LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Mesalazin ESPL
# (mesalazine)

# SE/H/1654/01/DC

**This module reflects the scientific discussion for the approval of Mesalazin ESPL. The procedure was finalised on 2018-01-18. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

# I. INTRODUCTION

The application for Mesalazin ESPL, 1600 mg, modified-release tablet, is submitted according to Article 10(3) of Directive 2001/83/EC. The applicant, ESPL Regulatory Consulting Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CZ, DK, EE, EL, FI, IE, IS, LT, LU, LV, NL and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Asacol, 400 mg, gastro-resistant tablet authorised in SE since 1992, with Tillotts Pharma AB as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

## III.1 Discussion on the non-clinical aspects

Since mesalazine (5-ASA) has been used clinically for a very long time there is extensive clinical experience with 5-ASA that largely supersedes non-clinical data. No further non-clinical data have been submitted or are considered necessary. The non-clinical overview, based on submitted publications included in the dossier, is considered adequate.

# IV. CLINICAL ASPECTS

## IV.1 Introduction

Mesalazine, also known as mesalamine (USAN), 5-aminosalicylic acid, or 5-ASA is an amino salicylate. This drug substance has been used for more than 30 years for the treatment of inflammatory bowel disease including ulcerative colitis and Crohn's disease.
The present application concerns a new modified-release tablet containing 1600 mg mesalazine developed for induction and maintenance of remission in mild to moderate ulcerative colitis.

## IV.2 Pharmacokinetics

The pharmacokinetic documentation supporting the approval of Mesalazin ESPL 1600 mg modified release tablets consists of two studies to help choose the final formulation (Pilot study 8 and Pharmaco-scintigraphic Study TP0502) and two pharmacokinetic studies with the final formulation (Studies TP0504 and TP0506):

- Pilot Study 8: One pilot study to investigate the excretion of two formulations of TP05 1600 mg tablets in the stools.
- Study TP0502 and Amendment TP0502A: A scintigraphic investigation of the release of mesalazine from three different formulations of TP05. The aim was to choose the final formulation for use in the clinical development program (e.g. the phase III clinical study).
- Study TP0504: A single dose study (1.6 g/day) of TP05 1600 mg with one 1600 mg tablet under fasted and one 1600 mg tablet under fed conditions compared to 4 x 400 mg ASACOL (the Reference Product for this application) in the fasted state and
- Study TP0506: A single dose and steady state study after multiple doses (4.8 g/day for 5 days) of TP05 1600 mg, three 1600 mg Tablets vs. MEZAVANT 1200 mg, four 1200 mg tablets (another Reference Product).

*Summary of pharmacokinetic results*

The pharmacokinetics of mesalazine are characterised following single and multiple-dose of Mesalazin ESPL. The PK studies are considered descriptive and not pivotal for bridging efficacy data to Asacol since a Phase III efficacy study has been performed with the final formulation and the product is locally acting. The systemic plasma exposure is only relevant for safety concerns.

Results in study TP0504:
After single dose administration of Mesalazin ESPL 1600 mg modified-release tablets under fasting conditions, the mean (± SD) $C_{max}$ and $AUC_{0\text{-}tlast}$ were 2490 ± 1890 ng/ml and 15700 ± 7260 ng·h/ml, respectively. In the single-dose study TP0504 the plasma exposure was higher

for the test product compared to the reference product Asacol ($C_{max}$ 2.4-fold and AUC 1.6-fold), see figure 1.

The influence of food was evaluated for the test product in the single-dose study TP0504 and resulted in a 1.5-fold higher plasma exposure (AUC and $C_{max}$) following fasted state compared to fed state. These results are contrarily compared to previously reported results of the reference product Asacol where fed conditions resulted in higher plasma exposure. Since the food recommendation in the clinical Phase III study (TP0503 Induction and TP0503 Maintenance) were that the tablets should be taken with or without food, this is not regarded as an issue.

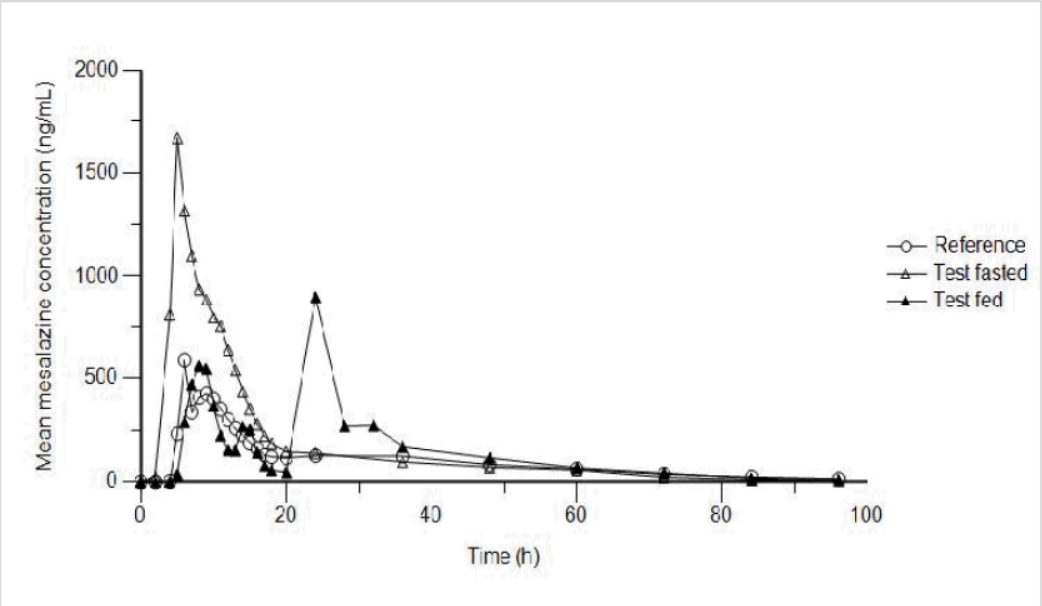



**Figure 1.** Mean plasma concentration vs. time curves of mesalazine after oral single dose administration of one tablet of TP05 1600 mg (Test) under fasting or fed (high-fat, high-caloric breakfast) conditions and four tablets of ASACOL 400 mg (Reference) under fasting conditions to 26 subjects (1600 mg mesalazine per treatment).

