section 4.4 for further information					

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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

There are rare 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. 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
Asacol 800 mg 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 including 787 patients, of whom 559 received Asacol 400 mg Modified Release 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 g/day to 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 – 4.8 g mesalazine.

Maintenance of remission of ulcerative colitis

The efficacy of Asacol 400 was investigated in a double blind randomized placebo-controlled study including 264 patients. Treatment success Asacol 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). Asacol 400 mg enteric coated Tablets were safe and effective in maintaining remission in quiescent ulcerative colitis.

5.2 Pharmacokinetic properties

Absorption

Asacol tablets are coated with a pH-responsive polymer which enables the release of mesalazine only at a pH above 7, i.e. within the terminal ileum and colon, which are the main sites of inflammation in IBD. After any initial disruption of the coating mesalazine will continue to be released irrespective of the pH. Asacol tablets have been designed to minimize the absorption of mesalazine from the digestive tract.

After a single dose of 2.4 g of mesalazine (3 Asacol 800 mg enteric coated Tablets) in healthy volunteers under fasting conditions quantifiable amounts (> 2.00 ng/mL) of mesalazine were observed in plasma after 4.5 h (median tlag). The geometric mean Cmax-value of mesalazine was 387.86 ng/mL with a median tmax of 14.0 h, whereas that of N-acetyl mesalazine was 971.09 ng/mL with an identical median tmax, 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 tlag). The geometric mean Cmax-value of mesalazine was 653.56 ng/mL with a median tmax of about 30.0 h, whereas that of N-acetyl mesalazine was 1245.46 ng/mL with a median tmax 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 Cmax-values of mesalazine increased 1.69-fold, and the extent of exposure (AUC0-tlast) increased 1.23-fold. Concerning N-acetyl mesalazine after concomitant food intake the Cmax-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 (Vdw) was 147.73 L/kg (geometric mean: 76.06 L/kg) after a single dose of 2.40 g of mesalazine (3 enteric coated 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 enteric coated 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 enteric coated 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 Cmax'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

Preclinical data with mesalazine reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity or toxicity to reproduction.

Renal toxicity (renal capillary necrosis and epithelial damage in the proximal convoluted tubule or the whole nephron) has been seen in repeat-dose toxicity studies with high oral doses of mesalazine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

lactose monohydrate
sodium starch glycolate
methacrylic acid-methyl methacrylate copolymer (1:2)
talc
povidone
magnesium stearate
Triethyl citrate
ferric oxide red and yellow pigment
macrogol 6000

6.2 Incompatibilities

None.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25° C.

6.5 Nature and contents of container

Packs of 60 tablets in a blister pack (PVC/aluminium).

6.6 Special precautions for disposal and other handling

Not applicable.

7. Manufacturer:

Tillotts Pharma AG, SWITZERLAND

8. Registration Holder and Importer:

Tradis Gat Ltd. 32 Shacham St. Petach Tikva ISRAEL

9. Registration Number: 133-39-31029

Revised in February 2023 according to MOHs guidelines