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# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# Mesavancol 1200 mg, gastro-resistant, prolonged-release tablets Giuliani S.p.A., Italy

# mesalazine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow–organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

**EU-procedure number: NL/H/0733/001/DC**
**Registration number in the Netherlands: RVG 33597**

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|---|---|
| Pharmacotherapeutic group: | intestinal anti-inflammatory agents, aminosalicylic acid and similar agents |
| ATC code: | A07EC02 |
| Route of administration: | oral |
| Therapeutic indication: | induction of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis and for maintenance of remission. |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 27 February 2008 |
| Concerned Member States: | Decentralised procedure with IT |
| Application type/legal basis: | Directive 2001/83/EC, Article 8(3) |

For product information for healthcare professionals and users, including information on pack sizes and presentations see Summary of Product Characteristics (SPC), package leaflet and labelling.

# I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Mesavancol 1200 mg, gastro-resistant, prolonged-release tablets from Giuliani S.p.A.

The product is indicated for the induction of clinical and endoscopic remission in patients with mild to moderate, active ulcerative colitis and for the maintenance of remission.

A comprehensive description of the indications and posology is given in the SPC.

The dossier has been submitted as a full dossier according to art. 8(3). This decentralised application concerns an application for Mesavancol 1200 mg, gastro-resistant, prolonged-release tablets a new product of mesalazine (5-aminosalicylic acid; 5-ASA), an anti-inflammatory agent used in the treatment of ulcerative colitis.

The MAH received Scientific Advice from the MEB on 12 March 2003 and 16 June 2005. In general, the MAH followed the advice of the MEB. Advice was given on non-clinical, clinical (among others design Phase-III studies, once daily dosing, proposed indication) and procedural aspects.

As mesalazine is a well-established drug substance in the EU (first approval 1984), the non-clinical components of this dossier have relied on an assessment of available data in the literature. The non-clinical overview, submitted by the MAH, has adequately described the pre-clinical pharmacology, pharmacokinetics and toxicology of mesalazine. The clinical programme comprised ten studies, of which five were in healthy volunteers and five in subjects with ulcerative colitis.

Ulcerative colitis is a chronic, relapsing/remitting, inflammatory disease of the colon and rectum. When active, ulcerative colitis is characterised by inflammation, bleeding and often ulceration of the affected area, resulting in urgent passage of bloody stools, abdominal/pelvic cramping and lassitude. In the treatment of ulcerative colitis, mesalazine is an intestinal, anti-inflammatory product with apparent topical activity. Whilst its mechanism of action is not fully understood, mucosal production of arachidonic acid metabolites, are increased in patients with chronic inflammatory bowel disease, and mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. As mesalazine also inhibits the activation of NFκB, a nuclear transcription factor that regulates the transcription of many genes for proinflammatory proteins, this activity may additionally underpin its effects.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC (i.e. a stand alone dossier or full application).

# II SCIENTIFIC OVERVIEW AND DISCUSSION

## II.1 Quality aspects

**Compliance with Good Manufacturing Practice**
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisations.

**Active substance and excipients**
The active substance is mesalazine, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Mesalazine (5-Amino-salicylic acid) is an almost white to light pink/grey/brown powder or crystals, which is very slightly soluble in water, practically insoluble in acetone, alcohol, and ether. The drug substance dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid. Polymorphism of the drug substance has been demonstrated to be no issue. The substance possesses no chiral centres in the molecular structure. Two suppliers were used for the active substance. The active substance specification from both suppliers is considered adequate to control the quality, and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 15 production-scale batches.

The CEP procedure is used for both suppliers of the active substance. Under this official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

The CEP for one supplier granted a retest period and storage condition on basis of the submitted stability data of “3 years, no storage conditions”. The CEP for the other supplier does not include these claims, and therefore stability data were assessed. Stability data on the active substance have been provided for 6 batches for this supplier in accordance with applicable European guidelines demonstrating the stability of the active substance over 2 years, without storage conditions.

The excipients used are common in the manufacture of gastro-resistant and prolonged-release tablets. All excipients and solvents comply with the requirements laid down in their respective Ph.Eur. monographs, except for red ferric oxide. For red ferric oxide the USP specifications were used. This specification also complies with EU directives 78/25/EC and 95/45/EC.

** Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU or USA, respectively.*

**Medicinal Product**

Composition
Mesavancol 1200 mg, gastro-resistant, prolonged-release tablets contain 1200 mg mesalazine. The tablets are red-brown, ellipsoidal, film-coated tablet, debossed on one side with S476.

The tablets are packed in polyamide/aluminium/PVC foil blister pack with aluminium push-through foil.

