SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mesavancol 1200 mg maagsapresistent, tabletten met een verlengde afgifte

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1200 mg mesalazine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant, prolonged release tablets.

Red-brown, ellipsoidal, film-coated tablet (dimensions 20.5 × 9.5 × 7.5 mm), debossed on one side with S476.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the induction and maintenance of clinical and endoscopic remission in patients with mild to moderate, active
ulcerative colitis.

4.2 Posology and method of administration

Mesavancol is intended for once daily, oral administration. The tablets must not be crushed or chewed and should be taken with food.

Adults, including the elderly (>65 years)

For induction of remission: 2.4 g to 4.8 g (two to four tablets) should be taken once daily. The highest dose of 4.8 g/day is recommended for patients not responding to lower doses of mesalazine. When using the highest dose (4.8 g/day), the effect of the treatment should be evaluated at 8 weeks.
For maintenance of remission: 2.4 g (two tablets) should be taken once daily.

Children and adolescents
Mesavancol is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

Hepatic and renal impairment

Specific studies have not been performed to investigate Mesavancol in patients with hepatic or renal impairment (see sections 4.3 and 4.4).

4.3 Contraindications

History of hypersensitivity to salicylates (including mesalazine) or any of the excipients
listed in section 6.1.

Severe renal impairment (GFR <30 ml/min/1.73 m^2) and/or severe hepatic impairment.

4.4 Special warnings and precautions for use

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.

Reports of renal impairment, including minimal change nephropathy, acute / chronic interstitial nephritis and renal failure have been associated with preparations containing mesalazine and pro-drugs of mesalazine.
Mesavancol should be used with caution in patients with confirmed mild to moderate renal impairment. It is

recommended that all patients have an evaluation of renal function prior to initiation of therapy and at least twice a year, while on treatment based on clinical judgement taking baseline renal function into account. **Mesalazine treatment should be discontinued if renal function deteriorates.**

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.

Patients with chronic lung function impairment, especially asthma, are at risk of hypersensitivity reactions and should be closely monitored.

Following mesalazine treatment, serious blood dyscrasias have been reported rarely. If the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat, haematological investigations should be performed. If there is suspicion of blood dyscrasia, treatment should be terminated. (see sections 4.5 and 4.8).

Mesalazine induced cardiac hypersensitivity reactions (myo- and peri-carditis) have been reported rarely with Mesavancol and with other mesalazine containing preparations. Caution should be used in prescribing this medication to patients with conditions predisposing to the development of myo- or pericarditis. If such hypersensitivity reaction is suspected, products containing mesalazine must not be reintroduced.

Mesalazine has been associated with an acute intolerance syndrome that may be difficult to distinguish from a flare of inflammatory bowel disease. Although the exact frequency of occurrence has not been determined, it has occurred in 3% of patients in controlled clinical trials of mesalazine or sulphasalazine. Symptoms include cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and rash. If acute intolerance syndrome is suspected, prompt withdrawal is required and products containing mesalazine must not be reintroduced.

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

Caution should be exercised when treating patients allergic to sulphasalazine due to the potential risk of cross sensitivity reactions between sulphasalazine and mesalazine.

Organic or functional obstruction in the upper gastrointestinal tract may delay onset of action of the product.

This medicine contains less than 1 mmol sodium (23 mg) per the maximum recommended dose (4 tablets), that is to say essentially ‘sodium-free’.

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).

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.

Interference with laboratory tests

Use of mesalazine may lead to spuriously elevated test results when measuring urinary normetanephrine by liquid chromatography with electrochemical detection, because of the similarity in the chromatograms of normetanephrine and mesalazine’s main metabolite, Nacetylaminosalicylicacid (N-Ac-5-ASA). An alternative, selective assay for normetanephrine should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Drug-drug interaction studies in healthy adult subjects have been conducted with Mesavancol to investigate any effect of Mesavancol on the pharmacokinetics and safety of three commonly used

antibiotics. There were no clinically significant interactions of Mesavancol with amoxicillin, metronidazole or sulfamethoxazole.

However, the following drug-drug interactions have been reported for products containing Mesalazine

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

- Mesalazine inhibits thiopurine methyltransferase. In patients receiving azathioprine or 6-mercaptopurine, and/or any other active substances known to cause myelotoxicity, caution is recommended for concurrent use of mesalazine as this can increase the potential for blood dyscrasias, bone marrow failure, and associated complications (see sections 4.4 and 4.8).

