

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Pentasa, Quintasa  
Salofalk  
Asacol  
Mesalazina  
(Mesalazine)**

**DK/W/001/pdWS/001**

<b>Rapporteur:</b>	DK
<b>Start of the procedure (day 0):</b>	28-01-2009
<b>Date of this report:</b>	04-12-2009
<b>Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):</b>	08-04-2009
<b>Deadline for CMS's comments (day 85):</b>	23-04-2009
<b>Date re-start procedure (day 90):</b>	02-11-2009
<b>Deadline for CMS's comments (day 115):</b>	27-11-2009
<b>Finalisation procedure (day 120):</b>	02-12-2009

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Pentasa, Quintasa Salofalk Asacol Asacol Mesalazina
INN (or common name) of the active substance(s):	Mesalazine (5-aminosalicylic acid)
MAH (s):	Ferring Dr. Falk Pharma Procter & Gamble Pharmaceuticals Tillotts Pharma AG Wyeth Lederle SpA
Pharmaco-therapeutic group (ATC Code):	A 07 EC 02
Pharmaceutical form(s) and strength(s):	<p><i>Ferring</i> Prolonged release granules 1 g, 2g Prolonged release tablet 500 mg Rectal suspension 1 g, 2 g, 4 g Suppositories 1 g</p> <p><i>Dr. Falk Pharma</i> Gastro-resistant tablets, enteric coated capsules 250 mg, 500 mg Gastro-resistant, prolonged release granules 500, 1000 mg Suppositories 250, 500 mg Foam 1000 mg Rectal enema 2 g/60 ml, 4 g/60 ml</p> <p><i>Procter &amp; Gamble Pharmaceuticals</i> Modified release tablets 400 mg, 800 mg Suppositories 250 mg, 500 mg Foam enema 1 g/metered dose</p> <p><i>Tillotts Pharma AG</i> Gastro resistant tablets 400 mg Suppositories 500 mg</p> <p><i>Wyeth Lederle SpA</i> No information</p>

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## I. EXECUTIVE SUMMARY

There are approved paediatric posologies for the indication of mesalazine; however these posologies vary between MAHs. The indication and doses are largely based on expert opinion and extrapolation from pharmacokinetic studies in children and adults.

The data packages submitted by the MAHs under article 45 of the Paediatric Regulation comprises both company sponsored studies and clinical non-sponsored studies. All studies have been performed with oral delayed or prolonged release preparations. Studies are mostly small and have limitations in methodology weakening the indication for oral mesalazine in children and adolescents with inflammatory bowel diseases.

However, inflammatory bowel disease has serious growth and development implications in the paediatric population. Because of this, and since there is no reason to believe that inflammatory bowel disease in children behaves differently from inflammatory bowel disease in adults (where mesalazine has been shown to be highly effective), and due to the established safety profile of mesalazine in paediatric patients, it is the rapporteur's opinion that the benefit-risk ratio tips in favour of an upholding of an indication for oral mesalazine in paediatric patients.

The MAHs also have summarised the spontaneous adverse events which have been received by the companies relating to use in children.

## II. RECOMMENDATION

For consistency between mesalazine containing products across the EU, it is recommended that the SmPC contains the following statement:

### For orally administered mesalazine

#### 4.2 Posology and administration

There is only limited documentation for an effect in children (age 6-18 years).

#### Children 6 years of age and older

- Active disease: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).
- Maintenance treatment: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

### For rectally administered mesalazine

- There is little experience and only limited documentation for an effect in children.

### III. INTRODUCTION

On 6 November 2008, the MAH (Ferring), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted 4 efficacy and safety studies and 1 bioavailability study for mesalazine where either Ferring or a Ferring partner was the sponsor. Further, the MAH has submitted copies of 10 published studies of mesalazine in the paediatric age group.

A short critical expert clinical overview has also been provided. The MAH proposes the following posology in children and adolescents for oral Pentasa in the SPC:

- *Active disease: To be determined individually, starting with 20-30 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).*
- *Maintenance treatment: To be determined individually, starting with 20-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).*

On 5 November 2008, the MAH (Dr. Falk Pharma GmbH), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted 1 efficacy and safety study for mesalazine where Dr. Falk Pharma was the sponsor. Further, the MAH has submitted copies of 3 published studies of mesalazine in the paediatric age group and a list of 9 pharmacokinetic studies, including 2 studies in children, and 7 efficacy studies including children.

A short critical expert clinical overview has also been provided. The MAH finds no grounds for updating the SPC. The present posology in children and adolescents for Salofalk in the SPC reads:

*Children older than 6 years of age*

***In acute attacks**, depending on disease severity, 30-50 mg mesalazine/kg/day should be given once daily preferably in the morning or in 3 divided doses. For **maintenance of remission**, 15-30 mg mesalazine/kg/day may be given in 2 divided doses. It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 mg.*

On 20 January 2009, the MAH (Proctor & Gamble Pharmaceuticals), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted 1 pharmacokinetic study for mesalazine where the MAH was the sponsor. The MAH does not give any information on other published studies of mesalazine in the paediatric age group.

A short critical expert clinical overview has also been provided. The MAH finds no grounds for updating the SPC, and adds that *"in section 4.2 of the SPC it is stated that the products are not recommended for children or that there is no dosage recommendation"*.

On 23 January 2009, the MAH (Tillotts Pharma AG), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted copies of 14 studies of mesalazine in the paediatric age group.

The MAH has not submitted a short critical expert clinical review.

The MAH proposes following updating to the SPC for Asacol (tablets, suppositories and enema):

#### Section 4.2 Posology and administration

*There is no specific dose recommendation for children (see section 4.4)*

#### Section 4.4 Special warnings and special precautions for use

*A limited number of clinical studies have been performed in children suggesting that mesalazine dose-range 15-100 mg/kg/day that was shown to be effective and tolerated by the majority of children (age 9-18).*

On 23 January 2009, the MAH (Wyeth Lederle SpA), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted copies of 16 studies of mesalazine in the paediatric age group. However, the MAH informs that Mesalazine Wyeth never has been on the market and the marketing authorization of the product has not been reviewed in 2004; and further that the company is waiting the BoH issuing the formal provision of cancellation of registration. Consequently, the MAH has not submitted a short critical expert clinical review and has not remarked on the SPC.

#### **Assessor's comment**

The MAH's have not provided detailed information regarding the methods used for review of the literature. One MAH has not submitted a short critical expert clinical review.

#### **Mesalazine and its indication**

Mesalazine, also known as Mesalamine (in the US) or 5-aminosalicylic acid (5-ASA), is an anti-inflammatory drug used to treat inflammation of the digestive tract. In order to overcome rapid absorption and inactivation of pure mesalazine in the proximal gastrointestinal tract, and to avoid the sulfapyridine related side effects of Salazopyrin (SASP), oral mesalazine preparations have been developed to ensure delivery of therapeutic amounts of mesalazine to the distal small intestine and colon by encapsulating of mesalazine in special matrices resulting in delayed release in the distal intestine. One example is the coating of mesalazine with pH-sensitive acrylic resins. Alternatively, mesalazine can be encapsulated with a semipermeable ethylcellulose membrane.

Mesalazine is used in the following indications:

- Via the oral route (delayed release) for the treatment of acute inflammatory bowel diseases (Crohn's disease and ulcerative colitis), and for maintenance therapy to reduce the risk of disease recurrence.
- Via the rectal route (suppositories, enemas, foams) for the treatment of acute inflammatory bowel diseases (Crohn's disease and ulcerative colitis), and for maintenance therapy to reduce the risk of disease recurrence.

Mesalazine has its effects locally in the intestine. The absorption of mesalazine demonstrate large variations, however is generally from 30-50 % after oral administration and 10-20 % after rectal administration.