The excipients are:
tablet core - carmellose sodium, carnauba wax, stearic acid, silica colloidal hydrated, sodium starch glycolate, talc, magnesium stearate.
film-coating – talc, methacrylic acid copolymer type A, methacrylic acid copolymer type B, triethylcitrate, titanium dioxide (E171), red ferric oxide (E172), macrogol 6000.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The aim was to formulate a tablet, to be administered once daily in a relatively high daily dose. The gastro-resistant properties and prolonged-release properties have been well described. Each Mesavancol 1200 mg tablet contains mesalazine 1200 mg, formulated in a multi-matrix system. The tablet core is a double matrix system made of an inert lipophilic matrix (in which some of the mesalazine is incorporated), and a hydrophilic matrix, that includes a hydrophilic polymer and the remaining mesalazine. The tablet core is coated with a gastro-resistant, pH-dependent polymer film, which only breaks down at pH 7 or higher, normally in the terminal ileum. Thus, the Mesavancol 1200 mg formulation provides a combination of delayed and extended drug release, thereby aiming for homogenous release of mesalazine throughout the colon. The composition of the proposed formulation and release characteristics are essentially similar to those of the batches used in the clinical trials including the phase III trials.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 4 pilot batches and 3 production-scale batches in accordance with the relevant European guidelines.

Quality control of the medicinal product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for appearance, identification of drug substance and of the colouring agents, assay, content related substances, dissolution, microbiological limits and uniformity of dosage limits. Limits in the specifications have been justified and are considered appropriate for adequate quality control of the product. The MAH committed to re-evaluate the limits for dissolution (tightening) when more batch and stability data have become available.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data for 16 batches (clinical, validation and stability batches) have been provided, demonstrating compliance with the specification. The majority of the batches included are at production scale.

Stability tests on the finished product
Stability data on the product have been provided for 10 batches in accordance with applicable European guidelines demonstrating the stability of the product over 2 years when stored below 25°C in the original packaging to protect against humidity. The MAH committed to submit the results of the ongoing stability studies (with a.o. the full scale, recently manufactured production batches), up to the granted shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

## II.2 Non-clinical aspects

As mesalazine is a well-established drug substance in the EU, the non-clinical components of the dossier have relied on an assessment of available data in the literature. The non-clinical overview, submitted by the MAH, has adequately described the pre-clinical pharmacology, pharmacokinetics and toxicology of mesalazine. No further studies are required, and the MAH provides none. This is acceptable for this application.

Environmental risk assessment
Considering that no new indications are added in this application, it is expected that Mesavancol 1200 mg will substitute parts of the prescriptions of the currently marketed comparable drugs. Therefore, the approval of this product will not result in an increase in the total quantity of mesalazine released into the environment. Consequently, no changes in the environment are to be expected, which are unknown for

mesalazine. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

## II.3 Clinical aspects

For this application, ten clinical studies have been submitted, which include two pivotal, double-blind, placebo controlled, phase III efficacy and safety studies with active, mild to moderate ulcerative colitis, in support of the proposed dose of 2.4 to 4.8 g/day once daily (QD). Efficacy was compared to placebo and to an active mesalazine containing comparator, 400 mg Asacol®.

**Pharmacokinetics**
Each Mesavancol 1200 mg tablet contains 1200 mg mesalazine, formulated in a multi-matrix system. The tablet core is a double matrix system made of an inert lipophilic matrix (in which some of the mesalazine is incorporated), and a hydrophilic matrix, that includes a hydrophilic polymer and the remaining mesalazine. The tablet core is coated with a gastro-resistant, pH-dependent polymer film, which only breaks down at pH 7 or higher, normally in the terminal ileum. Thus, the Mesavancol 1200 mg formulation provides a combination of delayed and extended drug release, thereby aiming for homogenous release of mesalazine throughout the colon.

Furthermore, with 1200 mg of mesalazine in each tablet (a higher dose than any currently commercially available mesalazine product) the number of tablets needed for a therapeutic dose is reduced. A 2.4 g daily dose requires only two tablets to be taken once per day.

In adults (including the elderly), a dose of 2.4 to 4.8 g (equivalent to 2-4 tablets) QD under fed conditions is proposed for induction of remission, and 2.4 g QD, for maintenance of remission.

Mesalazine (5-ASA) and, its acetylated metabolite, Ac-5-ASA pharmacokinetics have been investigated in five phase-I healthy volunteer studies (table 1). In two of these studies the transit of the tablet through the gastrointestinal tract and its dissolution behaviour was investigated using scintigraphic methods. Furthermore, local mucosal exposure has been assessed in one Phase-II study.

**Table 1. Phase-I pharmacokinetic and biopharmaceutical studies on Mesavancol 1200 mg**

| Study ref. | Short title | Subjects entered | Mesavancol dose | Key measure |
|---|---|---|---|---|
| CRO-00-15 | SD, DB, CO, Pharmacoscintigraphic study of 2 CR formulations | 12 M HV ≥19 years | 1.2 g | PK/scintigraphy |
| SPD476-101 | SD, OL, CO pilot Pharmacoscintigraphic distribution study | 8 M HV ≥18 years | 1.2 g | PK/scintigraphy |
| CRO-PK-00-42 | RD, OL Pharmacokinetic study | 12 M HV 18-45 years | 1.2 g BID 7 days | PK |
| SPD476-102 | SD, OL, CO, Pharmacokinetic study to develop an IVIVC | 48 HV, 18-55 years | 1.2 g (slow, medium, fast release formulations) | PK / IVIVC |
| SPD476-103 | SD, OL, CO, effect of food on Bioavailability | 34 HV, 18-55 years | 4.8 g | PK |

The analysis methods were adequate for the purpose of the studies.