Results in study TP0506:
After repeated oral administration of Mesalazin ESPL 1600 mg modified-release tablets once daily of 4800 mg for five days, the highest mean (± SD) $C_{max}$ and $AUC_{0\text{-}24h}$ were 3820 ± 3730 ng/ml and 40200 ± 19900 ng·h/ml, respectively.

## IV.3 Pharmacodynamics

The therapeutic effect of mesalazine is considered to be due to a topical anti-inflammatory effect on the colonic mucosal cells through mechanisms that have not yet been fully clarified.

## IV.4 Clinical efficacy

**Main clinical study**
The assessment of efficacy in the sought indication is based on the results of one phase III non-inferiority study to evaluate the safety and efficacy of 3.2 g of TP05/day compared to 3.2 g/day of Asacol with an open label extension to assess the long-term safety and tolerability of TP05 administered over a 26 week period in patients with active UC.

*Patient population*
Patients with mild to moderate active UC were included in the induction phase of the study.

Inclusion criteria

1. Male or non-pregnant, non-lactating females, 18 years of age or older. Females of child bearing potential must have a negative serum pregnancy test prior to randomisation, and must use a hormonal (oral, implantable or injectable) or barrier method of birth control throughout the study. Females unable to bear children must have documentation of such in the source records (i.e., tubal ligation, hysterectomy, or post-menopausal [defined as a minimum of one year since the last menstrual period]).
2. Documented diagnosis of UC with disease extending at least 15 cm from the anal verge: the diagnosis of UC is based on the site investigator's assessment and should be available at randomisation.
3. Active UC defined by:
    a. Mayo score of $\geq 5$
    b. Sigmoidoscopy component score $\geq 2$ confirmed by central review and
    c. Rectal bleeding component score $\geq 1$
4. Ability of the subject to participate fully in all aspects of this clinical trial.
5. Written informed consent must be obtained and documented.

Exclusion criteria (selected)

1. Severe UC defined by the following criteria: $\geq 6$ bloody stools daily with one or more of the following:
    a. oral temperature > 37.8°C or > 100.0°F
    b. pulse > 90 beats/min
    c. haemoglobin < 10 g/dL
2. Proctitis: distal disease involving the rectum only i.e. disease extending less than 15 cm from the anal verge.
3. Treatment with oral mesalamine at a dose of > 2.5 g/day within 4 weeks prior to randomisation. Prestudy mesalamine therapy at a dose of 2.5 g/day or less must be stopped at Visit 2.
4. Treatment with rectal mesalamine within 2 weeks prior to randomisation.
5. Treatment with systemic or rectal steroids within 4 weeks prior to randomisation.
6. Treatment with immunosuppressants within 6 weeks prior to randomisation.
7. Treatment with infliximab or other biologics within 3 months prior to randomisation.
8. Treatment with antibiotics within 7 days prior to randomisation.
9. History of definite dysplasia in colonic biopsies.
10. Crohn's disease.
11. Immediate or significant risk of toxic megacolon.
12. Hypersensitivity to salicylates, aspirin, sulfasalazine or 5-ASA.
13. Serum creatinine > 1.5 times the upper limit of the normal range.
14. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin or alkaline phosphatase > 2 times the upper limit of the normal range.
15. Serious underlying disease other than UC which in the opinion of the investigator may interfere with the subject's ability to fully participate in the study.

The main criteria for inclusion in the OLE were:

1. Attendance at the Week 8 visit and completion of disease activity assessments prior to enrolment in OLE at Week 12 (responders or remitters) or Week 8 (non-responders).
2. At least 75% compliance with study medication in the induction phase.

Main criteria for exclusion from the OLE include:

1. Withdrawal from the induction phase prior to the Week 8 visit.

*Treatment*

Induction phase

Test group (TP05): Subjects received 3.2 g/day as two TP05 tablets plus four appearance- and taste-matched Asacol placebo tablets in the morning and four placebo tablets in the evening.
Reference group (Asacol): Subjects received 3.2 g/day as four 400 mg tablets plus two appearance- and taste-matched TP05 placebo tablets administered in the morning and four 400 mg tablets in the evening.
The study drugs were administered orally for up to 12 weeks.

Open labelled extension

Eligible subjects received TP05. The administered dose depended upon the response to study drug during the induction study, as follows:

- Remitters: 1.6 g/day (1 tablet in the morning) beginning at Week 12
    - Subjects who lose responsiveness to 1.6 g/day of TP05 during the OLE may have the dose increased to a maximum of 4.8 g/day.
- Responders: 3.2 g/day (2 tablets in the morning) beginning at Week 12
    - Responders who lose response during OLE may have the dose increased to a maximum of 4.8 g/day.
- Non-responders: 4.8 g/day (3 tablets in the morning) beginning at Week 8.
    - Subjects who fail to exhibit at least a response to an 8 week course (Week 16) of 4.8 g/day of TP05 or lose response after the 8-week period were withdrawn from the study.

