פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

ASACOL® 800 mg enteric coated Tablets

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

Maintenance of remission in ulcerative colitis and for treatment of acute episodes in crohn's disease.

4.2 Dosage and mode of administration

Ulcerative colitis:

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

There is no specific dose recommendation for children.

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

There is no specific dose recommendation for children.

Use in the elderly should be handled with caution and only for patients having a normal renal function. 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 salicylates.
- Hypersensitivity to mesalazine or 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

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, anemia, persistent fever or sore throat), and patients should seek immediate medical advice. It is recommended that hematological 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 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.

Intolerance to carbohydrates
Patients with rare hereditary problems of galactose intolerance, 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 the 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
Safety and effectiveness of Asacol tablets have not been fully established in pediatric patients.

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 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.

The use of mesalazine during pregnancy and lactation should be restricted to those cases where in the physician's opinion potential benefits from this therapy outweigh potential risks.

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 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 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 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.

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.

Common: ≥ 1/100 to < 1/10, uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1000, 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 pleuropericarditis 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	
Uncommon:	pyrexia, chest pain.
Investigations	
Not known:	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.

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.

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.

In principle, the signs and symptoms would be expected to be similar to those observed in cases of salicylate intoxication: mixed acidosis-alkalosis, hyperventilation, pulmonary edema, dehydration as a result of sweating and vomiting, and hypoglycemia.

Treatment for mixed acidosis-alkalosis: restoration of the acid-base balance in line with the specific situation and replacement of electrolytes.

For dehydration due to sweating and vomiting: administration of fluids.

For hypoglycemia: glucose administration.

In addition gastric lavage and intravenous transfusion of electrolytes to promote diuresis. 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 Asacolo 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 Asacol 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 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 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 Asacol 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 Asacol 400 group 0.17 (±0.09) vs. 0.38 (±0.09); P=0.021. The results of the study indicate that Asacol 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
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 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 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 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 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

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 excipient(s)

lactose monohydrate
sodium starch glycollate
magnesium stearate
talc
povidone
methacrylic acid-methyl methacrylate copolymer (1:2)
Triethyl citrate
ferric oxide red and yellow (E172)
macrogol 6000

6.2 Incompatibilities

None.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25° C. Store in the original package to protect from moisture.

6.5 Nature and contents of container

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

6.6 Instructions for use / handling

Not applicable.

7. **Manufacturer: Tillotts Pharma AG**, SWITZERLAND

8. License holder and Importer: Tradis Gt Ltd. 32 Hashacham St. Petach Tikvah ISRAEL

9. DATE OF APPROVAL

December 2014