Absorption

Scintigraphic studies indicate that the Mesavancol 1200 mg tablet core remains intact in the upper gastrointestinal tract, avoiding release of 5-ASA where absorption of 5-ASA is most efficient. Initial tablet disintegration of Mesavancol 1200 mg occurred at 4.75 ± 1.31 h (range 2.3 - 5.9 h) post-dose, when the tablet was located between the mid small bowel and the ascending colon. Complete tablet disintegration of Mesavancol 1200 mg occurred at 17.34 ± 8.6 h (range 9.0 - 34.0 h) hours post-dose, respectively. Although this information complemented with clinical data may be sufficient for registration, the Mesavancol 1.2 g tablet has been also compared with a 400 mg Asacol® tablet with respect to transit time, disintegration times and pharmacokinetics. For this purpose a dedicated batch of Samarium oxide labelled Asacol was manufactured. However, it is unclear how comparable this specially labelled Asacol batch was as compared to the commercial Asacol® tablet, and therefore no comparative conclusions can be drawn on transit of the two formulations through the gastrointestinal tract from this study. However, information on the Mesavancol 1.2 g tablet from the two scintigraphic studies provided sufficient evidence that transit time and disintegration is adequate for the proposed indications.

Under fasted conditions, plasma 5-ASA and Ac-5-ASA were detectable in plasma after a lag time of approximately 3 hours and maximum plasma concentrations were obtained after approximately 8-12 hours. Total absorption from Mesavancol 1.2 g given twice a day (BID) to healthy volunteers was relatively low, i.e., 24% ± 16% of the administered dose. Plasma steady state was reached after 4 to 5 days.

A single and multiple dose pharmacokinetic study applying the clinically relevant Mesavancol dose of 2.4 and 4.8 g administered with standard meals was also submitted. After a single dose of the clinically relevant 2.4 and 4.8 g dose of Mesavancol administered with standard meals, mean 5-ASA $C_{max}$ levels of 2932 and 4385 ng/ml, respectively, were obtained after 8 hours. At steady-state, 5-ASA accumulation ($AUC\tau/AUC_{inf}$) was 1.4- and 1.1- fold for the 2.4 g and 4.8 g dose, respectively. At the highest 4.8 g QD dose level at steady state, the mean maximum plasma concentration of 5-ASA was 5280 ± 3146 ng/mL and mean area under the plasma concentration-time curve within a dosage interval was 49,559 ± 23,780 ng.h/mL.

Administration of a 4.8 g dose under fed (high-fat) conditions resulted in delayed and further prolonged absorption as compared to fasted conditions. Under fed conditions, mesalazine plasma levels are detectable after a lag time of approximately 6 hours, reaching $t_{max}$ after approximately 24 hours.

The scintigraphic studies were performed under fasting conditions. Since the lag time increases under fed conditions, this could theoretically indicate that release of 5-ASA from the formulation occurs lower in the gastro-intestinal tract. However, this possibility seems unlikely, since the AUC and $C_{max}$ under fed and fasted conditions were not statistically significantly different, which indicates that absorption, which mainly takes place at the higher parts of the GI tract, is comparable under fasted and fed conditions.

Distribution

Mucosal concentration data obtained from endoscopically obtained histological samples from patients receiving Mesavancol 1.2 g, 2.4 g or 4.8 g/day indicate that adequate mucosal concentrations are obtained at a 2.4 and 4.8 g/day regimen. Biopsy samples were collected during the morning after dosing.

Metabolism

It is well-known that mesalazine is extensively metabolized almost exclusively to an acetylated product, Ac-5-ASA. Upon oral administration, this metabolism predominantly occurs in the intestinal mucosa. N-acetylation does not occur in the rectum and any contribution to metabolism by intestinal bacteria appears to be minimal.

Excretion

Based on literature data, it is known that the main clearance route for mesalazine in man is via metabolism to N-Ac-5-ASA (acetylation), which is then renally eliminated by glomerular filtration and active tubular secretion. However, there is also limited excretion of the parent drug in urine. Following Mesavancol 2.4 g or 4.8 g once daily, on average, 2-3% of the dose was excreted unchanged in the urine after 24 hours, compared with 13-17% for N-acetyl-5-aminosalicylic acid.

Biliary excretion of mesalazine and its acetylated and glucuronide metabolites have been shown to be very low, with 0.01-0.75% of a single dose being recovered in the bile of subjects with T-tube drainage.

Dose-proportionality

After a single dose of Mesavancol, $AUC_{inf}$ of 5-ASA increased more than dose proportionally, with area under the plasma concentration-time curve increasing approximately 2.5-fold for a 2-fold dose increase from 2.4 g to 4.8 g. There was no evidence of supra-proportionality seen at steady state. The metabolite/drug mean AUC ratio after a single dose of 1.2 g compared with that of 4.8 g Mesavancol under fasted conditions decreased from 5.2 to 1.5 suggesting saturation of the metabolic clearance of mesalazine as the reason for this non-linear pharmacokinetic behaviour. This is in line with data described for other mesalazine preparations, in which metabolic clearance of mesalazine appeared to be capacity limited. Accumulation ($AUC\tau/AUC_{inf}$) of Ac-5-ASA was somewhat below what was expected based on single dose pharmacokinetics, i.e., 0.9- and 0.7-fold for a 2.4 or 4.8 g Mesavancol dose, respectively. This effect is likely to be due to a lower metabolite/drug-ratio at higher dose and at steady-state, due to saturation of 5-ASA metabolism.