#### **Condition to be treated**

Inflammatory bowel disease (IBD) first presents in childhood and adolescence in approximately 20% of all cases). The incidence of Crohn's disease seems be more than double the incidence of ulcerative colitis. The anatomic distribution of inflammatory bowel disease is similar to that seen in adults. The underlying pathogenesis of IBD in children appears to be similar to that in adult onset such that IBD results from a complex interaction of environmental, genetic, and immune factors. Genetics, however, may play an even greater role in disease onset and

susceptibility in patients who present earlier in life. Growth failure is a unique complication of paediatric IBD, caused by a combination of inadequate calorie intake, increased losses and active inflammation. Efficacy of medical treatment and concomitant mucosal remission is characterised by normal linear growth and pubertal development.

## **IV. SCIENTIFIC DISCUSSION**

### **IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)**

Many studies do not specify which kind of oral formulation that has been used. In the studies with this information, almost all studies have used oral prolonged or delayed release preparations, either tablets or granules. No studies but only abstracts have been presented with rectal administration of mesalazine.

In the MAH sponsored studies the following pharmaceutical formulation has been used:

#### **Study 93-PTA-01.**

Prolonged release mesalazine (Pentasa), 250 mg tablets.

#### **Study Pen 2a-30.**

Prolonged release mesalazine (Pentasa), 250 mg tablets.

#### **Study PE-CR-0187.**

Prolonged release mesalazine (Pentasa), 250 mg tablets.

#### **Study PENTACOMP/90/01.**

Prolonged release mesalazine (Pentasa), 500 mg tablets.

#### **Bioavailability of 5-aminosalicylic acid from slow release 5-aminosalicylic acid drug and sulfalazine in normal children. Dig Dis Sci 1993;38:1831.**

Prolonged release mesalazine (Pentasa), 250 mg tablets.

#### **Study SAG-24/UCA.**

Gastro resistant-prolonged release mesalazine (Salofalk) granules, 500, 1000 mg.

#### **Study 2005018.**

Delayed release mesalazine (Asacol), 400 mg tablets.

### **IV.2 Non-clinical aspects**

No studies have been submitted.

## **IV.3 Clinical aspects**

### **1. Introduction**

#### **1. Ferring**

The MAH has submitted 4 efficacy and safety studies and 1 bioavailability study where the MAH or partner was the sponsor:

**Study 93-PTA-01. A study to evaluate efficacy and tolerability of mesalazine slow-release tablets in the treatment of acute mild to moderate ulcerative colitis and in the remission's maintenance in the paediatric age.**

**Study Pen 2a-30. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. J Pediatr Gastroenterol Nutr 1993;17:186.**

**Study PE-CR-0187. Effect of an oral slow-release 5-aminosalicylic acid preparation in the treatment of children and adolescents with Crohn's Disease of the small bowel.**

**Study PENTACOMP/90/01. Efficacy of mesalazine 500 mg tablets in preventing relapses of quiescent Crohn's disease in children.**

**Bioavailability of 5-aminosalicylic acid from slow release 5-aminosalicylic acid drug and sulfalazine in normal children. Dig Dis Sci 1993;38:1831.**

#### **2. Dr Falk Pharma**

The MAH has submitted 1 efficacy and/or safety study where Dr Falk Pharma was the sponsor:

**Study SAG-24/UCA. Observational study of the efficacy and safety of Salofalk® 500 mg/1000 mg Granu-Stix® for the acute and maintenance of remission treatment of ulcerative colitis patients.**

#### **3. Proctor & Gamble Pharmaceuticals**

The MAH has submitted 1 pharmacokinetic study where Proctor and Gamble was the sponsor:

**Study 2005018. A randomized, open-label, parallel-group study to determine the pharmacokinetics of mesalamine following administration of 30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day as 400 mg delayed-release tablets given every 12 Hours for 28 Days to children and adolescents with active ulcerative colitis.**

#### **4. Tillots Pharma AG**

No sponsored studies have been submitted.

## **2. Clinical study(ies)**

### **1. Ferring**

#### **Sponsored studies**

**Study 93-PTA-01. A study to evaluate efficacy and tolerability of mesalazine slow-release tablets in the treatment of acute mild to moderate ulcerative colitis and in the remission's maintenance in the paediatric age.**

#### **Description**

This single centre, single blinded study was performed to assess the therapeutic efficacy and tolerability of the mesalazine 20 mg/kg/day versus 40 mg/kg/day in the acute treatment of paediatric patients suffering from mild to moderate ulcerative colitis, and to assess the efficacy and tolerability of the mesalazine 20 mg/kg/day versus sulphasalazine (SASP) 20 mg/kg/day of in the maintenance of the state of remission of ulcerative colitis.

#### **Methods**

##### **Objective(s):**

To evaluate and compare the therapeutic efficacy and tolerability of a slow release mesalazine 40 mg/kg/day versus 20 mg/kg/day in the treatment of paediatric patients suffering from acute, mild to moderate ulcerative colitis.

To evaluate and compare the efficacy and tolerability of a 20 mg/kg/day slow release mesalazine versus 20 mg/kg/day of sulphasalazine in the prevention of disease occurrence.

##### **Study design:**

The study was designed as a single blind, single centre clinical trial. Randomisation was performed by the investigator (according to a randomization list). The study was divided in two phases:

##### *Phase 1*

Thirty patients with acute ulcerative colitis, divided into two groups, were treated with 5-ASA 20 mg/kg/day versus mesalazine 40 mg/kg/day for a period of 8 weeks.

##### *Phase 2*

All patients in remission from phase 1 were treated with mesalazine 20 mg/kg/day versus SASP 20 mg/kg/day for a period of 12 months.

##### **Study population /Sample size:**

Twenty-seven patients, age range 2-16 years suffering from active, mild to moderate ulcerative colitis.

##### **Treatments:**

##### *Phase 1*

Fifteen patients (group A) mesalazine slow release tablets (Pentasa 250 mg tablets) at a dosage of 20 mg/kg/day in three divided dosages. Twelve patients (group B) mesalazine slow release tablets (Pentasa 250 mg tablets) at a dosage of 40 mg/kg/day in three divided dosages during a period of 8 weeks.

### *Phase 2*

All patients of the group A and B who reached the remission were randomized to receive either mesalazine slow release tablets (Pentasa 250 mg tablets) at a dosage of 20 mg/kg/day or SASP at a dosage of 20 mg/kg/day during a period of 12 months.

#### **Outcomes/endpoints:**

Efficacy of the 2 dose regimens was assessed by clinical, endoscopic and histological examination, performed at baseline, after 4 weeks (clinical examination only) and after 8 weeks, in the acute treatment of ulcerative colitis.

Once remission had occurred, efficacy was evaluated by clinical examination, performed every 3 months, and by endoscopic examination, performed every 6 months, in the 12 months' maintenance treatment.

Safety and tolerability to the dose regimens was observed by means of measurement of laboratory parameters. Moreover, safety was also evaluated reporting at each visit all adverse events experienced by the patients.

#### **Statistical Methods:**

Friedman's test was used to compare clinical and endoscopic data between periods. Mann Whitney U test was used to compare clinical and endoscopic data between groups. No power calculations were made.

### **Results**

#### **Recruitment/ Number analysed:**

One patient treated with 20 mg/kg/day (group A) failed to reach the remission during the acute treatment, and was withdrawn from the study. Two patients treated with mesalazine 20mg/kg/day and 1 treated with SASP 20mg/kg/day in the maintenance period were withdrawn from the study, because of recurrence of the disease.

#### **Baseline data:**

The treatment groups were comparable with respect to demographics.

#### **Pharmacokinetic results:**

None

#### **Efficacy results:**

### *Phase 1*

Stool consistency, bowel frequency, bleeding, mucus in stools, abdominal pain, tenesmus, and endoscopic and histological findings improved significantly in both treatment groups after 8 weeks' treatment, however no statistically significant differences were found between groups.

### *Phase 2*

The state of remission was maintained in 14 patients out of 17 (82.3%) admitted to the second phase of the study, 7 out of 9 (77.7%) in the mesalazine group, 7 out of 8 (87.5%) in the SASP group. Two mesalazine-treated patients did not maintain the state of remission between the month 3 and 6. One SASP-treated patient withdrew from the study between month 3 and 6 because of worsening of symptoms. The statistical comparison between the two groups showed no significant difference.