*Endpoints*

The primary efficacy endpoint for the *induction phase* of the study was the proportion of subjects in clinical and endoscopic remission after 8 weeks of treatment.

Clinical and endoscopic remission was defined as a Mayo score of ≤ 2 points with no individual sub-score > 1 point.

Secondary efficacy endpoints were ranked and tested for non-inferiority in a hierarchical manner. Efficacy endpoints included additional analyses based on the Mayo score, i.e. endoscopic remission/response at week 8, clinical remission at week 8, and clinical remission remission/response at both weeks 8 and 12. Examples of further endpoints evaluated are SF-36, EQ-5D, and WPAI-UC, Physician and Subject Global Ratings and faecal calprotectin.
For the *open label extension* phase of the study efficacy evaluations included clinical remission (defined as score 0 for stool frequency and rectal bleeding), flexible sigmoidoscopy, the Mayo score and partial Mayo clinic score (PMCS), the SF-36, the EQ-5D , WPAI-UC, SGA and PGA ratings, and measurement of faecal calprotectin levels.
Safety evaluations included documentation of adverse events, physical examinations, vital signs and clinical laboratory evaluations (haematology, chemistry, and urinalysis).

*Blinding*

The computer generated randomisation schedule was prepared by an independent statistician who was not involved in the conduct of the trial. A randomisation list was also generated for the packaging of study drug packs. To maintain blinding, appearance and taste-matched placebo tablets of both TP05 and Asacol were supplied. All study drug supplies were packaged and labelled in an identical manner.

The investigator and site study personnel remained blinded to the subject's treatment assignment. The blind was to be broken only if the subject experienced a medical emergency and knowledge of the blinded treatment assignment would be deemed necessary for further management of the subject. Emergency unblinding was to be handled through the IWRS.

*Sample size*
The primary efficacy endpoint was the proportion of subjects in clinical and endoscopic remission. It was assumed that the remission rate would be 40% in both the active comparator and TP05 groups.

Three hundred and seventy-seven evaluable subjects per group were required to achieve 80% power to demonstrate a non-inferiority margin of at most, 10% at the two-sided 5% significance level. It was assumed that no more than 6% of the subjects would be excluded from the PP analysis. The target sample size of 800 subjects was expected to provide the required 754 evaluable subjects needed to determine that TP05 was not inferior to Asacol. In a randomised, placebo-controlled trial that evaluated the efficacy of MMX mesalazine, the treatment effect of MMX mesalazine given 2.4 g/day and 4.8 g/day was observed at 19.6% and 19.1%, respectively (MMX mesalazine 2.4 g/day at 41.7%; MMX mesalazine 4.8 g/day at 41.2%; placebo at 22.1%) (Kamm et al, 2007). Furthermore, in a meta-analysis of seven randomised placebo-controlled trials that compared 5-ASA given at a dose of ≥3 g/day versus placebo for the induction of remission in UC,(Feagan et al, 2012) the risk difference was estimated at 17% with the 95% confidence interval at 10 to 24%. Therefore, a 10% non-inferiority margin was considered a clinically acceptable difference.

*Statistical methods*
The primary efficacy evaluation in the induction phase was at week 8 and was analysed once all subjects had completed the induction phase of the study. The open-label extension phase of the study was to be analysed and reported separately.

Statistical tests were two-sided and performed at the 0.05 level of significance. All subjects who had been provided with study medication were included in the intent-to-treat (ITT) population. The per-protocol (PP) analysis set included ITT subjects without major protocol violations that could have affected the primary endpoint. This concerned e.g. compliance and patients that took less than 75 % of the prescribed study medication during the 8 week induction treatment were considered as protocol violators and were excluded from the per-protocol population. Efficacy analyses were primarily based on the PP analysis set but were also repeated based on the ITT analysis set. The safety (SAF) population included all subjects who had received at least one dose of study medication.

For the proportion of subjects achieving clinical and endoscopic remission after 8 weeks of treatment the between group difference (TP05 minus Asacol) was to be calculated and a two-sided 95.0% confidence interval was to be constructed using the method described by Newcombe (2). Subjects who withdraw from the study due to failure of the treatment were to be considered non-remitters. If the lower limit of the confidence interval was no less than the pre-defined clinically acceptable non-inferiority margin of 10% then it was to be concluded that treatment with TP05 is no worse than the active comparator in inducing clinical and endoscopic remission. The associated test for non-inferiority was also to be reported.

For each dichotomous response, remission, and rectal bleeding score secondary endpoint the between group difference (TP05 minus Asacol) was to be calculated and interpreted using the same method and approach as for the primary endpoint. If a subject had withdrawn from the study prior to Week 8 or whose response status was not evaluable due to incomplete and/or