Variability

Data from the submitted studies indicate high interindividual variability with respect to 5-ASA, i.e., approximately 60-65% for AUC, and 90-110% for $C_{max}$. No difference was observed in interindividual variability between the fasted and fed state. This high variability is in line with that found for other mesalazine preparations.

Target population

Only limited plasma concentration data were obtained in the targeted population. However, mucosal concentrations were analysed in patients with ulcerative colitis. The mucosal concentrations obtained after the mid-dose of Mesavancol 1200 mg (2.4 g/day) appeared to be comparable with those reported for Asacol®, and the exposure obtained by the 4.8 g dose is higher. These data are supportive for an effective local exposure of the mucosa to 5-ASA obtained by Mesavancol 1200 mg.

Special populations

It is known that clearance of mesalazine is decreased in patients with renal impairment, which may give rise to increased risk of nephrotoxicty. A warning on this matter is included in the SPC, which is acceptable.

Hepatic impairment is not expected to affect clearance of mesalazine to a clinically significant extent. Still, it is acceptable that in the SPC it is mentioned that severe hepatically impaired patients were excluded from the clinical studies of Mesavancol 1200 mg, and caution is recommended on the use of Mesavancol 1200 mg in hepatically impaired patients.

The lack of pharmacokinetic data for elderly patients is mentioned in the SPC.

Pharmacokinetics of Mesavancol 1200 mg in children has not been investigated. The MAH committed to conduct a clinical-pharmacokinetic study in children.

Gender

5-ASA AUC was up to 2-fold higher in females compared to males, both under fasted and fed conditions. Differences in average body weight between the males and females may account for some, but not all, of this difference. No gender-related differences were observed for 5-ASA $t_{lag}$, $t_{25\%}$ (time to obtain 25% of the total exposure) and $t_{max}$. Between-subject variability was not different between males and females. The differences in exposure are unlikely to be relevant for safety and efficacy. The fact that $t_{lag}$ and $t_{max}$ are comparable between males and females indicate that local exposure in males and females is not expected to be different in a relevant manner. Based on the clinical studies provided, no indications of increased toxicity in either gender were apparent. Currently, the higher exposure in females is sufficiently mentioned in SPC section 5.2. It is agreed not to include a possible explanation for differences in the exposure between males and females.

Race

Based on analysis from three pharmacokinetic studies, 5-ASA and Ac-5-ASA pharmacokinetics appear comparable between Caucasian and Hispanic subjects. Although a small number of Black, Asian or American Indian subjects were present in the studies, there was no indication that race contributes to the variability of the exposure to mesalazine.

Weight
The effect of weight on AUC appears small as compared to the effect of dose. However, a rough estimation is that the 5-ASA AUC decreases by approximately 1% per kg weight increase. This difference is not expected to be clinically relevant. It is therefore agreed not to include specific data on the effect of weight.

Interactions
Drug interaction studies have not been conducted with Mesavancol 1200 mg as the potential for clinically significant adverse reactions between 5-ASA and other co-administered drugs is considered to be low. Metabolism of 5-ASA is not mediated by any isoform of cytochrome P450. The proposed labelling for Mesavancol 1200 mg takes account of literature reports from clinical practice, which suggests the possibility of drug interactions concerning other mesalazine products. The MAH has adequately discussed, based on provided literature, the lack of pharmacokinetic interaction studies. The possible effect of concomitantly administered antacids or drugs that affect transit times was discussed by the MAH, and based on literature, no mentioning of such interactions in the SPC seems warranted.

Overall conclusion on pharmacokinetics
In conclusion, pharmacokinetics of mesalazine from the Mesavancol 1200 mg tablet were adequately measured at the clinically relevant 2.4 and 4.8 g dose. Scintigraphic and pharmacokinetic data indicate that mesalazine is released from the tablet after a delay, avoiding the upper parts of the gastrointestinal tract where absorption is most pronounced, and that mesalazine is released in a sustained fashion over the lower parts of the colon. Furthermore, adequate local mucosal exposure to mesalazine is obtained upon treatment of patients with the advised 2.4 and 4.8 g/day doses.
Clinical pharmacokinetics in children remains to be studied. The MAH committed as such.

**Clinical efficacy**
Five studies are included in the assessment of the clinical efficacy of Mesavancol 1200 mg in the treatment of subjects with mild to moderate active ulcerative colitis (see table 2).