**Safety results:**

One patient treated with mesalazine 20mg/kg/day in the acute treatment reported headache. One patient coming from the group B and in the maintenance period treated with SASP 20mg/kg/day reported headache at month 9 (but he was already taking 5-asa enema in addition to the oral therapy).

No patients reported a deviation from the normal range of the laboratory values.

**Discussion**

The study demonstrated similar efficacies on remission rates of mild to moderate ulcerative colitis of slow release mesalazine at dosage levels of 20 mg/kg/day and 40 mg/kg/day. Further that dosage of mesalazine 20 mg/kg/day was as effective as sulphasalazine in maintaining remission of ulcerative colitis.

**Assessor's comments**

An old study with a small study population and hence with a limited statistical power. Also, it was performed single blind with no placebo group. Intent to treat statistics are not presented, and randomisation and outcomes are very vaguely described. Equipotent dosages of mesalazine and sulphalazine are not administered.

**Study Pen 2a-30. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. J Pediatr Gastroenterol Nutr 1993;17:186.****Description**

A clinical efficacy study of children with active Crohn's disease involving the small intestine. The study is in 2 parts: an open drug efficacy and safety study with slow release mesalazine (Pentasa; 30.6 ±9.0 mg/kg treated for 8.1 ±3.9 weeks; n = 12), and a double-blind, placebo-controlled cross-over study where the effect of slow-release mesalazine (Pentasa; 50 mg/kg/day for 8 weeks; n = 14) is compared with placebo.

**Methods****Objective(s):**

To study the clinical response and safety of slow release mesalazine in children with Crohn's disease.

**Study design:**

Open study (1 treatment arm).

Blinded study: Placebo-controlled double-blind cross-over study.

**Study population /Sample size:**

Open study: 14 children, mean age 14.1 ±0.7 years (range 10.5-18.5 years) were included.

Blinded study: 14 children, with a mean age of 13.8 ±0.5 years (range: 9.3-16.1 years).

**Treatments:**

Open study: Slow-release mesalazine, 250-750 mg three times daily, providing a mean daily dosage of 30.6 ±9.0 mg/day (range 12.8-53.8 mg/kg/day). Treatment duration: 8.1 ±3.9 weeks (range: 2-15 weeks).

Blinded study: Slow release mesalazine 50 mg/kg/day (maximum 3 g/day) or placebo, divided into 3 dosages for 8 weeks and subsequently crossed over after an intervening 4 weeks' wash-out period to receive the second drug for 8 weeks.

**Outcomes/endpoints:**

Activity of disease using different disease activity indices: The Harvey Index, CDAI, Lloyd-Still Index, van Hees Index; standard blood tests (haemoglobin, haematocrit, leucocyte count, platelet count, erythrocyte sedimentation rate, and serum albumin; adverse reactions were recorded at follow-ups.

**Statistical Methods:**

Open study: paired t-test.

Blinded study: non-parametric test. Sample size calculation based on a remission rate of 70 % on slow release 5-ASA and 25 % on placebo required 24 patients to be entered. A high drop-out rate and low recruitment rate required the study to be terminated prior to accrual of the calculated number.

**Results****Recruitment/ Number analysed:**

Open study: Two patients discontinued medication very early because of persistent abdominal pain and vomiting, which left 12 patients for evaluation.

Blinded study: 12 patients with disease localized to the terminal ileum, 2 patients with newly diagnosed disease. Two patients with colonic involvement were excluded. One patient dropped out prior to study medication and 5 patients dropped out prior to completion of phase 1. A further 2 patients dropped out during the wash-out period. 6 patients completed the entire 20 weeks.

**Baseline data:**

Open study: In 9 patients the inflammation was confined to the small bowel, the remaining 5 had coexistent involvement of the large intestine.

Blinded study: Disease localized to the terminal ileum.

**Pharmacokinetic results:**

Not presented.

**Efficacy results:**

Open study: Significant improvement in clinical symptoms based on the Harvey Index. There was a significant relation between disease activity and administered dose of slow release mesalazine.

Blinded study: The clinical disease activity indices in patients who were entered into the first study phase (i.e. patients with early withdrawal and patients who completed the first phase) did not differ significantly between active treatment and placebo. Clinical disease activity in the 6 patients who completed the entire 20 weeks demonstrated some significant differences within groups, in favour of slow release mesalazine; however, except for a significantly better van Hees Index Score after mesalazine compared to placebo, no differences in the other scores were demonstrated between groups.

**Safety results:**

No serious adverse effects were observed. In the open study 1 child developed mild hair loss after 3 months therapy which resolved 1 week after stopping treatment. No effects on blood tests were observed.

## Discussion

Results might suggest a role for slow release 5-ASA in Crohn's disease in children. However the study has serious methodological limitations.

### Assessor's comments

The sample size is very small and the post-hoc statistical evaluation limits the significance of the findings. The dropout rate was high and the study design (cross over study) inappropriate with a high risk of carry over effect.

## Study PE-CR-0187. Effect of an oral slow-release 5-aminosalicylic acid preparation in the treatment of children and adolescents with Crohn's disease of the small bowel.

### Description

This study was a randomized, double-blind, placebo-controlled crossover trial in paediatric patients with Crohn's disease localised to the small bowel. Study medication was Pentasa at a dosage 50 mg/kg daily. The trial lasted 20 weeks: each drug period lasted 8 weeks with an intervening "washout" period of 4 weeks.

### Methods

#### Objective(s):

The purpose of this study was to evaluate the efficacy of a slow release mesalazine in the treatment of Crohn's disease of the small bowel in children.

#### Study design:

This study was a randomized, double-blind, placebo-controlled crossover trial in paediatric patients with Crohn's disease of the small bowel. The trial lasted 20 weeks: each drug period lasted 8 weeks with an intervening "washout" period of 4 weeks. Data were collected every 4 weeks. Patients were randomly assigned either to the group Pentasa-Placebo or to the group Placebo-Pentasa by using coded numbers.

#### Study population /Sample size:

Fourteen patients aged 5-18 years with newly diagnosed or relapsed moderate to severe Crohn's disease involving the small intestine with or without cecal involvement, were included.

#### Treatments:

Patients were randomly assigned to receive as initial treatment either 250 mg Pentasa capsules or identical placebo capsules. The dosage was 50 mg/kg, approximated to the closest 250 mg, max. 3.0 g/day divided in 3 doses taken before meals.

#### Outcomes/endpoints:

Disease activity at four weekly intervals during the study (at entry and at each follow-up visit) for calculation of the following disease indices: 1) the Crohn's Disease Activity Index (CDAI), 2) the Van Hees Activity Index, 3) the Lloyd-Still Activity Index and 4) the Harvey Bradshaw Index of Crohn's disease.

At each four-weekly clinical visits, complete general physical examinations including temperature, blood pressure, height and weight were performed. In addition, detailed abdominal and perianal examinations were performed, along with assessments of extra intestinal symptoms, stool consistency, blood and mucus, and symptoms of lassitude, anorexia and nausea.

Laboratory evaluations (haematology, serum biochemistry and urinalysis) were obtained at baseline and at 4 weekly intervals. Adverse events were documented at each visit.

**Statistical Methods:**

Due to the small number of patients entered and a high drop-out rate data from the two treatment periods were pooled together (assuming no period and no sequence effects). The statistical technique used for comparison was the Wilcoxon Sign Rank Test.

**Results**

**Recruitment/ Number analysed:**

Due to difficulties in recruitment, a total of 14 patients were enrolled in this study. Among the 8 drop-outs, 1 did not receive medication' (dropped at baseline), and therefore not considered in any statistical analyses. During the course of the trial, six patients completed all visits.

**Baseline data:**

The treatment groups were comparable with respect to demographics.