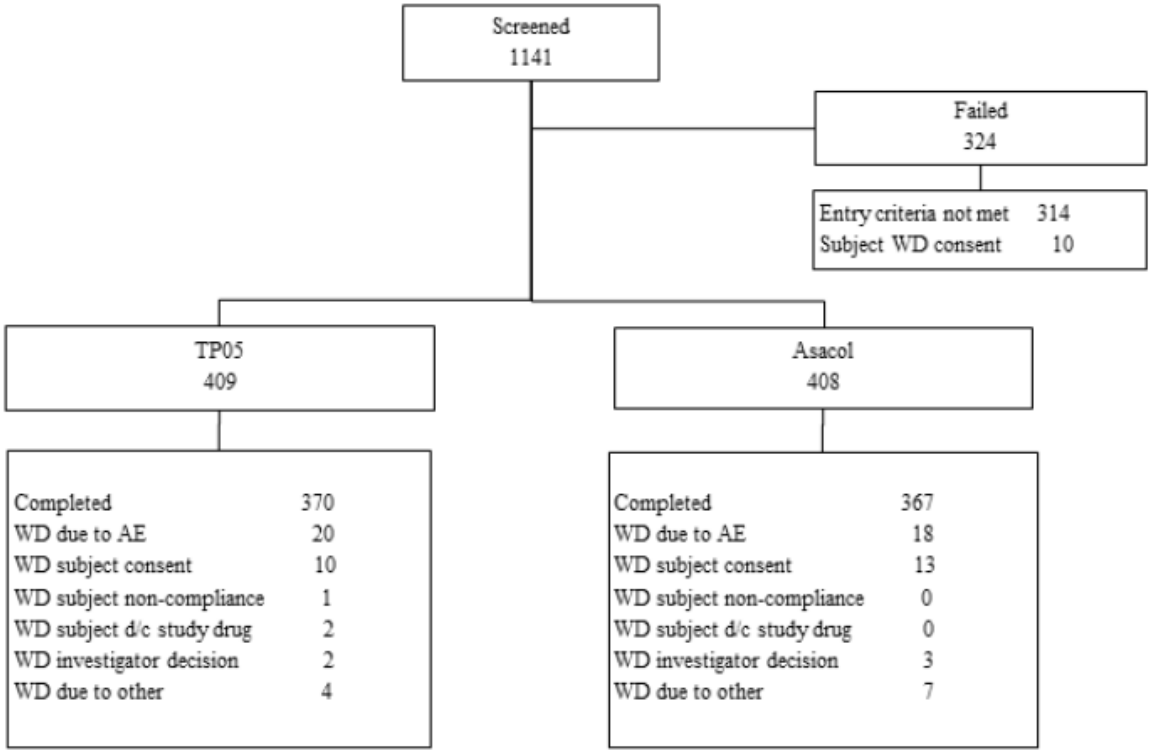
invalid data, the subjects was considered a non-remitter or non-responder. To minimize problems inherent to multiple comparisons the secondary endpoints were ranked and were to be formally tested for non-inferiority in a hierarchical manner using a non-inferiority margin of 10%. At the point where non-inferiority testing failed, formal testing was to stop.

*Results*

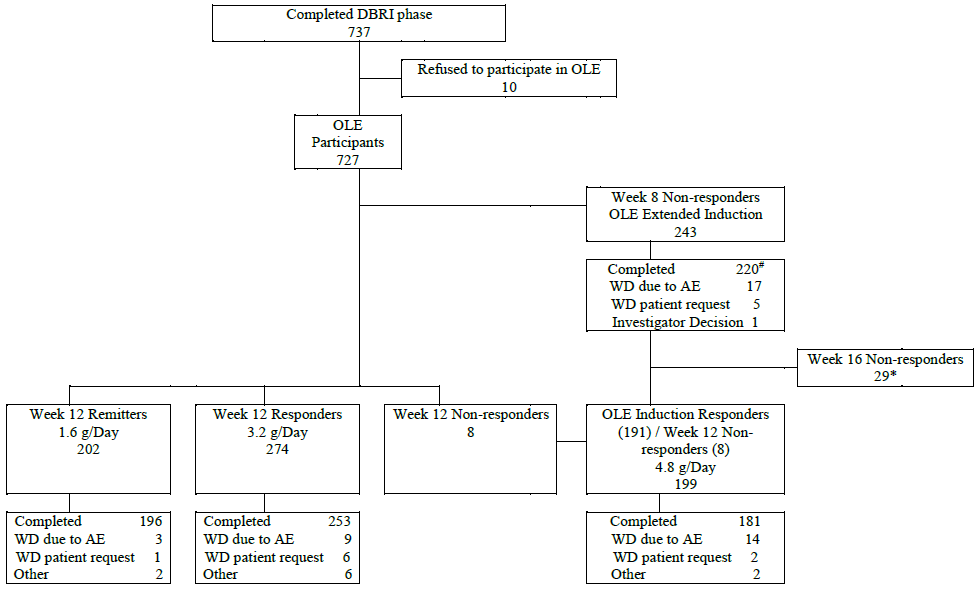
*Double-blind randomised induction phase*

In the figures and tables below the baseline disposition, demographic characteristics and disease history are presented.

**Figure 1. Disposition of patients, double-blind randomised induction phase**



## Figure 2. Disposition of patients, open label extension phase




*Note: In Table 10.3 it was reported that the reason for withdrawal for 16 subjects was 'Non-Responder' at Week 16. In addition, it was reported that 13 subjects withdrew for 'other' reasons. Review of the details indicated that all 13 'other' subjects were in fact Week 16 non-responders. Hence, in this figure, 29 subjects are reported as Week 16 non-responders and 220 subjects as having completed the OLE extended induction phase.
#Note: In this table, 220 subjects are reported as having completed the OLE extended induction phase, whereas efficacy tables report the results for 221 subjects. This is due to the fact that one subject (2500205) was an early withdrawal from the OLE extended induction phase at Week 10, however Week 16 assessments were performed and thus included in the analyses.