**Table 2. Summary of Efficacy Studies**

| Study reference | Short title | Design | Subjects randomised | Duration of treatment | Treatment arms, daily dose and regimen |
|---|---|---|---|---|---|
| SPD476-201 | Pilot efficacy study of SPD476 vs. Asacol enema | R, DB, PG | 79 subjects with active, left-sided UC | 8 weeks | SPD476 3.6g/day TID<br>Asacol 4g/day QD (enema) |
| SPD476-202 | Dose-ranging, exploratory study | R, DB, PG | 38 subjects with active, mild to moderate UC | 8 weeks | SPD476 1.2g/day QD<br>SPD476 2.4g/day QD<br>SPD476 4.8g/day QD |
| SPD476-301 | Efficacy & safety study; placebo vs. SPD476 | R, DB, PG placebo-controlled | 280 subjects with active, mild to moderate UC | 8 weeks | SPD476 2.4g/day BID<br>SPD476 4.8g/day QD<br>placebo |
| SPD476-302 | Efficacy & safety study; placebo vs. SPD476 and Asacol | R, DB, PG placebo-controlled | 343 subjects with active, mild to moderate UC | 8 weeks | SPD476 2.4g/day QD<br>SPD476 4.8g/day QD<br>Asacol 2.4g/day TID<br>placebo |
| SPD476-303 (interim analysis) | 12-14 month extension safety study | R*, Open, extension | 542 subjects from studies SPD476-301 and -302 | Acute Phase 8 weeks. Maintenance Phase: 12 months | Acute Phase: SPD476 4.8g/day BID<br>Maintenance Phase: SPD476 2.4g/day QD<br>SPD476 2.4g/day BID |

QD=once daily; BID=twice daily; TID=three times daily; UC=ulcerative colitis; R=randomised; DB=double-blind; PG=parallel group; SPD476=Mesavancol 1200 mg tablet *Only the Maintenance Phase was randomised.

The inclusion and exclusion criteria of studies SPD476-301 and SPD476-302 mirrored well the population intended to be treated. The various treatment groups were well balanced for the key parameters (gender, number of relapses, duration of disease, disease classification, see table 3). It is not to be expected that the results will be biased due to disbalance between treatment groups. In both studies approximately 80% of subjects completed the study in the Mesavancol treatment groups compared to approximately 60% of subjects completing the studies in the placebo group.

**Table 3. Demographic Baseline Characteristics . ITT Population (Studies SPD476-301 and 302)**

| | SPD476-301 | | | SPD476-302 | | | |
|---|---|---|---|---|---|---|---|
| | Placebo (N=85) | SPD476 2.4g/day BID (N=88) | SPD476 4.8g/day QD (N=89) | Placebo (N=86) | SPD476 2.4g/day QD (N=84) | SPD476 4.8g/day QD (N=85) | Asacol 2.4g/day TID (N=86) |
| Gender; n (%) | | | | | | | |
| Male | 41(48.2) | 46 (52.3) | 48 (53.9) | 43 (50.0) | 39 (46.4) | 39 (45.9) | 41 (47.7) |
| Mean (SD) age (years) | 42.6 (11.68) | 40.2 (11.97) | 41.8 (13.62) | 43.2 (14.06) | 43.3 (13.30) | 44.6 (13.13) | 41.9 (13.34) |
| Ethnic origin; n (%) | | | | | | | |
| Caucasian | 56 (65.9) | 57 (64.8) | 54 (60.7) | 86 (100) | 84 (100) | 85 (100) | 86 (100) |
| Other | 29 (34.1) | 31 (35.2) | 35 (39.3) | 0 | 0 | 0 | 0 |
| Diagnosis; n (%) | | | | | | | |
| Newly diagnosed | 16 (18.8) | 10 (11.4) | 22 (24.7) | 10 (11.6) | 11 (13.1) | 12 (14.1) | 13 (15.1) |
| History of ulcerative colitis | 69 (81.2) | 78 (88.6) | 67 (75.3) | 76 (88.4) | 73 (86.9) | 73 (85.9) | 73 (84.9) |
| Median (range) duration of current episode (days) | 21.0 (4 . 364) | 21.0 (1 . 147) | 21.0 (4 . 42) | 21.0 (5 . 84) | 21.0 (6 . 42) | 21.0 (3 . 35) | 21.0 (7 . 70) |
| Mean (SD) baseline UC-DAI total score | 6.68 (1.767) | 6.13 (1.532) | 6.44 (1.629) | 6.60 (1.50) | 6.56 (1.57) | 6.27 (1.34) | 6.43 (1.55) |
| Classification of disease; n (%) | | | | | | | |
| Left-sided* | 66 (77.6) | 78(88.6) | 71(79.8) | 63 (73.3) | 59 (70.2) | 67 (78.8) | 69 (80.2) |
| Involvement of transverse colon | 4 (4.7) | 4 (4.5) | 6 (6.7) | 6 (7.0) | 7 (8.3) | 4 (4.7) | 2 (2.3) |
| Pancolitis | 15 (17.6) | 6 (6.8) | 11 (12.4) | 17 (19.8) | 18 (21.4) | 14(16.5) | 15 (17.4) |

The pooled assessment is most valuable establishing efficacy in the Mesavancol 4.8 g/day QD arm as the lower dose was investigated in different dosing regimens between the two pivotal studies (BID and QD in study SPD476-301 and SPD476-302, respectively). A formal statistical analysis plan for the pooled Integrated Efficacy Summary (IES) was produced prior to the unblinding of studies SPD476-301 and 302 and included analyses of primary and secondary efficacy endpoints included in the original studies.