**Pharmacokinetic results:**

None

**Efficacy results:**

The change from baseline (or washout) values was used to compare placebo and Pentasa treatment after 4 weeks and 8 weeks under medication. A significant difference ( $P = 0.0313$ ) in favour of Pentasa was found with respect to the total Van Hees Index after 8 weeks of treatment. There were no significant changes with respect to other disease activity indices. The mean change from baseline after 8 weeks of treatment was a drop of 18 for Pentasa versus an increase of 14 points for placebo. Symptoms showed no trend from baseline toward general improvement or deterioration. There were no obvious changes in patients' subjective complaints and physician's rating of therapeutic effect after 4 and 8 weeks of treatment, respectively.

**Safety results:**

Within each of the two treatment periods, only one patient had adverse event in the Pentasa group and 1 patient in the placebo group. No obvious changes in laboratory data occurred.

**Discussion**

The improvement in the Van Hees Score after 8 weeks of Pentasa treatment compared to placebo may serve to express a possible treatment effect in favour of Pentasa; however the interpretation of the study results is hampered by the small number of patients accrued and the high drop-out rate.

**Assessor's comments**

The study included only 14 paediatric patients and only 6 patients completed the study. This fact makes it very difficult to interpret the study results. An inappropriate study design (cross-over study) with a high risk of carry-over effect was used. Data from the two treatment periods were pooled together, wrongly assuming no period and no sequence effects.

## **Study PENTACOMP/90/01. Efficacy of mesalazine 500 mg tablets in preventing relapses of quiescent Crohn's disease in children**

### **Description**

A large efficacy and safety double-blind randomised multicenter study including 137 children and young people <20 years with Crohn's disease. Slow release mesalazine (Pentasa; 50 mg/kg) or placebo was taken orally for 12 months after a flare-up was treated with medications and/or nutrition. Recurrence of disease was the effect variable tested.

### **Methods**

#### **Objective(s):**

The primary objective was to assess relapse rate at 1 year associated with administration of slow release mesalazine (Pentasa) immediately after a flare-up of Crohn's disease in comparison with administration of placebo.

The secondary objectives were to assess clinical and biological safety in children.

#### **Study design:**

Multicenter, prospective, randomised, controlled, double blind trial comparing administration of oral Pentasa as preventive treatment of relapse in comparison with placebo in children with Crohn's disease. Patients were randomised in 2 strata according to the treatment received for initial flare-up, medications only and parenteral or enteral feeding as part of the therapy.

#### **Study population /Sample size:**

137 patients, aged <20 years, were pre-included, 132 randomised, 122 in the per protocol population. Patients were at the end of treatment of the flare-up (Harvey-Bradshaw score <5) by one of the following treatments: parenteral and enteral feeding, steroids, sulphasalazine and/or metronidazole as long as this treatment had not been used for more than 6 months at initial dosage when clinical remission was obtained.

The initial trial was planned to recruit 60 patients based on power calculations (50 % difference in relapse rate). The results of the analysis performed on this population (57 recruited patients; period 1) failed to show any statistical difference between mesalazine and placebo groups, but a trend was present. It was therefore decided to extend the study, increasing the number of patients to 120 evaluable patients (period 2).

#### **Treatments:**

Mesalazine (Pentasa®), 500 mg tablets, oral route, 2 daily administration, daily dose = 50 mg/kg. Placebo tablets contained excipients only, and were identical in appearance to mesalazine. Duration of treatment was 12 months.

#### **Outcomes/endpoints:**

##### *Efficacy*

Maintenance of clinical remission in patients after withdrawal of all treatments. The occurrence of a flare-up during the trial was defined as a Harvey-Bradshaw score  $\geq 5$ . Secondary efficacy endpoint: possibility to withdraw steroid treatment.

##### *Safety*

Adverse events occurrence, ECG monitoring, biological monitoring for hepatic, renal and pancreatic parameters

## **Statistical Methods:**

### *Efficacy*

Comparisons were performed using chi-square test or Fisher exact-test or Mann-Whitney test for quantitative ones. Time-to-event curves were compared using log-rank test: univariate analysis, proportional hazards model (Cox model): univariate and multivariate analyses with relative hazard ratio estimate  $\pm$  standard error and with backward selection, if necessary, through likelihood ratio test.

### *Safety*

Description of Adverse Events and Serious Adverse Events, comparison of amylasaemia evolution using ANOVA, ECG presented as descriptive tables.

## **Results**

### **Recruitment/ Number analysed:**

132 patients were randomized (68 mesalazine, 64 placebo). 10 patients were excluded (8 mesalazine, 2 placebo), leaving 122 (60 mesalazine, 62 placebo) for the per protocol analysis.

### **Baseline data:**

No statistically significant differences between groups regarding demography data at pre-inclusion and at randomization were observed. Disease baseline characteristics were also similar in the 2 groups. The majority of patients were males (60%) mean age was  $11.8 \pm 2.7$  years, range 3-19 years.

### **Pharmacokinetic results:**

Not examined.

### **Efficacy results:**

Regarding the maintenance of remission (absence of relapse), whatever the statistical technique used, the "mesalazine medication period 1" group (N=17) had always the most favourable prognosis with the lowest rate of relapse and the "mesalazine nutrition period 2" (N=12) had always the most unfavourable prognosis with the highest rate of relapse. The "mesalazine nutrition period 1" (N=9) group is indistinguishable from placebo in one analysis and better than placebo in the other model. The "mesalazine medication period 2 group" (N=18) and the 4 placebo groups (N=62) had an intermediate prognosis.

The same results have been demonstrated for failure.

In the Per Protocol Population, 12 months after withdrawal, the rate of patients still in remission in the mesalazine group was  $43 \pm 7$  % versus  $37 \pm 7$  % in the placebo group. Median time without relapse was  $10.7 \pm 2.1$  months in the mesalazine group versus  $6.2 \pm 1.8$  in the placebo group. On the whole Per Protocol Nutrition Stratum Population, 12 months after withdrawal, the rate of patients still in remission in the mesalazine group was  $33 \pm 11$  % versus  $42 \pm 12$  % in the placebo group. Median time without relapse was  $7.3 \pm 1.8$  months in the mesalazine group versus  $8.9 \pm 2.8$  in the placebo group. On the whole Per Protocol Medication Stratum Population, 12 months after withdrawal, the rate of patients still in remission in the mesalazine group was  $48 \pm 9$  % versus  $35 \pm 8$  % in the placebo group. Median time without relapse was 11.5months in the mesalazine group versus  $6.2 \pm 2.5$  in the placebo group.

No p-values are given

### **Safety results:**

163 AE were reported (72 in the mesalazine group and 91 in the placebo group), most frequently headache, diarrhoea, abdominal pain, vomiting. These AEs were equally distributed

between the groups. Only a few AEs (in 1 patient (1.5%) for the mesalazine group and 2 (3.1%) in the placebo group) were considered related to treatment. One patient stopped prematurely the study medication in the placebo group and 2 in the mesalazine group due to AEs.

SAEs were reported in 10 patients in the mesalazine group, hospitalisation for relapse of Crohn's disease in 6 patients, hospitalization for abdominal pain in 2 patients (with complete recovery) and occurrence of interstitial nephritis of unknown origin in the last one. 8 patients in the placebo group reported SAEs: 5 hospitalizations for Crohn's disease relapse, one vagal malaise with complete recovery, one serum lipase and amylase levels increase, one interstitial pneumopathy.

The evolution of amylasaemia was not different between the two groups and was not significant within groups.

Regarding ECGs, no variation of ECG was reported in the mesalazine group when 2 patients in the placebo group had an ECG considered as normal at entry and an abnormal ECG when they stopped the study.

### **Discussion**

The efficacy results of this study are quite unclear, as the treatment effect varies with the period of recruitment of patients. The results cannot be used to argue for a better effect of Pentasa on Crohn's disease remission rates compared to placebo. Regarding safety, adverse events reporting was similar in placebo and mesalazine groups.

### **Assessor's comments**

Intent-to-treat analysis is not performed on the whole population – only on the stratified populations. Only descriptive data analyses, statistical analysis of the data are not presented. Although the study is large and designed properly, results cannot be used to argue for the superiority of slow release 5-ASA over placebo in reducing the risk of Crohn's disease recurrence.