**Table 1. Demographic baseline characteristics, SAF Analysis Set**

| | | TP05 (n=409) | Asacol (n=408) | Overall (n=817) |
|---|---|---|---|---|
| Age (Years) | N | 409 | 408 | 817 |
| | Mean | 43.97 | 43.31 | 43.64 |
| | Std Dev | 14.54 | 14.11 | 14.32 |
| | Median | 42.68 | 41.67 | 41.95 |
| | Minimum | 19.4 | 18.1 | 18.1 |
| | Maximum | 80.9 | 82.1 | 82.1 |
| Gender | Male | 238 ( 58.2%) | 230 ( 56.4%) | 468 ( 57.3%) |
| | Female | 171 ( 41.8%) | 178 ( 43.6%) | 349 ( 42.7%) |
| Ethnic origin | White | 378 ( 92.4%) | 386 ( 94.6%) | 764 ( 93.5%) |
| | Black | 1 ( 0.2%) | 1 ( 0.2%) | 2 ( 0.2%) |
| | Asian or Pacific Islander | 7 ( 1.7%) | 3 ( 0.7%) | 10 ( 1.2%) |
| | Not Available | 23 ( 5.6%) | 17 ( 4.2%) | 40 ( 4.9%) |
| | Other/Mixed Race | 0 ( 0.0%) | 1 ( 0.2%) | 1 ( 0.1%) |
| Height (cm) | N | 409 | 408 | 817 |
| | Mean | 171.8 | 172.0 | 171.9 |
| | Std Dev | 8.9 | 9.2 | 9.1 |
| | Median | 172.0 | 172.0 | 172.0 |
| | Minimum | 149 | 143 | 143 |
| | Maximum | 197 | 200 | 200 |
| Weight (kg) | N | 409 | 407 | 816 |
| | Mean | 74.92 | 74.24 | 74.58 |
| | Std Dev | 15.47 | 16.27 | 15.87 |
| | Median | 74.00 | 72.90 | 73.05 |
| | Minimum | 44.4 | 40.0 | 40.0 |
| | Maximum | 137.7 | 160.0 | 160.0 |
| BMI | N | 409 | 407 | 816 |
| | Mean | 25.28 | 25.03 | 25.16 |
| | Std Dev | 4.33 | 4.84 | 4.59 |
| | Median | 25.06 | 24.53 | 24.69 |
| | Minimum | 16.9 | 16.9 | 16.9 |
| | Maximum | 43.4 | 54.1 | 54.1 |
| Partial Mayo Score | N | 409 | 408 | 817 |
| | Mean | 5.4 | 5.3 | 5.4 |
| | Std Dev | 1.1 | 1.2 | 1.1 |
| | Median | 5.0 | 5.0 | 5.0 |
| | Minimum | 3 | 2 | 2 |
| | Maximum | 8 | 8 | 8 |
| Mayo Score | N | 409 | 408 | 817 |
| | Mean | 7.7 | 7.6 | 7.7 |
| | Std Dev | 1.3 | 1.3 | 1.3 |
| | Median | 8.0 | 8.0 | 8.0 |
| | Minimum | 5 | 5 | 5 |
| | Maximum | 11 | 11 | 11 |
| Smoking Status | Current Smoker | 32 ( 7.8%) | 26 ( 6.4%) | 58 ( 7.1%) |
| | Ex-Smoker | 115 ( 28.1%) | 101 ( 24.8%) | 216 ( 26.4%) |
| | Never Smoked | 262 ( 64.1%) | 281 ( 68.9%) | 543 ( 66.5%) |
| Nicotine Therapy | No | 409 (100.0%) | 408 (100.0%) | 817 (100.0%) |
| | Yes | 0 ( 0.0%) | 0 ( 0.0%) | 0 ( 0.0%) |
| Urgency | No | 54 ( 13.2%) | 102 ( 25.0%) | 156 ( 19.1%) |
| | Yes | 355 ( 86.8%) | 306 ( 75.0%) | 661 ( 80.9%) |

**Table 2. Ulcerative Colitis History, SAF Analysis Set**

| | | TP05 (n=409) | Asacol (n=408) | Overall (n=817) |
|---|---|---|---|---|
| Time Since Diagnosis (Months) | N | 409 | 408 | 817 |
| | Mean | 66.19 | 64.55 | 65.37 |
| | Std Dev | 82.43 | 78.33 | 80.37 |
| | Median | 35.09 | 37.70 | 36.34 |
| | Minimum | 0.2 | 0.1 | 0.1 |
| | Maximum | 444.5 | 514.6 | 514.6 |
| Number of Normal Stools When UC is in Remission | N | 409 | 407 | 816 |
| | Mean | 1.3 | 1.3 | 1.3 |
| | Std Dev | 0.6 | 0.5 | 0.5 |
| | Median | 1.0 | 1.0 | 1.0 |
| | Minimum | 1 | 1 | 1 |
| | Maximum | 4 | 4 | 4 |
| Extent of Disease | Proctitis (<15 cm) | 5 ( 1.2%) | 6 ( 1.5%) | 11 ( 1.3%) |
| | Proctosigmoiditis (15-25 cm from anal verge) | 173 ( 42.3%) | 188 ( 46.1%) | 361 ( 44.2%) |
| | Left sided colitis (to splenic flexure) | 143 ( 35.0%) | 144 ( 35.3%) | 287 ( 35.1%) |
| | Portion of transverse colon | 14 ( 3.4%) | 11 ( 2.7%) | 25 ( 3.1%) |
| | Pancolitis | 70 ( 17.1%) | 55 ( 13.5%) | 125 ( 15.3%) |
| | Other | 4 ( 1.0%) | 2 ( 0.5%) | 6 ( 0.7%) |
| | No Endoscopy prior to Visit 1 | 0 ( 0.0%) | 2 ( 0.5%) | 2 ( 0.2%) |

Primary endpoint

**Table 3. Clinical and Endoscopic Remission at Week 8, PP Analysis Set**

| | TP05 (n=388) | Asacol (n=386) | Between Group Difference (95% CI) | Non-Inferiority P-Value |
|---|---|---|---|---|
| Yes | 87 ( 22.4%) | 95 ( 24.6%) | -2.2% ( -8.1% , 3.8%) | 0.005 |
| No | 301 ( 77.6%) | 291 ( 75.4%) | | |

Note: The between-group difference was calculated as the proportion of TP05 subjects in clinical and endoscopic remission minus the proportion of subjects in the Asacol group.