The primary efficacy variable for the pooled analysis was the percentage of **subjects in remission** at the end of 8 weeks of treatment. There was a notable difference between both active groups and placebo ($p<0.001$ for both comparisons) in the number of subjects who were in remission at Week 8. No statistical significant difference between active treatment arms could be demonstrated (see table 4). The odds ratio and its corresponding 95% CI were 2.89 (1.73, 4.82) for the 2.4 g/day group and 2.62 (1.57, 4.38) for the 4.8 g/day group. In a comparison of the two active groups, there was no evidence to suggest that the groups were different (odds ratio [95% CI]=0.91 [0.58,1.41]).

**Table 4.** **Analysis of Subjects in Remission in the SPD476 (Mesavancol) and Placebo Groups at Week 8. ITT Population (Pooled Studies SPD476-301 and 302)**

| | Placebo (N=171) | SPD476 2.4g/day (N=172) | SPD476 4.8g/day (N=174) |
|---|---|---|---|
| Number of subjects in remission | | | |
| n (%) | 30 (17.5) | 64 (37.2) | 61 (35.1) |
| 95% CI (%) | 12.0, 23.6 | 30.3, 44.7 | 28.2, 42.4 |
| Comparison of active vs. placebo* | | | |
| Odds ratio | | 2.89 | 2.62 |
| 95% CI | | 1.73, 4.82 | 1.57, 4.38 |
| p-value | | <0.001 | <0.001 |
| Comparison of 4.8g/day vs. 2.4g/day* | | | |
| Odds ratio | | | 0.91 |
| 95% CI | | | 0.58, 1.41 |
| p-value | | | 0.662 |

There was a notable difference between both active groups and placebo (p<0.001 for both comparisons) in the number of subjects, who showed **clinical improvement** at Week 8. The odds ratio and its corresponding 95% CI were 2.92 (1.87, 4.55) for the Mesavancol 2.4 g/day group and 3.44 (2.20, 5.38) for the Mesavancol 4.8 g/day group. In a comparison of the two active groups, there was no trend that the groups were different (odds ratio=1.18 [0.77,1.82]). Results in study SPD476-302 showed no statistically significant difference between Asacol 2.4 g/day three times daily (TID) and the Mesavancol groups.

There was a notable difference between both active groups and placebo (p<0.001 for both comparisons) for the number of subjects classed as a **treatment failure** at Week 8. In a comparison of the two active groups, there was no evidence to suggest that the groups were different (odds ratio=0.87 [0.53,1.44]). There was no statistically significant difference between the Mesavancol groups and the Asacol 2.4 g/day TID group.

At endpoint a dose-related response in ulcerative colitis **disease activity index (UC-DAI)** score was seen (table 5), with a mean change of 25% in the placebo group, 52% in the Mesavancol 2.4 g/day group and 57% in the Mesavancol 4.8 g/day group (p<0.001 for both the Mesavancol groups). However, there was no evidence of a difference in the comparison of the two active groups.

| Table 5. | Analysis of the Change from Baseline to Endpoint in UC-DAI Scores. ITT Population (Pooled Studies SPD476-301 and 302) | | |
|---|---|---|---|
| | Placebo (N=171) | SPD476 2.4g/day (N=172) | SPD476 4.8g/day (N=174) |
| Change from baseline to endpoint | | | |
| n (%) | 158 (92.4) | 167 (97.1) | 165 (94.8) |
| LS mean | -1.60 | -3.29 | -3.74 |
| Comparison of active vs. placebo* | | -1.69 | -2.14 |
| 95% CI | | -2.34, -1.06 | -2.78, -1.50 |
| p-value | | <0.001 | <0.001 |
| Comparison SPD476 4.8g/day vs. 2.4g/day* | | | -0.44 |
| 95% CI | | | -1.07, 0.19 |
| p-value | | | 0.168 |

In study SPD476-302 there was no statistically significant difference between the Mesavancol groups and the Asacol 2.4 g/day TID group.

The majority of subjects in all groups had a baseline stool **frequency and rectal bleeding** score of ≥1, with the percentages being similar in all groups. The proportion of subjects with scores <1 increased in all groups from baseline to endpoint.

In both studies there was no statistically significant difference between the Mesavancol groups with regard to changes in **sigmoidoscopy scores** from baseline to endpoint, or in study SPD476-302 between the Mesavancol groups and the Asacol 2.4 g/day TID group, with a trend toward greater improvement in mucosal appearance in favour of the 4.8 g/day group.

The results reported for the supportive studies are in line with the results mentioned for the pivotal studies.

