SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Asacol 1600 mg modified-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains: 1600 mg mesalazine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablet.

Film-coated, red/brown oblong tablets dimension of 23 x 11 x 9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative colitis.

For the treatment of mild to moderate acute disease. For the maintenance of remission.

4.2 Posology and method of administration

Posology

Adults, including the elderly (>65 years)

The dose should be adjusted according to the severity of the disease and tolerance.

Acute disease: In the event of exacerbation, the dose can be increased to 4800 mg daily, once daily or in 2-3 divided doses.

Once clinical remission is achieved, the dose should gradually be decreased to maintenance dose.

Continued therapy should be carefully considered in subjects not responding by week 8.

Maintenance treatment: 1600 mg once daily.

Other oral mesalazine formulations are available if an alternative dose for maintenance treatment is considered more appropriate.

Elderly population

No studies have been carried out in older people.

Paediatric population

The safety and efficacy of Asacol in children and adolescents aged younger than 18 years of age has not been established.

Method of administration: oral.

The tablets must be swallowed whole with a glass of water. They must not be chewed, crushed or broken before swallowing. The tablets can be taken with or without food. If one or more doses have been missed, the next dose is to be taken as usual.

4.3 Contraindications

- Hypersensitivity to salicylates (including mesalazine) or any of the excipients listed in section 6.1.
- Severe liver impairment.
- Severe renal impairment (GFR < 30 ml/min/1.73 m^2)

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, 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.

Renal impairment

Asacol should not be used in patients with renal impairment. Asacol-induced renal toxicity shall be suspected if the renal function is impaired during the treatment and the treatment should be stopped immediately.

It is recommended that the renal function is monitored prior to and repeatedly whilst on Asacol therapy.

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.

Urine Discoloration

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

Very rarely have serious blood dyscrasia been reported. Asacol therapy should be stopped immediately if there is a suspicion or evidence of blood dyscrasia (signs of unexplained bleeding, bruising, purpura, anaemia, persistent fever or sore throat), and the patient should seek immediate medical advice.

Liver impairment

There have been reports of increased liver enzyme levels in patients taking preparations containing Asacol. Caution is recommended if Asacol is administered to patients with liver impairment.

Cardiac hypersensitivity reactions

Asacol-induced hypersensitivity reactions (myo- and pericarditis) have been reported rarely with Asacol. In case of a suspected 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.

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 Asacol.

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

Caution is recommended when treating patients with active gastric or duodenal ulcer.

Asacol contains sodium

Each tablet contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially ‘sodium-free’.

Elderly patients

Asacol should be administered with caution in elderly patients, it should only be given to patients with normal renal or hepatic function or mild to moderate renal or hepatic impairment (see section 4.3).

Paediatric population

There is only limited documentation for an effect in children, see section 4.2.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

Caution is recommended for the concomitant use of mesalazine with known nephrotoxic agents, including non-steroidal anti-inflammatory drugs (NSAIDs) and azathioprine, or methothrexate as these may increase the risk of renal adverse reactions.

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

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 of exposed pregnancies indicate no adverse effect of mesalazine on pregnancy or on 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. Asacol should only be used during pregnancy if the potential benefit outweighs the possible risk.

Breastfeeding

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

No studies on the effects on the ability to drive and use machines have been performed. Asacol is considered to have negligible influence on these abilities.

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. Headache (1.7%), haematuria (1.7%), abdominal pain (1.5%), ulcerative colitis (1.5%) and proteinuria (1.5%) are the most commonly reported drug related adverse events in the clinical development programme.

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 and other sources are listed below:

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), not known (cannot be estimated from the available data).

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)	Not known (Cannot be estimated from the available data)
Blood and Lymphatic System Disorders		Eosinophilia (as part of an allergic reaction).		Altered blood counts (aplastic anemia, agranulocytosis, pancytopenia, neutropenia, leukopenia, thrombocytopenia), blood dyscrasia.	
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	

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)	Not known (Cannot be estimated from the available data)
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 and renal insufficiency, nephrotic syndrome, 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 and/or exacerbation of disease, C-reactive protein increased
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 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, 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 no 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

Mesalazine is an aminosalicylate, and signs of salicylate toxicity include tinnitus, vertigo, headache, confusion, drowsiness, pulmonary oedema, dehydration as a result of sweating, diarrhoea and vomiting, hypoglycaemia, hyperventilation, disruption of electrolyte balance and blood-pH and hyperthermia.

Conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage. Hypoglycaemia, fluid and electrolyte imbalance should be corrected by the administration of appropriate therapy. Adequate renal function should be maintained.

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 a topical anti-inflammatory effect on the colonic mucosal cells through mechanisms that have not yet been fully clarified.

Asacol has been shown to inhibit LTB4-stimulated migration of intestinal macrophages by restricting migration of macrophages to inflamed areas. The production of pro-inflammatory leukotrienes (LTB_4 and 5-HETE) in macrophages of the intestinal wall is thereby inhibited. Asacol has been shown to activate PPAR-γ receptors which counteract nuclear activation of intestinal inflammatory responses.