Secondary endpoints

**Table 4. Secondary Efficacy Endpoints Evaluated for Non-Inferiority, PP Analysis Set**

| | TP05 (n=388) | Asacol (n=386) | Between Group Difference (95% CI) | Non-Inferiority P-Value |
|---|---|---|---|---|
| Endoscopic Remission at Week 8 | | | | |
| Yes | 36 ( 9.3%) | 44 ( 11.4%) | -2.1% ( -6.5% , 2.2%) | <0.001 |
| No | 352 ( 90.7%) | 342 ( 88.6%) | | |
| Endoscopic Response at Week 8 | | | | |
| Yes | 185 ( 47.7%) | 196 ( 50.8%) | -3.1% (-10.1% , 3.9%) | 0.026 |
| No | 203 ( 52.3%) | 190 ( 49.2%) | | |
| Clinical Remission at Week 8 | | | | |
| Yes | 92 ( 23.7%) | 110 ( 28.5%) | -4.8% (-10.9% , 1.4%) | 0.048 |
| No | 296 ( 76.3%) | 276 ( 71.5%) | | |
| Rectal Bleeding Sub-score of 0 at Week 8 | | | | |
| Yes | 212 ( 54.6%) | 226 ( 58.5%) | -3.9% (-10.8% , 3.1%) | 0.042 |
| No | 176 ( 45.4%) | 160 ( 41.5%) | | |
| Clinical and Endoscopic Response at Week 8 | | | | |
| Yes | 221 ( 57.0%) | 236 ( 61.1%) | -4.2% (-11.0% , 2.7%) | 0.048 |
| No | 167 ( 43.0%) | 150 ( 38.9%) | | |
| Clinical Remission at Week 12 | | | | |
| Yes | 93 ( 24.0%) | 113 ( 29.3%) | -5.3% (-11.5% , 0.9%) | 0.068 |
| No | 295 ( 76.0%) | 273 ( 70.7%) | | |
| Clinical Response at Week 12 | | | | |
| Yes | 223 ( 57.5%) | 233 ( 60.4%) | -2.9% ( -9.8% , 4.0%) | 0.021 |
| No | 165 ( 42.5%) | 153 ( 39.6%) | | |
| Rectal Bleeding Sub-score of 0 at Week 12 | | | | |
| Yes | 193 ( 49.7%) | 205 ( 53.1%) | -3.4% (-10.3% , 3.7%) | 0.031 |
| No | 195 ( 50.3%) | 181 ( 46.9%) | | |
| Clinical Remission at Both Weeks 8 and 12 | | | | |
| Yes | 66 ( 17.0%) | 80 ( 20.7%) | -3.7% ( -9.2% , 1.8%) | 0.013 |
| No | 322 ( 83.0%) | 306 ( 79.3%) | | |
| Clinical Response at Both Weeks 8 and 12 | | | | |
| Yes | 216 ( 55.7%) | 230 ( 59.6%) | -3.9% (-10.8% , 3.0%) | 0.042 |
| No | 172 ( 44.3%) | 156 ( 40.4%) | | |

Note: The between-group difference was calculated as the proportion of TP05 subjects exhibiting the secondary dichotomous end-point minus the proportion of subjects in the Asacol group

*Open label extension phase*

Efficacy evaluations were secondary objectives of the open-labelled extension study.

**Table 5. Efficacy Endpoints evaluated in the OLE part, Week 38 (PP, study TP0503)**

| | Number (%) of subjects | | | |
|---|---|---|---|---|
| | 1.6 g/day | 3.2 g/day | 4.8 g/day | Total |
| Responder/Remitter | Remitter after induction N = 202 | Responder after induction N = 274 | Non-responder N = 199 | N = 675 |
| **Clinical (1)** | | | | |
| Non-responder | 12 (5.9) | 44 (16.1) | 43 (21.6) | 99 (14.7) |
| Responder* | 190 (94.1) | 230 (83.9) | 156 (78.4) | 576 (85.3) |
| Remitter | 142 (70.3) | 93 (33.9) | 61 (30.7) | 296 (43.9) |
| **Clinical and endoscopic (2)** | | | | |
| Non-responder | 21 (10.4) | 60 (21.9) | 61 (30.7) | 142 (21.0) |
| Responder* | 181 (89.6) | 214 (78.1) | 138 (69.3) | 533 (79.0) |
| Remitter | 133 (65.8) | 108 (39.4) | 59 (29.6) | 300 (44.4) |
| **Endoscopic (3)** | | | | |
| Non-responder | 53 (26.2) | 113 (41.2) | 93 (46.7) | 259 (38.4) |
| Responder* | 149 (73.8) | 161 (58.8) | 106 (53.3) | 416 (61.6) |
| Remitter | 76 (37.6) | 64 (23.4) | 27 (13.6) | 167 (24.7) |
| **Blood in stool, stool frequency** | | | | |
| Blood in stool, score = 0 | 178(88.1) | 209 (76.3) | 149 (74.9) | 536 (79.4) |
| Stool frequency above normal = 0 | 148 (73.3) | 101 (36.9) | 66 (33.2) | 315 (46.7) |