- Administration with coumarin-type anticoagulants e.g. warfarin, could result in decreased anticoagulant activity. Prothrombin time should be closely monitored if this combination is essential.

Mesavancol is recommended to be administered with food (see sections 4.2 and 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited experience with mesalazine in pregnancy. Mesalazine crosses the placental barrier, but provides foetal concentrations much lower than those seen with adult therapeutic use. Animal studies do not indicate harmful effects of mesalazine in pregnancy, embryonal/foetal development, parturition or postnatal development. Adverse outcomes (including disturbances in blood counts such a leukopenia, thrombocytopenia, and anemia) were reported in infants born to mothers who were exposed to mesalazine during pregnancy.Mesalazine should be used during pregnancy only when the benefits outweigh the risks. Caution should be exercised when using high doses of mesalazine.

Breast-feeding
Mesalazine is excreted in breast milk at low concentration. Acetylated form of mesalazine is excreted in breast milk at higher concentration. Caution should be exercised if using Mesalazine while breast-feeding and only if the benefit outweighs the risks. Sporadically acute diarrhoea has been reported in breast fed infants.

Fertility
Data on mesalazine show no sustained effect on male fertility.

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. Mesavancol is considered to have negligible influence on these abilities.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) within the pooled safety analysis of clinical studies with Mezavant, including 3,611 patients, were colitis (including ulcerative colitis) 5.8%, abdominal pain 4.9%, headache 4.5%, liver function test abnormal, 2.1%, diarrhoea 2.0%, and nausea 1.9%.

Adverse reactions are listed by system organ class (see table below). Within each system organ class, adverse reactions are listed under headings of frequency using the categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

Adverse drug reactions (ADRs) Associated with Mesavancol

System organ class	Incidence category	Adverse drug reaction
Blood and Lymphatic System Disorders	Uncommon	Thrombocytopenia*
	Rare	Agranulocytosis*
	Not known	Aplastic anemia*, leukopenia*, neutropenia*, pancytopenia*
Immune system disorders	Rare	Face oedema
	Not known	Hypersensitivity*, anaphylactic shock, angioedema, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
Nervous system disorders	Common	Headache*
	Uncommon	Dizziness, somnolence, tremor
	Not known	Idiopathic intracranial hypertension (see section 4.4), Neuropathy
Ear and Labyrinth Disorders	Uncommon	Ear pain
Cardiac Disorders	Uncommon	Tachycardia
	Not known	Myocarditis*, pericarditis*
Vascular disorders	Common	Hypertension
	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Pharyngolaryngeal pain*
	Not known	Hypersensitivity pneumonitis (including interstitial pneumonitis, allergic alveolitis, eosinophilic pneumonitis) Bronchospasm
Gastrointestinal Disorders	Common	Abdominal distension, abdominal pain*, colitis, diarrhea*, dyspepsia, vomiting, flatulence, nausea
	Uncommon	Pancreatitis, rectal polyp
General Disorders and Administration Site Conditions	Common	Asthenia, Fatigue , Pyrexia*
Hepatobiliary disorders	Common	Liver function test abnormal* (e.g. ALT, AST, Bilirubin)

	Not known	Hepatitis, cholelithiasis, hepatotoxicity
Musculoskeletal and Connective Tissue Disorders	Common	Arthralgia, back pain
	Uncommon	Myalgia
	Not known	Sistemic-lupus erythematosus-like syndrome, Lupus-like syndrome
Renal and urinary disorders	Rare	Renal failure*
	Not known	Interstitial nephritis* nephrotic syndrome* nephrolithiasis*
Reproductive system and breast disorders	Not known	Oligospermia (reversible)
Skin and Subcutaneous Tissue Disorders	Common	Pruritus, rash*
	Uncommon	Acne, alopecia, urticaria
	Rare	Photosensitivity
	Not known	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS)

* See also section 4.4 for further information

Summary of safety profile:
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).

Description of selected adverse reactions:

Increased intracranial pressure

Cases of increased intracranial pressure with papilledema (pseudotumor cerebri or benign intracranial hypertension) have been reported with the use of mesalazine. If undetected, this condition may result in restriction of the visual field and may progress to permanent loss of vision. Mesalazine should be discontinued, if this syndrome occurs.

Photosensitivity

More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema.