The choice of the maintenance dose has been sufficiently motivated, although a 1200 mg/day dose has not been studied. At the moment, it is generally accepted that a drop in dose below 1.5 g/day could provide sub-optimal efficacy and could be considered inappropriate to investigate in a long-term study. Therefore, considering all the available information about the clinical profile of Mesavancol, published studies and prescribing habits of marketed mesalazine products in maintenance of remission, a Mesavancol dose of 2.4 g/day for maintenance of remission is considered appropriate.
Results from the long-term open-label study SPD476-303 show that the proportion of subjects withdrawing due to relapse was low, with the proportion of subjects who had not relapsed being approximately 88% in the Mesavancol 2.4 g/day QD group. Higher doses of mesalazine do not introduce an increased safety risk. The use of higher doses of mesalazine is in accordance with the current practice and fits with the latest opinions of the leading gastroenterologists. Given the resemblance between the results demonstrated in the submitted studies and the picture emerging from the general literature it can safely be concluded that Mesavancol 2.4 g/day is effective in maintaining patients in remission.

Overall conclusion on clinical efficacy
In conclusion, the clinical studies clearly demonstrated superior efficacy of Mesavancol over placebo. No statistical significant differences between Mesavancol and Asacol or both Mesavancol doses could be identified. The studies were not powered for a formal non-inferiority analysis. Therefore it will not be possible to conclude on the comparison of the two active treatment arms Mesavancol and Asacol. The secondary endpoints show a trend that both Mesavancol doses are more effective compared to Asacol with the higher 4.8 g/day dose consequently reporting the highest efficacy scores. The results reported in the studies are more or less comparable with the results mentioned in literature. Therefore, the clinical

studies strongly suggest that the efficacy of Mesavancol is comparable with other mesalazine containing products. Moreover, it can safely be concluded that Mesavancol 2.4 g/day is effective in maintaining patients in remission. The proposal in the SPC to restrict the higher 4.8 g/day dose for patients insufficiently treated with 2.4 g/day is in line with the observed effectiveness of both Mesavancol doses.
Both BID and QD dosing of Mesavancol are effective in the treatment of ulcerative colitis, with a trend in favour of the BID regimen, the clinical impact of this difference, however, is modest. It is to be expected that the adherence of the patient with mesalazine is better with once daily dosing compared to the twice daily dosing. A better adherence is associated with a lower risk of relapses.

For the maintenance indication it was considered appropriate to base it on extrapolation from other registered mesalazine-containing products, these being approved in both active disease and maintenance of remission. The results of study SPD476-303, can be used as a justification of this extrapolation. Study SPD476-303 has already been submitted. Two studies, SPD476-304 and SPD476-306, are ongoing. Study SPD476-304 is a non-inferiority study of Mesavancol 2.4 g/day given QD vs. Asacol 1.6 g/day given TID in the maintenance of remission in 410 subjects for 6 months treatment period, whereas study SPD476-306 is a 12-month superiority study, to investigate Mesavancol 2.4 g/day QD vs. Asacol 2.4 g/day given BID in patients with left-sided ulcerative colitis.

The final study reports of the studies SPD476-304 and SPD476-306 should be submitted upon completion. Given the resemblance between the results demonstrated in the already submitted study SPD476-303 and the picture emerging from the general literature it can be safely concluded that Mesavancol 2.4 g/day is effective in maintaining patients in remission. The MAH has agreed to submit the reports of SPD476-304 and SPD476-306 upon completion as a post-marketing commitment.

**Clinical safety**
The most common individual events with Mesavancol were headache, for which the incidence was considerably higher than with placebo, and flatulence, for which the incidence was similar. The safety profile as depicted in the placebo controlled safety pool was comparable with those found in literature. No unexpected adverse events were reported.
There was only one death during the clinical studies, in the long-term extension study SPD476-303. This death was not related to the study.
Overall, the incidence of serious adverse events was low (13/356) and consistent with the presence of acute ulcerative colitis. With the exception of the two cases of pancreatitis (one reported as possibly related and one as probably related), all other serious adverse events were reported to be unrelated to study medication.
The data for all haematology, biochemistry or urine analysis parameters analysed were unremarkable.

Data on active comparator Asacol in the clinical programme are limited to those from 86 subjects in study SPD476-302, receiving Asacol tablets 2.4 g/day (i.e. the recommended daily dose for acute disease). For the maintenance study SPD476-303, the following safety data were obtained. Overall, 174 subjects (37.9%) had a total of 384 treatment-emergent adverse effects in the Maintenance Phase Safety population over the 12 month period. The number and type of adverse effects were similar between both treatment groups (2.4 g/day BID and 2.4 g/day QD) and from data from the literature similar to other available 5-ASA formulations. The majority of adverse effects were of mild or moderate intensity, with just 12 subjects (2.6%) experiencing severe adverse effects.

However, the most relevant safety data are those obtained from long-term use of other mesalazine products, especially from those products where high doses have been used.
A comparison with other marketed mesalazine compounds thus indicates that overall, there were no novel or unexpected observations or concerns over the safety profile of Mesavancol, which was typical of that of other mesalazine products, including those prescribed at a lower dose than the maximum dose of Mesavancol 1200 mg used in the clinical program.
Additionally, there was no increase in adverse experiences with the higher Mesavancol dose compared with the lower dose.

The MEB has been assured that the clinical studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Mesalazine was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. It is unlikely that the number of patients taking mesalazine containing preparations will dramatically increase post-approval. A full assessment is performed in 114 healthy volunteers and 655 subjects with ulcerative colitis across ten studies, which did not raise concerns about the risks associated with mesalazine use.