N = total number of subjects; OLE = open label extension; PP = per-protocol set
* Figures for responders include remitters
(1) Clinical remission: rectal bleeding = 0, stool frequency = 0 above normal
(2) Clinical and endoscopic remission: Mayo score ≤ 2, no individual sub score > 1
(3) Endoscopic remission: Endoscopic sub score = 0 (central reader scores)
Source: CSR TP0503_M

**Summary of main efficacy results**
The proportion of patients with both clinical and endoscopic remission at week 8 was 22.4 % and 24.6 % for TP05 and Asacol, respectively. The non-inferiority margin of -10 % was met and was supported also by the analysis based on the ITT data set.
A conclusion of non-inferiority is also considered to be supported by the analyses of the secondary efficacy endpoints although most of them formally failed to show non-inferiority (i.e. the lower limit of the 95% confidence interval was below -10.0%). However, the deviations/discrepancies are considered to be of minor clinical importance.
Efficacy results from the OLE phase support a continuation of the effect up to week 38 with a majority of patients in response or remission. In general the treatment was most efficient in subjects that were in remission at the start of the OLE phase as could be expected.
However, due to the study design, a strict evaluation and comparison of the results between the three treatment groups is not possible. Although, responders and non-responders after induction therapy at week 8 seemed to benefit from continuous treatment it is not clear whether or not a lower dose would have induced equal remission/response rates.

## IV.5 Clinical safety

**Clinical safety**
The clinical development programme for Mesalazin ESPL consisted of one pivotal Phase III study (study TP0503).

*Exposure*
In this study, a dose of 3.2 g/day was administered during the double-blind induction phase of the study followed by dosing between 1.6 – 4.8 g daily in the open labelled extension phase.

All subjects who received at least 1 dose of study drug during the 12-week induction trial were included in the SAF analysis set. A total of 817 subjects were included: 409 from the TP05 treatment group and 408 from the Asacol treatment group.
For subjects in the OLE extended induction, the numbers in whom the extent of exposure could be calculated was n=220. Subjects were exposed to TP05 for a mean (SD) of 54.5 (9.9) days and took 158.5 (30.8) tablets during the period.
Overall, for all dose groups combined, subjects were exposed to TP05 for a mean (SD) of 170.2 (27.1; n=573) days and took a mean (SD), 331.1 (115.1; n=576) tablets, in subjects for which the extent of exposure could be calculated, during the OLE maintenance phase.

*Adverse events*
All TEAEs occurring within the randomised, double-blind, 12-week induction study for subjects that were responder/remitters at Week 8 are included. For subjects who were non-responders at Week 8, only TEAEs occurring on or before the Week 8 visit are included.

**Table 6. Treatment-Emergent Adverse Events, SAF Analysis Set**

| | TP05 (N = 409) | Asacol™ (N = 408) | TOTAL (N = 817) |
|---|---|---|---|
| Any adverse events | 131 (32.0%) | 108 (26.5%) | 239 (29.3%) |
| Severe adverse events | 13 ( 3.2%) | 8 ( 2.0%) | 21 ( 2.6%) |
| Drug related adverse events | 42 (10.3%) | 40 ( 9.8%) | 82 (10.0%) |
| Serious adverse events | 8 ( 2.0%) | 7 ( 1.7%) | 15 ( 1.8%) |
| Drug related serious adverse events | 2 ( 0.5%) | 1 ( 0.2%) | 3 ( 0.4%) |
| Adverse events leading to drug interruption* | 3 ( 0.7%) | 2 ( 0.5%) | 5 ( 0.6%) |
| Adverse events leading to drug discontinuation** | 27 ( 6.6%) | 23 ( 5.6%) | 50 ( 6.1%) |

*AEs that resulted in temporary discontinuation of the Study Drug
**AEs that resulted in permanent discontinuation of the Study Drug

**Table 7. Treatment-Emergent Adverse Events Reported by ≥ 5% of Subjects in Any Treatment Group, SAF Analysis Set**

| | TP05 (N = 409) | Asacol™ (N = 408) | TOTAL (N = 817) |
|---|---|---|---|
| COLITIS ULCERATIVE | 27 ( 6.6%) | 22 ( 5.4%) | 49 ( 6.0%) |

**Table 8. Treatment-Emergent Adverse Events, OLE maintenance phase**

| | 1.6g/day Remitter after Induction ( N = 202 ) | 3.2g/day Responder after Induction ( N = 274 ) | 4.8g/day Non-responder ( N = 199 ) | TOTAL ( N = 675 ) |
|---|---|---|---|---|
| Any adverse events | 59 (29.2%) | 73 (26.6%) | 38 (19.1%) | 170 (25.2%) |
| Severe adverse events | 4 ( 2.0%) | 6 ( 2.2%) | 4 ( 2.0%) | 14 ( 2.1%) |
| Drug related adverse events | 28 (13.9%) | 24 ( 8.8%) | 11 ( 5.5%) | 63 ( 9.3%) |
| Serious adverse events | 10 ( 5.0%) | 12 ( 4.4%) | 3 ( 1.5%) | 25 ( 3.7%) |
| Drug related serious adverse events | 1 ( 0.5%) | 3 ( 1.1%) | 0 ( 0.0%) | 4 ( 0.6%) |
| Adverse events leading to drug interruption* | 0 ( 0.0%) | 0 ( 0.0%) | 1 ( 0.5%) | 1 ( 0.1%) |
| Adverse events leading to drug discontinuation** | 4 ( 2.0%) | 8 ( 2.9%) | 13 ( 6.5%) | 25 ( 3.7%) |