## **Bioavailability of 5-aminosalicylic acid from slow release 5-aminosalicylic acid drug and sulfalazine in normal children. Dig Dis Sci 1993;38:1831**

### **Description**

A bioavailability study comparing slow-release mesalazine with sulphalazine (SASP). Mesalazine was given first for 7 days immediately followed by SASP for 7 days.

### **Methods**

#### **Objective(s):**

To compare the bioavailability of slow release mesalazine with the bioavailability of mesalazine (5-ASA) from SASP.

#### **Study design:**

Open and non-randomized. Faeces and urine collected on days 6 and 7 in each medication period. Fasting plasma values and hourly plasma values were obtained on day 6 for the first 4 hours after the morning dose.

#### **Study population /Sample size:**

Nine healthy children; median age 10 years (range: 7-13).

**Treatments:**

Slow-release mesalazine, 250 mg 4 times daily for 1 week, and then SASP, 1000 mg on day 1 and 2, gradually increased to 500 mg 4 times daily on days 3 to 7.

**Outcomes/endpoints:**

Faecal water concentrations, urinary excretions and plasma concentrations of mesalazine and acetyl-5-ASA.

**Statistical Methods:**

Non-parametric.

**Results****Recruitment/ Number analysed:**

One child was withdrawn due to dyspepsia during SASP treatment. The other 8 completed the study.

**Baseline data:**

Not presented.

**Pharmacokinetic results:**

Median concentrations of mesalazine in faecal water was 4.44 (2.49-9.25) mmol/l during slow release mesalazine and 6.25 (3.36-10.0) during SASP (NS), while acetyl-5-ASA was 29.86 (21.64-38.2) mmol/l during mesalazine compared to 8.33 (2.79-20.62) mmol/l during SASP (P <0.001). The median total urinary excretion (in % of the daily dosage) was 32.4 % (28.3-47.7) after mesalazine and 25 % (16.3-35.8) after SASP (NS). The median excretion of acetyl-5-ASA was 31.9 % (27.7-45.8) after mesalazine and 23.8 % (16.1-34.7) after SASP (P <0.05). Mesalazine and acetyl-5-ASA plasma concentrations were higher after slow release mesalazine compared to treatment with SASP (statistics not given).

**Efficacy results:**

None.

**Safety results:**

One child developed a rash that subsided two days after the end of the study. One child developed dyspepsia during SASP treatment that required reduction dosage.

**Discussion**

Data suggest that the systemic bioavailability of mesalazine is higher in children after slow release mesalazine compared to SASP. The faecal water concentrations of mesalazine were comparable during the 2 regimens, albeit somewhat higher during treatment with SASP.

**Assessor's comments**

An open non-randomized study with a very small study population, with design limitations and with a limited statistical power. The study did not use comparable mesalazine dosages (1000 mg mesalazine with slow release mesalazine and 800 mg with sulfalazine). The study included healthy children; the bioavailability of the drugs might be different in children with IBD.

## **Additional references**

Furthermore, the MAH has enclosed copies of the following publications after a search of the literature:

**Fallingborg J et al. Measurement of gastrointestinal pH and regional transit times in normal children. J Pediatr Gastroenterol Nutr 1990;11:211.**

The study does not include treatment with mesalazine and children with IBD, and is only indirectly suggestive of the effect of 5-ASA in children.

**Cezard JP et al. Oral mesalamine (Pentasa) as maintenance treatment in pediatric Crohn's disease patients with recently induced remission. A multicenter placebo-controlled study. J Pediatr Gastroenterol Nutr 1996;22:430.**

The study is published in abstract form. Study PENTACOMP/90/, reviewed above.

**Cezard JP et al. Prevention of recurrence by mesalamine (Pentasa) in pediatric Crohn's disease. A multicentric double blind trial.**

The study is published in abstract form. Study PENTACOMP/90/, reviewed above.

**Scagnelli GP et al. Treatment of inflammatory bowel disease (IBD) with oral 5-amino salicylic acid (5-ASA) (Pentasa) in the pediatric age group. Gastroenterology 1991;100:A248.**

The study is published in abstract form only.

**Barden L et al. Mesalazine in childhood inflammatory bowel disease. Aliment Pharmacol Ther 1989;3:597.**

Descriptive tolerability study in which 67 children and adolescents with inflammatory bowel disease 5-19 years of age were followed. 45 patients had changed treatment from sulphalazine to slow release mesalazine and 22 newly diagnosed patients started mesalazine treatment. Patients were followed for 6 months. No serious adverse reactions occurred.

**D'Agata ID et al. Mesalamine in pediatric inflammatory bowel disease: a 10-year experience. Inflamm Bowel Dis 1996;2:229.**

Charts of 153 paediatric patients with inflammatory bowel disease who were treated with mesalamine were reviewed. Treatment dosage for both acute disease and maintenance therapy was 36 mg/kg/day, increasing slightly over the years. Diarrhoea was the most common side effect. No serious adverse reactions were observed.

**Escher JC. Treatment of inflammatory bowel disease in childhood: best available evidence. Inflamm Bowel Dis 2003;9:34.**

An overview of different therapies for inflammatory bowel diseases in children is presented.

**Cuffari C. Crohn's jejunoileitis: the pediatrician's perspective on diagnosis and management. Inflamm Bowel Dis 2005;11:696**

An overview of different diagnostic modalities and therapies for Crohn's disease in children is presented.

**Greifer MK et al. Update in the treatment of paediatric ulcerative colitis. Expert Opin Pharmacother 2006;7:1907.**

An overview of different therapies for ulcerative colitis in children is presented.

**Tung J et al. A population-based study of the frequency of corticosteroid resistance and dependence in pediatric patients with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 2006;12:1093.**

Charts were reviewed for patients who were diagnosed with inflammatory bowel disease before age 19 years to examine the 1 year outcome after a first course of corticosteroids. Mesalazine treatment effects or safety were not examined.

**Assessor's comments**

There were no clinical efficacy studies among those submitted. Many were descriptive or only presented in abstract form. The overview reports (no systematic reviews are presented) did not supply new information with respect to mesalazine treatment for inflammatory bowel disease in childhood and adolescence. The MAH does not describe the search strategy.

**2. Dr. Falk Pharma**

**Sponsored studies**

**Study SAG-24/UCA. Observational study of the efficacy and safety of Salofalk® 500 mg/1000 mg Granu-Stix® for the acute and maintenance of remission treatment of ulcerative colitis patients.**

**Description**

A prospective observational study of patients with ulcerative colitis, acute or in remission, who were treated with delayed and sustained release mesalazine at no fixed dosage.

## Methods

### Objective(s):

To obtain post-marketing surveillance data regarding the safety, efficacy, and patient's acceptance with treatment in ulcerative colitis (UC) out-patients, who were treated with Salofalk® 500 mg/1000 mg GranuStix® for the acute or maintenance treatment.

### Study design:

A prospective, multicentre, non-interventional, observational, post-marketing surveillance study. It was planned that approximately 200 physicians should participate. Overall, 273 physicians participated and 128 physicians recruited patients into the study.

### Study population /Sample size:

Adults and adolescents with endoscopically diagnosed ulcerative colitis with disease in remission or in an acute disease stage.

### Treatments:

Salofalk® 500 mg/1000 mg Granu-Stix® (delayed and sustained release mesalazine). The dosage and treatment duration were only recommended.

### Number of Patients (Total and for each centre):

It was planned to observe approximately 1000 patients over a period of 12 weeks.

### Outcomes/endpoints:

#### *Efficacy*

- Rate of clinical remission, defined as Clinical Activity Index (CAI)  $\leq 4$ , at the final/withdrawal examination.
- CAI in the course of the study.
- Frequency of stools per day, rectal bleeding, and the severity of abdominal pain/cramps, as well as the general well-being was assessed.
- Rating of therapy success (very good, good, satisfying, bad).
- Patient's assessment of therapy.
- Patient's acceptance and preference of the study drug.