Pharmacodynamic effects

The Asacol tablet contains a core of 1600 mg mesalazine covered by a multi-layer coating system. This system consists of a layer of methacrylic acid - methyl methacrylate copolymer (Eudragit S) combined with starch particles on top of a middle alkaline buffer layer (which accelerates drug release). The coating is designed to delay release of mesalazine until intestinal fluids reach a pH of 7. The starch can be digested by colonic bacteria which also provides a second trigger for release of mesalazine from the coated tablet. Systemic bioavailability/plasma concentrations of mesalazine therefore are of no relevance for therapeutic efficacy, but rather a criterion for safety.

The risk of colorectal cancer (CRC) is slightly elevated in ulcerative colitis.

The effects observed by mesalazine in experimental models and from patient biopsies supports that mesalazine prevents colitis-associated CRC through down regulation of both the inflammation-dependent and non-dependent inflammatory signalling pathways that are involved in the development of colitis-associated CRC. Data from meta-analyses with populations both in remission and relapsing, provide however, an inconsistent clinical information on risk-benefit of mesalazine in the carcinogenesis of ulcerative colitis.

Clinical efficacy and safety

Mild to moderate acute ulcerative colitis

This indication was investigated in a randomised, active-controlled, double-blind, multi-centre, non-inferiority induction trial study with 817 patients receiving 3.2 g mesalazine daily for 8 weeks.

At week 8, 22.4% of the Per-Protocol patients treated with Asacol 1600 mg modified-release tablets and 24.6% of those treated with mesalazine 400 mg tablets achieved clinical and endoscopic remission. The unadjusted between group difference was 2.2% (95% confidence interval: - 8.1% up to 3.8%). Taking into account the predefined non-inferiority margin of – 10%, once daily Asacol 1600 mg modified-release tablets were considered to be non-inferior to twice daily mesalazine 400 mg tablets in inducing clinical and endoscopic remission.

A total of 10.3% of patients treated with Asacol 1600 mg modified-release tablets and 9.8% of patients receiving mesalazine 400 mg tablets reported treatment related adverse events. The incidence of serious adverse events (SAEs) in both treatment groups was 2.0% versus 1.7%.

Maintenance

727 patients participated in an open label extension (OLE) of the induction study. A total of 243 patients who showed no response at week 8 entered an extended induction period of 8 weeks on a daily dose of 4.8g.

The daily dose of Asacol in the maintenance phase was allocated depending on the 8 or 12-week induction results. Patients in clinical remission (202) received 1.6g/day whereas patients with a clinical response (274) received 3.2 g/day. Initial non-responders at week 8 who responded after a further 8 weeks on 4.8 g Asacol per day (199), remained on 4.8 g for another 22 weeks.

At week 38 70.3% (142/202) with 1.6 g/day maintained remission. Additionally 33.9% (93/274) and 30.7% (61/199) of patients in the 3.2 g/day and 4.8 g/day dose groups, respectively achieved a later clinical remission.

The incidence of SAEs in the maintenance OLE was low and independent of daily dose, with 5.0% (10/202), 4.4% (12/274) and 1.5% (3/199) of patients in the 1.6, 3.2 and 4.8 g/day dose groups affected.

5.2 Pharmacokinetic properties

Absorption

Asacol tablets have a modified release of mesalazine starting only at pH above 7, i.e. within the terminal ileum and colon. Approximately 31% of an oral dose (fasted state) is absorbed based on urinary excretion data for 60 hours.

A single dose of a Asacol 1600 mg modified -release tablets in healthy volunteers in the fasted state resulted in a 1.5-fold increase of mesalazine C_{max} and a 1.5-fold increase of AUC compared to fed state.

Distribution

About 43% mesalazine and 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 (Vdw) was 12.1 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. Based on urinary excretion data, the absorbed dose is excreted to >95% as metabolites.

Elimination

The elimination of mesalazine is essentially urinary and faecal in the form of mesalazine and its N-acetyl metabolite. About 23% of the dose administered was recovered in the urine within 60 hours after fed and 31% under fasted administration (single dose of 1600 mg tablet). The median elimination half-life of mesalazine was 20 hours (range: 5 to 77 hours).

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of this SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate E470B

Methacrylic acid methyl methacrylate copolymer (1:2)

Triethylcitrate

Iron oxide yellow (E172)

Iron oxide red (E172)

Macrogol

Microcrystalline cellulose

Glycerol monostearate (40-55)

Hypromellose

Maize starch

Polysorbate 80

Potassium dihydrogen phosphate

Colloidal anhydrous silica

Sodium starch glycolate (type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/aluminium blister 30 tablets, 60 tablets or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 Manufacturer

Haupt Pharma Wülfing GmbH, Germany

8. Registration Holder and Importer

Tradis Gat Ltd.
32 Shacham St. Petach Tikva
Israel

9 Registration Number

174-09-36782-99

Revised on June 2025