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 www.lareb.nl

4.9 Overdose
Mesavancol 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 maintaine

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminosalicylic acid and similar agents
ATC code: A07EC02

Mechanism of Action
Mesalazine is an aminosalicylate. The mechanism of action of mesalazine is not fully understood, but appears to have a topical anti-inflammatory effect on the colonic epithelial cells. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.
Mesalazine has the potential to inhibit the activation of nuclear factor kappa B (NFκB) and consequently the production of key proinflammatory cytokines. More recently, it has been proposed that impairment of PPAR-γ nuclear receptors, (γ-form of the peroxisome proliferator-activated receptors) may be implicated in ulcerative colitis. PPAR-γ receptor agonists have shown efficacy in ulcerative colitis and evidence has been accumulating that the mechanism of action of mesalazine may be mediated by PPAR-γ receptors.

Pharmacodynamic effects

The Mesavancol tablet contains a core of mesalazine (5-aminosalicyclic acid) 1.2g, formulated in a multimatrix system. This system is coated with methacrylic acid – methyl methacrylate copolymer (1:1) and methacrylic acid – methyl methacrylate copolymer (1:2), which are designed to delay release of mesalazine until exposure to approximately pH 7.

Clinical efficacy and safety
Mesavancol was investigated in two similarly designed, Phase III, placebo controlled studies (SPD476-301 and SPD476-302) in 623 randomised patients with mild to moderate, active Ulcerative Colitis. Mesavancol 2.4 g/day and 4.8 g/day administered with food achieved statistical superiority over placebo in terms of the number of patients achieving remission from Ulcerative Colitis after 8 weeks treatment. Using the Ulcerative Colitis Disease Activity Index (UC-DAI), remission was defined as a UC-DAI score of ≤1 with a score of 0 for rectal bleeding and stool frequency and at least a 1-point reduction in sigmoidoscopy score from baseline. Study SPD476-302, included a comparator, mesalazine pH 7-dependent modified release 2.4 g/day (0.8g administered in 3 divided doses), as an internal reference arm. On the primary variable of remission, the following results were achieved:

Study SPD476-301 (n=262#)			
	Placebo	Mesavancol 2.4 g/day in two divided doses	Mesavancol 4.8 g/day once daily
% patients in remission	12,9	34,1*	29,2*

Study SPD476-302 (n=341#)				
	Placebo	Mesavancol 2.4 g/day once daily	Mesavancol 4.8 g/day once daily	Mesalazine pH-7dependent modified release 2.4 g/day in three

				divided doses
% patients in remission	22,1	40,5*	41,2*	32,6[NS]

[#]Based on the ITT Population; * Statistically different from placebo (p<0.025); NS Not significant(p>0.05)

5.2 Pharmacokinetic properties

The mechanism of action of mesalazine (5-ASA) is not fully understood but appears to be topical, and therefore the clinical efficacy of Mesavancol does not correlate with the pharmacokinetic profile. A major pathway of clearance of mesalazine is via metabolism to N-acetyl-5-aminosalicylic acid (Ac-5-ASA), which is pharmacologically inactive.

Absorption

Gamma-scintigraphy studies have shown that a single dose of Mesavancol 1.2 g passed rapidly and intact through the upper gastrointestinal tract of fasted healthy volunteers. Scintigraphic images showed a trail of radio-labelled tracer through the colon, indicating that mesalazine had spread throughout this region of the gastrointestinal tract. Complete disintegration of Mesavancol and complete release of mesalazine occurred after approximately 17.4 hours.

The total absorbtion of mesalazine from Mesavancol 2.4 g or 4.8 g given once daily for 14 days to healthy volunteers was found to be approximately 21-22% of the administered dose.

In a single dose study, Mesavancol 1.2 g, 2.4 g and 4.8 g were administered in the fasted state to healthy subjects. Plasma concentrations of mesalazine were detectable after 2 hours (median) and reached a maximum by 9-12 hours (median) on average for the doses studied. The pharmacokinetic parameters are highly variable among subjects. Mesalazine systemic exposure in terms of area under the plasma concentration-time curve (AUC) was dose proportional between 1.2 g and 4.8 g Mesavancol. Maximum plasma concentrations (Cmax) of mesalazine increased approximately dose proportionately between 1.2 g and 2.4 g and less than dose proportional between 2.4 g and 4.8 g Mesavancol, with the dose normalised value at 4.8g representing, on average, 74% of that at 2.4 g based on geometric means.

In a single and multiple dose pharmacokinetic study of Mesavancol 2.4 and 4.8 g administered with standard meals in 56 healthy volunteers plasma concentrations of mesalazine were detectable after 4 hours and were maximal by 8 hours after the single dose. At steady state (achieved generally by 2 days after dosing), 5-ASA accumulation was 1.1- to 1.4- fold for the 2.4 g and 4.8 g dose, respectively, above that expected on the basis of single dose pharmacokinetics.