#### *Safety*

- Suspected adverse drug reactions (ADRs).
- Assessment of tolerability by physician and patient.

### Statistical Methods:

Descriptive statistics were used to summarize the results. Sample size calculation not performed.

## Results

### Recruitment/ Number analysed:

Only 9 patients, 8 with active disease and 1 adolescent in remission, were younger than 18 years (range of 12 to 17 years) at the beginning of the individual observation period.

### Baseline data:

None presented.

### Pharmacokinetic results:

None presented.

### Efficacy results:

Data suggest that CAI decreases in paediatric patients with acute disease from a mean of around 6 to 1 after 12 weeks treatment. Data for children and adolescents with respect to the remaining efficacy variables are not presented.

**Safety results:**

No adverse reactions were reported.

**Discussion**

Data suggest that delayed and sustained release mesalazine is effective in decreasing acute ulcerative colitis in children and adolescents.

**Assessor's comments**

A very small prospective observational study. The only efficacy data presented is disease activity index. The study can hardly be used to argue for clinical efficacy of mesalazine in the paediatric patient.

**Additional references**

Furthermore, the MAH has enclosed copies of the following publications:

**Hadziselimovic F et al. Case controlled open-study on the pharmacokinetics and treatment effect of 5 aminosalicyl acid (5-ASA) in children with ulcerative colitis. In Inflammatory Bowel Diseases – Progress in Basic Research and Clinical Implications. Falk-Symp No. 60, 1990.**

The study is published in abstract form only, albeit with an enclosed poster.

**Hadziselimovic F. Therapy of chronic inflammatory bowel disease during childhood. Pädiat Prax 1991;42:443.**

An overview of medical therapies for inflammatory bowel disease is presented.

**Hadziselimovic F et al. Long-term effect of the treatment with 5-ASA in children with IBD. World Congress of Pediatric Gastroenterology, Hepatology and Nutrition. Boston, Massachusetts, USA, 2000.**

The study is published in abstract form only.

**Assessor's comments**

The 2 abstracts submitted give too insufficient information to judge the scientific value of the presented data. The overview gives no new information with respect to the treatment with mesalazine in the paediatric patient group. The MAH does not describe their search strategy.

### 3. Proctor & Gamble Pharmaceuticals

#### Sponsored studies

**Study 2005018.** A randomized, open-label, parallel-group study to determine the pharmacokinetics of mesalazine following administration of 30 mg/kg/day, 60 mg/kg/day, and 90 mg/kg/day as 400 mg delayed-release tablets given every 12 Hours for 28 Days to children and adolescents with active ulcerative colitis

#### Description

This is an open label study examining pharmacokinetics of delayed release mesalazine in children and adolescents 4 weeks after start of therapy.

#### Methods

##### Objective(s):

###### *Primary objective*

To characterize mesalazine pharmacokinetics following 28 days of oral administration of 30 mg/kg, 60 mg/kg, or 90 mg/kg given in divided doses every 12 hours as Asacol 400 mg tablets to children and adolescents with ulcerative colitis.

###### *Secondary objectives*

To obtain safety and tolerability data concerning the use of mesalazine in children and adolescents with ulcerative colitis.

##### Study design:

Open-label, randomized, 28-day parallel-group study in children and adolescents with active UC. Patients were stratified by age (5-8 years and 9-17 years) and randomly assigned to receive every 12 hours one of the 3 doses of delayed release mesalazine.

##### Study population /Sample size:

Children and adolescents diagnosed with mild to moderate ulcerative colitis.

##### Treatments:

Patients were administered 400 mg delayed release mesalazine tablets. Patients took study medication twice daily every 12 hours, at approximately the same time each day without regard to meals. In cases where the total daily dose was an uneven number of tablets, patients took the greater number of tablets at the morning dose.

##### Number of Patients (Total and for each centre):

A total of 38 patients were screened. Thirty-four patients (6 in the 5-8 years cohort and 28 in the 9-17 years cohort) were enrolled at 9 study sites in the United States: 10 patients in the 30 mg/kg group and 12 patients each in the 60 and 90 mg/kg groups. An additional 12 sites did not enrol patients.

##### Outcomes/endpoints:

For the evaluation of pharmacokinetics urine samples were collected at baseline and at 2 intervals after the evening dose on day 27 and the morning dose on day 28. Blood samples were collected at baseline and days 7, 14, 21 27 and 28.

Safety assessments included clinical laboratory evaluations (chemistry and haematology) and the collection of adverse events reported by the patient or parent/guardian, or observed by the investigator or study site personnel.

**Statistical Methods:**

Analysis of variance model analyzing trough concentrations was used to determine the time point at which steady state was achieved for mesalazine and N-Acetyl-5-ASA. Pharmacokinetic parameters were summarized for mesalazine and N-Acetyl-5-ASA by age cohort and dose level. Regression analyses were used to explore relationships between mesalazine and N-Acetyl-5-ASA pharmacokinetics.

**Results**

**Recruitment/ Number analysed:**

Thirty-one patients completed the study and 3 (all in the 9-17 years cohort) discontinued early. Thus, the intention-to-treat (ITT) population included 33 patients. Pharmacokinetic data were obtained from 27 patients.

**Baseline data:**

There was approximately the same number of males and females in each age cohort and the majority of the patients were Caucasian. No obvious differences between randomized treatment groups with respect to age at screening, sex, race, and baseline height and weight were observed.

**Pharmacokinetic results:**

In the table are presented summary pharmacokinetic data by dose and age group for evaluable patients.

Overall Summary Table of Geometric Mean (Range) PK Parameters by Dose and Age Group for PK Evaluable Patients						
PK parameters	30 mg/kg/day		60 mg/kg/day		90 mg/kg/day	
	5-8 years (n = 0)	9-17 years (n = 7)	5-8 years (n = 2)	9-17 years (n = 8)	5-8 years (n = 3)	9-17 years (n = 7)
<b>5-ASA</b>						
C <sub>max</sub> (ng mL)	No data	1501.6 (441, 9050)	1419.4 (1380, 1460)	3633.5 (1980, 6840)	1801.878 (789, 3340)	4640.4 (1770, 9210)
AUC <sub>0-24</sub> (ng.hr mL)	No data	15812.67 (5383, 47752)	9585.48 (4452, 20637)	35000.54 (11477, 101508)	19479.65 (13515, 39019)	50325.13 (20167, 112036)
C <sub>avg</sub> (ng mL)	No data	658.861 (224.30, 1989.66)	399.395 (185.51, 859.88)	1458.356 (478.22, 4229.50)	811.653 (563.14, 1625.77)	2096.880 (840.31, 4668.18)
<b>N-Ac-5-ASA</b>						
C <sub>max</sub> (ng mL)	No data	2246.2 (953, 5360)	1116.6 (878, 1420)	3511.2 (2610, 6830)	2061.50 (1170, 3840)	4674.6 (2200, 9980)
AUC <sub>0-24</sub> (ng.hr mL)	No data	29606.98 (11937, 69384)	9896.86 (4201, 23316)	41061.72 (20358, 71617)	26977.16 (15965, 51757)	58746.20 (27584, 106728)
C <sub>avg</sub> (ng mL)	No data	1233.624 (497.39, 2891.00)	412.369 (175.04, 971.50)	1710.905 (848.23, 2984.06)	1124.048 (665.21, 2156.53)	2447.758 (1149.35, 4447.00)

The mean plasma concentrations at steady state ranged from 400 to 2100 ng/ml, based on data from all dose levels, a variability that reflects that seen in adults. Steady state was achieved with respect to both mesalazine and N-Acetyl-5-ASA by Day 7, i.e., 144 hours 21 following the first study dose (p = 0.6756 and p = 0.5618, respectively). Results indicate that for a given mg/kg dose, age and body weight are significant covariates in predicting systemic exposure, i.e. identical mg/kg dosages will result in higher systemic exposures in patients with higher body weight and age, a finding consistent with the rationale that the same mg/kg dosage level in a person with a higher body weight will result in a higher total daily dose.