* AEs that resulted in temporary stoppage of the Study Drug
** AEs that resulted in permanent discontinuation of the Study Drug

**Table 9. Treatment-Emergent Adverse Events Reported by ≥5% of Subjects (OLE Maintenance phase)**

| PREFERRED TERM | 1.6g/day Remitter after Induction ( N = 202 ) | 3.2g/day Responder after Induction ( N = 274 ) | 4.8g/day Non-responder ( N = 199 ) | TOTAL ( N = 675 ) |
|---|---|---|---|---|
| Colitis ulcerative | 36 ( 17.8%) | 38 ( 13.9%) | 20 ( 10.1%) | 94 ( 13.9%) |

*Serious adverse events*

Double-blind randomised induction phase

Of 817 subjects included in the SAF dataset, 17 SAEs were experienced by 15 (1.8%) subjects in this 12-week induction study. Of those 17 SAEs, 10 (58.8%) were experienced by subjects in the TP05 group (1 subject experienced 3 SAEs) and 7 (46.7%) in the Asacol group. Two SAEs experienced by 2 TP05 subjects (worsening of UC) were considered possibly related to treatment and 1 SAE (worsening of anaemia in the Asacol group) was considered as definitely related. These 3 SAEs did not emerge due to study drug use, but were due to treatment failure. All other SAEs were listed as unrelated to the study drug.

Double-blind randomised induction phase and open-labelled maintenance phase

A total of 46 SAEs were reported by 42 (5.1%) study subjects during the entire 38-week study period. The most frequently reported SAE was worsening or exacerbation of UC, which occurred in 16 (2.0% of study subjects) of the 46 reported SAEs (37.8%). Four of those cases were considered possibly or probably related to the study drug.

Deaths

No deaths occurred during this study.

### IV.6 Risk Management Plans

The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Mesalazin ESPL.

Safety specification
The Applicant has updated the safety specification in accordance with the Assessor's comment (version 2.0, 27 July 2017)

Table SVIII.1: Summary of safety concerns

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Impairment of renal function<br>Impairment of hepatic function<br>Reversible myocarditis/pericarditis<br>Acute pancreatitis<br>Respiratory disorders<br>Blood dyscrasias |
| Important potential risks | None |
| Missing information | None |

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The RMP is approvable, an updated RMP has been submitted.

## V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Mezavant, assessed and accepted in NL/H/0732/001/DC. The bridging report submitted by the applicant has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present application concerns a new modified-release tablet containing 1600 mg mesalazine for induction and maintenance of remission of mild to moderate acute ulcerative colitis.

All quality issues are solved.

In support of the application the results of a clinical non-inferiority study have been submitted where the efficacy and safety of the new formulation has been compared with that of the reference product Asacol.

Results from the double-blind induction phase support that equal doses of the TP05 product once daily is non-inferior to Asacol bid after 8 weeks in inducing remission in patients with mild to moderate active UC.

The induction phase of the study was followed by an open maintenance phase. From week 12 up to 38 weeks, subjects in remission from the induction study continued receiving 1.6 g once daily and responders received 3.2 g. For non-responders and subjects losing remission/response the dose was increased to 4.8 g.

The recommended dose for induction of remission of mild to moderate active UC for the reference product is doses up to 4800 mg daily.

Concerning maintenance of remission, although a clear dose-response for maintenance of remission with 5-ASA has not been established; a systematic review of randomised controlled trials has confirmed greater benefit for doses of at least 2 g/day (Ford et al, Am J Gastroenterology 2011). Therefore, the recommendation in the ECCO clinical guideline for treatment to maintain remission is 2 g oral mesalazine/day (JCC 2017).

Both for induction and maintenance of remission, once daily dosing of mesalazine is recognised in clinical guidelines as being as effective as divided doses.

Due to the open-label design of study TP05 no strict evaluation of maintenance of efficacy in the different treatment groups can be performed. The initial proposed maintenance dose from the applicant (1.6-3.2 g) was not in line with reference product or the recommendations in clinical guidelines and is not supported by the open OLE phase of the study.

Treatment of patients with ulcerative colitis should be tailored to the need of the individual. With the present product containing 1600 mg mesalazine it may not be possible to correctly adjust the dose to the subject’s need and treatment recommendations. The Applicant has pointed out that the product has been developed to increase compliance in subjects in need for higher dosing and not for flexibility in dose adjustment.

The higher systemic exposure as compared with the reference was considered a major safety concern although the clinical safety observed in study TP0503 was in line with the well-known safety profile of mesalazine and there were no new or unexpected issue revealed.

This led to a safety MO in the Day 120 report. The applicant has now responded and by changing the wording in the SmPC section 4.2, to recommend a lower maintenance dose of 1600 mg/day. It is recognised that this may be sufficient for some patients and this dosage is approved for maintenance treatment for the reference product Asacol 400 mg although in clinical guidelines (ECCO) (as described above) it is recommended to use 2 g/dag as a minimum dose.

However, there might be patients for whom a maintenance dose of 1600 mg is sufficient and in addition this maintenance dosing is approved with the reference product.

Therefore, it is considered that the benefit risk profile of this product is positive from a clinical point of view.

The overall Benefit/Risk of Mesalazin ESPL, 1600 mg, modified-release tablet, is considered positive since all issues are resolved. The application for Mesalazin ESPL is therefore recommended for approval.

**List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The Mutual recognition/Decentralised procedure for Mesalazin ESPL, 1600 mg, modified-release tablet, was positively finalised on 2018-01-18.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| | | | | | |

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se