Administration of a single dose of Mesavancol 4.8 g with a high fat meal resulted in further delay in absorption and mesalazine plasma levels were detectable after approximately 4 hours following dosing. However, a high fat meal increased systemic exposure of mesalazine (mean Cmax by 91%; mean AUC 16%) compared to results in the fasted state. Mesavancol was administered with food in the Phase 3 trials

In a single dose pharmacokinetic study of Mesavancol, 4.8 g was administered in the fasted state to 71 healthy male and female volunteers (28 young (18-35years); 28 elderly (65-75years); 15 elderly (>75years)). Increased age resulted in increased systemic exposure (up to approximately 2-fold, based on AUC_{0-t}, $AUC_{0-\infty}$ and Cmax) to mesalazine and its metabolite N-acetyl-5-aminosalicylic acid but did not affect the percentage of mesalazine absorbed. Increased age resulted in a slower apparent elimination of mesalazine, though there was high between-subject variability. Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Distribution

Following dosing of Mesavancol the distribution profile of mesalazine is presumed to be the same as that of other mesalazine containing products. Mesalazine has a relatively small volume of distribution of approximately 18L confirming minimal extravascular penetration of systemically available drug. Mesalazine is 43% bound and N-acetyl-5-aminosalicylic 78 - 83% bound to plasma proteins when in vitro plasma concentrations are up to 2.5 µg/mL and up to 10 µg/mL respectively.

Biotransformation

The only major metabolite of mesalazine is N-acetyl-5-aminosalicylic acid, which is pharmacologically

inactive. Its formation is brought about by N-acetyltransferase-1 (NAT-1) activity in the liver and in the cytosol of intestinal mucosal cells.

Elimination
Elimination of absorbed mesalazine is mainly via the renal route following metabolism to N-acetyl-5-aminosalicylic acid (acetylation). However, there is also limited excretion of the parent drug in urine.
Of the approximately 21-22% of the dose absorbed, less than 8% of the dose was excreted unchanged in the urine at steady state after 24 hours, compared with greater than 13% for N-acetyl-5-aminosalicylic acid.
The apparent terminal half-lives for mesalazine and its major metabolite after administration of Mesavancol 2.4 g and 4.8g were, on average,7-9 hours and 8-12 hours, respectively.

Hepatic impairment
There are no data in patients with renal or hepatic impairment taking Mesavancol.
Systemic exposure to mesalazine increased by up to 2-fold in elderly subjects (>65 years, with a mean creatinine clearance of 68 – 76 ml/min) compared with youger adult subjects (18-35 years, mean creatinine clearance 124 ml/min) after a 4.8 g single dose of Mesavancol.

Renal impairment
Systemic exposures in individual subjects were inversely correlated with renal function as assessed by estimated creatinine clearance.

Elderly
The potential impact on the safe use of Mesavancol in the elderly population in clinical practice should be considered. Furthermore, in patients with renal impairment, the resultant decrease in the rate of elimination and increased systemic concentration of mesalazine may constitute an increased risk of nephrotoxic adverse reactions (see section 4.4).

In different clinical studies with Mesavancol, mesalazine plasma AUC in females appeared up to 2-fold higher than in males.

Based on limited pharmacokinetic data, 5-ASA and Ac-5-ASA pharmacokinetics appear comparable between Caucasian and Hispanic subjects.

Pharmacokinetics data have not been investigated in elderly people.

5.3 Preclinical safety data

Effects in nonclinical 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

Tablet core
Carmellose sodium
Carnauba wax
Stearic acid
Silica, colloidal hydrated
Sodium starch glycolate (Type A)
Talc
Magnesium stearate

Film-coating
Talc
Methacrylic acid –methyl methacrylate copolymer (1:1)
Methacrylic acid –methyl methacrylate copolymer (1:2)
Triethylcitrate
Titanium dioxide (E171)
Red ferric oxide (E172)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Tablets are packed in polyamide/aluminium/PVC foil blister packs with aluminium push-through foil.
Packs contain 60 or 120 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Giuliani S.p.A.
Via P. Palagi 2
20129 Milan
Italy

8. MARKETING AUTHORISATION NUMBER(S)

RVG: 33597

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORITIS

Datum van eerste verlening van de vergunning: 27 februari 2008
Datum van eerste hernieuwing van de vergunning: 13 december 2011

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8: 17 december 2024