**Efficacy results:**

Not presented.

**Safety results:**

A total of 24 patients experienced 49 adverse events. Mesalazine was well tolerated by the patients. The most frequent reported adverse events were cough, headache, nausea, haematochezia, and bruising at the venipuncture site with no pattern observed across treatment groups. One serious adverse event occurred (in the 9-17 year old 60 mg/kg group) – exacerbation of UC due to a viral intestinal syndrome, doubtfully related to study drug. Of the 49 reported adverse events, the majority were mild in severity (44), and only 8 were considered study drug-related. There were no clinically significant laboratory abnormalities.

**Discussion**

The systemic exposures to mesalazine and N-Acetyl-5-ASA in paediatric patients administered Asacol can be determined using total daily dose (mg) incorporated in the dose proportionality relationship, without regard to age or body weight. Asacol therapy is safe and well-tolerated in children and adolescents with ulcerative colitis.

**Assessor's comments**

This is an open pharmacokinetic study with a small study population, especially the 5-8 year stratum, showing a large variability in steady state concentrations, a phenomenon that also has been observed in adults. No efficacy data are presented.

**Additional studies**

The MAH has not submitted any additional references

**4. Tillots Pharma AG****Sponsored studies**

No sponsored studies have been submitted

**Additional references**

The MAH has enclosed copies of the following publications:

**D'Agata LD et al. Mesalamine in pediatric inflammatory bowel disease: a 10 year experience. Gastroenterology 1995;108(4):A805.**

The study is published in abstract form. Probably including the same patient population as in the study published in their report in Inflammatory Bowel Diseases (1996;2:229), mentioned above.

**Dubinsky M. Special issues in pediatric inflammatory bowel disease. World J Gastroenterol 2008;14:413.**

An overview of diagnostic possibilities and medical therapies for inflammatory bowel disease is presented.

**Grand RJ et al. Inflammatory bowel disease in the pediatric patient. Inflamm Bowel Dis 1995;24:613.**

An overview of clinical manifestations, complications, diagnosis and treatment of IBD is presented.

**Hadziselimovic F. Therapie der chronisch entzündlichen Darmkrankheiten im Kindesalter. Pädiatr Prx 1991;42:443.**

An overview of medical therapies for inflammatory bowel disease is presented. The study is described above.

**Machida H. The pediatric patient with IBD – “Am I special?” Can J Gastroenterol 1992;6:334.**

An overview of clinical manifestations, complications, diagnosis and treatments of IBD is presented.

**Punati JB et al. Safety of high dose mesalamine (Asacol) in pediatric patients with inflammatory bowel disease. Abstract # 1267 DDW New Orleans, 2004.**

An abstract describing a retrospective chart review examining the safety of mesalazine (Asacol) over a 3 months' period in 58 children with inflammatory bowel disease. There were no significant differences in side effects between those who received a high daily dose of >70 mg/kg (74%) compared to those children who received a conventional daily dose (36%).

**Biancone L et al. European evidence-based consensus on the management of ulcerative colitis: special situations. J Crohn's Colitis 2008;2:63.**

An extensive review (ECCO consensus report) of the clinical manifestations, diagnosis and treatments of ulcerative colitis. There is a section on specific conditions in children in which it is stated that for induction of ulcerative colitis: “the advised dose (oral and rectal mesalazine combined) in children aged 12 years or older of mesalazine, is 50–75 mg/kg/day with a maximum of 4 g/day”. This dosage is based on expert opinion and extrapolation from studies in adults and from pharmacokinetic studies.

**Barden L et al. Mesalazine in childhood inflammatory bowel disease. Aliment Pharmacol Ther 1989;3:597.**

Descriptive tolerability study in which 67 children and adolescents with inflammatory bowel disease 5-19 years of age were followed. 45 patients had changed treatment from sulphalazine to slow release mesalazine and 22 newly diagnosed patients started mesalazine treatment. Patients were followed for 6 months. No serious adverse reactions occurred.

**Escher JC. Treatment of inflammatory bowel disease in childhood: best available evidence. Inflamm Bowel Dis 2003;9:34.**

An overview of different therapies for inflammatory bowel diseases in children is presented.

**Griffiths A et al. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. J Pediatr Gastroenterol Nutr 1993;17:186.**

Study Pen 2a-30 described above.

**Kirschner BS. Diagnosis and medical management of Crohn's disease and ulcerative colitis in children. Probl Gen Surg 1993;10:16.**

An overview of clinical aspects of inflammatory bowel diseases is presented.

**Rufo PA & Bousvaros A. Current therapy of inflammatory bowel disease in children. Pediatr Drugs 2006;8:279.**

An overview of the efficacy of different drug treatments for inflammatory bowel diseases.

**Tolia V et al. Oral 5-amino-salicylic acid in children with colonic chronic inflammatory bowel disease: clinical and pharmacokinetic experience. J Pediatr Gastroenterol Nutr 1989;8:333.**

A study in which 5 children between ages 10 to 17 years with inflammatory bowel disease were treated with prolonged release mesalazine (Asacol). 3 children responded to therapy. Plasma levels and urinary excretion of 5-ASA and its major metabolite Acetyl-5-ASA, were similar to those observed in adults.

**Walker-Smith JA. Chronic inflammatory bowel disease in children: a complex problem in management. Postgrad Med J 2000;76:469.**

A short overview of the clinical presentations and treatment of ulcerative colitis and Crohn's disease.

**Assessor's comments**

Most studies are submitted in abstract form which makes it impossible to judge the scientific value of the presented results. Only 1 small and old efficacy trial is presented. The overviews (no

systematic reviews) give no new information with respect to treatment of the paediatric age group with mesalazine. The bibliographical search strategy is not presented.

➤ **Post-marketing safety surveillance.**

One MAH has supplied a summary of adverse reactions which takes account of 290 cases of adverse reactions with slow release mesalazine reported in patients younger than 18 years, and covering 24 years from February 1984 to May 2007.

In children (2-11 years of age) serious adverse reactions were reported for 34 cases (listed: 25; unlisted 9) and non-serious for 35 cases (listed 15; unlisted 20 for a total of 71). The most frequent organ classes affected in children were: gastrointestinal disorders (28%), skin and subcutaneous disorders (12%), renal and urinary disorders (10%) and general disorders (8%). The most frequently reported events were headache, pancreatitis, pyrexia, abdominal pain, vomiting and alopecia.

In adolescents (12-17 years of age) serious adverse reactions were reported for 114 cases (listed 80; unlisted 34) and non-serious for 79 (listed 45; unlisted 34). The most frequent organ classes affected in adolescents were gastrointestinal disorders (28%), blood and lymphatic system disorders (7%), renal and urinary disorders (7%), skin and subcutaneous disorders (7%), and general disorders (7%). The most frequent organ classes affected in adolescents were pancreatitis, abdominal pain, alopecia, pyrexia, interstitial nephritis, diarrhoea, thrombocytopenia, vomiting and pericarditis.

The MAH concludes that almost all adverse effects are listed in CCDS and the main part of the events could be associated with the disease rather than treatment with mesalazine. The unlisted events are with few exceptions reported only once.

Two other MAHs have submitted summaries of adverse reaction; however these summaries include all age groups, not specifically the paediatric population.

**Assessor's comment**

Only 1 MAH have provided post-marketing safety surveillance data. These data indicate that slow release mesalazine has the same safety profile in the paediatric population (> 2 years of age) compared to the adult population.

**RAPPORTEUR'S PPdAR OVERALL CONCLUSION AND RECOMMENDATION**

➤ **Overall conclusion**

All studies have been performed with oral delayed release preparations. Studies are mostly small and have limitations in methodology weakening the indication for oral mesalazine in children and adolescents with inflammatory bowel diseases.