The safety profile of mesalazine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post-authorisation, which are not adequately covered by the current SPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European risk management plan is not necessary for this product.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality part of the dossier is of sufficient standard for authorisation. There are a small number of outstanding issues for which the MAH has provided a commitment (see below). These issues can be dealt with post approval.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

As mesalazine is a well-established drug substance in the EU, the non-clinical components of the dossier have relied on an assessment of available data in the literature. The non-clinical overview, submitted by the MAH, has adequately described the pre-clinical pharmacology, pharmacokinetics and toxicology of mesalazine. This is acceptable for this application.

Pharmacokinetics of mesalazine from the Mesavancol 1200 mg tablet were adequately measured at the clinically relevant 2.4 and 4.8 g/day dose. Scintigraphic and pharmacokinetic data indicate that mesalazine is released from the tablet after a delay, avoiding the upper parts of the gastrointestinal tract where absorption is most pronounced, and that mesalazine is released in a sustained fashion over the lower parts of the colon.
Furthermore, adequate local mucosal exposure to mesalazine is obtained upon treatment of patients with advised 2.4 and 4.8 g/day dose.
Clinical pharmacokinetics in children remains to be studied. The MAH committed as such (see post-approval commitments below).

The clinical studies clearly demonstrate superior efficacy of Mesavancol over placebo. No statistical significant differences between Mesavancol and Asacol, or both Mesavancol doses could be identified. The studies were not powered to demonstrate non-inferiority of Mesavancol to Asacol. Therefore, it will not be possible to conclude on the comparison between the two active treatment arms. The secondary endpoints suggest that both Mesavancol doses are more effective compared to Asacol with the higher 4.8 g/day dose consequently reporting the highest efficacy scores. The results reported in the studies are more or less comparable with the results mentioned in literature. Therefore, the clinical studies strongly suggest that the efficacy of Mesavancol is comparable with other mesalazine containing products.
The proposal in the SPC to restrict the higher 4.8 g/day dose for patients insufficiently treated with 2.4 g/day is in line with the observed effectiveness of both Mesavancol doses.
Both BID and QD dosing of Mesavancol are effective in the treatment of ulcerative colitis, with a slightly statistically not significant difference in favour of the BID regimen, the clinical impact of this difference, however, is modest. It is to be expected that the adherence of the patient with mesalazine is better with once daily dosing compared to the twice daily dosing. A better adherence is strongly associated with a higher reduction of relapses.

For the maintenance indication it was considered appropriate to base it on extrapolation from other registered mesalazine-containing products, being approved in both active disease and maintenance of remission. The results of study SPD476-303 can be used as a justification of this extrapolation. Given the resemblance between the results demonstrated in the already submitted studies and the picture emerging from the general literature it can be safely concluded that Mesavancol 2.4 g/day is effective in maintaining patients in remission.

A comparison with other marketed mesalazine compounds thus indicates that overall, there were no novel or unexpected observations or concerns over the safety profile of Mesavancol 1200 mg, which was typical of that of other mesalazine products, including those prescribed at a lower dose that the maximum dose of Mesavancol used in the clinical program.

The Board followed the advice of the assessors. The concerned member states, on the basis of the data submitted, considered that Mesavancol 1200 mg demonstrated adequate evidence of efficacy for the approved indications as well as satisfactory risk/benefit profile and have therefore granted a marketing authorisation for Mesavancol 1200 mg, gastro-resistant, prolonged-release tablets from Giuliani S.p.A. The mutual recognition was finished on 14 December 2006.

There was no discussion in the CMD(h). Agreement between the concerned member states was reached during a written procedure.

The renewal date is 13 December 2011.

A European harmonised birth date has been allocated (20-02-1984) and subsequently the first data lock point for mesalazine is February 2010. The first PSUR is therefore expected in February 2010, after which a PSUR should be submitted every 3 years.

The following post-approval commitments were made during the procedure:

Quality – drug product

- The MAH committed to re-evaluate the limits for dissolution (tightening) when more batch and stability data have become available.
- The MAH committed to submit the promised results of the ongoing stability studies (with a.o. the full scale, recently manufactured production batches), up to the granted shelf-life.

Clinical

- The MAH committed to conduct a clinical-pharmacokinetic study in children.
- The MAH committed to submit the final study reports of the studies SPD476-304 and SPD476-306 upon completion.

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| ATC | Anatomical Therapeutic Chemical classification |
| AUC | Area Under the Curve |
| BP | British Pharmacopoeia |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Coefficient of Variation |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| OTC | Over The Counter (to be supplied without prescription) |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| PSUR | Periodic Safety Update Report |
| RH | Relative Humidity |
| SD | Standard Deviation |
| SPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |
| UC | Ulcerative colitis |
| USP | Pharmacopoeia in the United States |

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Scope | Procedure number | Type of modification | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| Deletion of contact details for the manufacturer as listed in the PIL under section 6. | NL/H/0733/ 001/P/001 | P | 1-11-2007 | 21-11-2007 | Approval | N |
| Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance; from a manufacturer currently approved. | NL/H/0733/ 001/IA/002 | IA | 29-5-2009 | 12-6-2009 | Approval | N |