However, inflammatory bowel disease has serious growth and development implications in the paediatric population. Because of this, and since there is no reason to believe that inflammatory bowel disease in children behaves differently from inflammatory bowel disease in adults (where mesalazine has been shown to be highly effective), and due to the established safety profile of mesalazine in paediatric patients, it is the rapporteur's opinion that the benefit-risk ratio is in favour of an upholding of an indication for oral mesalazine in paediatric patients. Studies have

demonstrated that the pharmacokinetic profile of slow release mesalazine in children is similar to the profile in adults.

➤ **PPdAR Recommendation**

For consistency between mesalazine containing products across the EU, it is recommended that the SmPC contains the following statement:

For orally administered mesalazine

4.2 Posology and administration

There is only limited documentation for an effect in children (age 5-18 years).

Children 5 years of age and older

- Active disease: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).
- Maintenance treatment: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

For rectally administered mesalazine

There is little experience and only limited documentation for an effect in children.

**COMMENTS FROM MEMBER STATES AND MAH RESPONSES**

**MS comment:**

At the present time, the MS cannot endorse the conclusion of the Rapporteur.

Given that no paediatric indication is currently granted in the MS for mesalazine, the poor level of clinical demonstration currently provided is far from being adequate for considering any paediatric statement in the SPC of mesalazine. If some degree of extrapolation between the disease in adults and paediatric patients could be acknowledged, at least a valid demonstration to support the dose regimen should have been required, which is not the case currently. Such a demonstration should be requested in the scope of a further article 46.

**Rapporteur's comment:**

It has already been recognized in the assessment report that studies in children and adolescents are small and have limitations in methodology weakening the indication for oral mesalazine in children and adolescents with inflammatory bowel diseases (see suggested sentence in the posology: *There is only limited documentation for an effect in children (age 5-18 years)*). However, as is also argued, inflammatory bowel disease has serious growth and development implications in the paediatric population. Because of this, and since there is no reason to believe that inflammatory bowel disease in children behaves differently from inflammatory bowel disease in adults (where mesalazine has been shown to be highly effective), and due to the established safety profile of mesalazine in paediatric patients, it is the rapporteur's opinion that the benefit-risk ratio tips in favour of an upholding of an indication for oral mesalazine in paediatric patients.

**MS comment:**

The MS agrees with the rapporteur's conclusion that based on the assumed similarities in behavior of IBD in children and adults, the efficacy shown in adults, and the well-established safety profile of mesalazine, the benefit-risk ratio favors an upholding of an indication for oral mesalazine in paediatric patients with IBD.

The dose recommendation of the Rapporteur appears to be based on the present posology for Salofalk, the only mesalazine product of those included with a specific dose recommendation for children, which is endorsed. There are, however, some deviations from the posology statement that are not well understood and the MS proposes to use the same age-range and wording as currently approved for Salofalk delayed release preparations. See SmPC comments.

**MS' proposal:**

To redefine the age range to 6-18 years, in line with the currently accepted SPC of Salofalk. Although the data submitted include patients of 5 years of age and even younger patients, there are no new data justifying a change of the previously defined age range. Also other agents used in the treatment for IDB like infliximab have a similar age range of 6-18 years included in the SPC.

To include for convenience a sentence stating that it is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg, as is included in the currently accepted SPC of Salofalk.

**Rapporteur's comment:**

The proposal from the MS to redefine the age range to 6-18 years is well taken. There are no specific data for the efficacy of mesalazine in the 5 year age group. Also, the convenience sentence can be added.

**MS comments:**

The MS considers that there is insufficient data to support the proposed increased posology in the treatment of children 5 years of age and older, in relation to the orally administered mesalazine medicinal products.

**Rapporteur's comment:**

See above.

**Ferring Pharmaceuticals**

The company has no comments to the overall conclusions and recommendations.

**Procter and Gamble Pharmaceuticals**

Procter & Gamble Pharmaceuticals (P&GP) accept the proposed statement for addition into the SPCs of rectally administered mesalazines.

P&GP do NOT agree with the recommendation of the Rapporteur for orally administered mesalazine because:

- a) Different mesalazines have different delayed-release control mechanisms, different local and systemic availability and consequently, different dosing recommendations. Therefore, paediatric doses should be recommended on a product specific basis. Two small studies performed in adults are enclosed to substantiate this argument.
- b) Two paediatric ulcerative colitis clinical trials with Asacol are ongoing. The specific dosages in the harmonized wording proposed by the Rapporteur are not appropriate for Asacol as they are not consistent with the dosing schemes devised for these ongoing trials or the global standard of care for either maintenance of remission or induction therapy of active disease.

- c) Although few clinical studies of mesalamine have been performed in children, the current standard of care is to use somewhat higher doses of mesalamine in children on a mg/kg basis than is used in adults.

**Rapporteur's comment:**

Different mesalazines may well have different local and systemic availabilities, however the clinical significance of these differences, if any, have yet to be disclosed, since no comparative efficacy studies with different formulations of mesalazine in paediatric inflammatory bowel disease have been published. Furthermore, there are characteristically large inter-individual variations in mesalazine pharmacokinetics, which makes it even more difficult to substantiate an optimal dosage for the individual formulations (and which is why a recommended dosage range has been suggested). With respect to the 2 trials mentioned (1 on-going and 1 not yet started), it seems neither reasonable nor appropriate to include these studies at this time in the assessment process. Three reviews are now enclosed to argue for a higher dosage (mg/kg) to children than that recommended by the Rapporteur (even though P&GP does not support the posology for orally administered mesalazine in children). However, until more data are available in children on clinical efficacy and side effects of higher dosages it seems prudent to maintain the somewhat lower initial dosage range of 30-50 mg/kg and a maximum dosage of 75 mg/kg.

**Dr. Falk Pharma GmbH**

Dr. Falk Pharma endorses the comments regarding redefining the age range to 6-18 years and addition of the convenience sentence, however otherwise the company agrees with the rapporteur's conclusions.

**Tillotts Pharma AG**

Tillotts Pharma agrees with the rapporteur's conclusions.

## **V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**

➤ **Overall conclusion**

All studies have been performed with oral delayed release preparations. Studies are mostly small and have limitations in methodology weakening the indication for oral mesalazine in children and adolescents with inflammatory bowel diseases.

However, inflammatory bowel disease has serious growth and development implications in the paediatric population. Because of this, and since there is no reason to believe that inflammatory bowel disease in children behaves differently from inflammatory bowel disease in adults (where mesalazine has been shown to be highly effective), and due to the established safety profile of mesalazine in paediatric patients, it is the rapporteur's opinion that the benefit-risk ratio is in favour of an upholding of an indication for oral mesalazine in paediatric patients. Studies have demonstrated that the pharmacokinetic profile of slow release mesalazine in children is similar to the profile in adults.

➤ **Recommendation**

For consistency between mesalazine containing products across the EU, it is recommended that the SmPC contains the following statement:

### For orally administered mesalazine

#### 4.2 Posology and administration

There is only limited documentation for an effect in children (age 6-18 years).

#### Children 6 years of age and older

- Active disease: To be determined individually, starting with 30-50 mg/kg/day in divided doses. Maximum dose: 75 mg/kg/day in divided doses. The total dose should not exceed 4 g/day (maximum adult dose).
- Maintenance treatment: To be determined individually, starting with 15-30 mg/kg/day in divided doses. The total dose should not exceed 2 g/day (recommended adult dose).

It is generally recommended that half the adult dose may be given to children up to a body weight of 40 kg; and the normal adult dose to those above 40 kg.

#### For rectally administered mesalazine

- There is little experience and only limited documentation for an effect in children.

### **DISCUSSIONS ON SmPC FOLLOWING CIRCULATION OF FINAL AR**

It has not been possible to achieve a fully EU harmonised paediatric wording for mesalazine during this work sharing procedure. Further to the circulation of the Rapporteur's Final AR one MS could not accept the final recommendation for paediatric posology. The Rapporteur maintains the final recommendation (see above), and recommends implementation of this wording in MS via type II variation. However, we acknowledge that one MS is not in agreement and that in this MS it may be necessary to retain the Product Information which is currently authorised.

The Rapporteur recommends that the MAH achieve full harmonisation regarding paediatric use through use of appropriate regulatory procedures.