ASACOL 800MG MR TABLETS
PL 10947/0012

UKPAR

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LAY SUMMARY

The MHRA granted Procter & Gamble Pharmaceuticals UK Ltd a Marketing Authorisation (licence) for the medicinal product Asacol 800mg MR tablets (PL 10947/0012). This is a prescription only medicine (POM) for the treatment of inflammatory bowel disease (IBD) in patients with ulcerative colitis and Crohn’s ileocolitis.

Asacol 800mg MR tablets contain the active ingredient mesalazine, which is an anti-inflammatory medicine.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Asacol 800mg MR tablets outweigh the risks, hence a Marketing Authorisation has been granted.
ASACOL 800MG MR TABLETS
PL 10947/0012

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Asacol 800mg MR tablets (PL 10947/0012) on 14 September 2007. This product is a prescription only medicine.

This is a national application submitted under Article 10a of Directive 2001/83/EC with a complete bibliography in support of well-established use.

The product contains the active ingredient mesalazine, an intestinal anti-inflammatory drug which acts topically on the intestinal mucosa.

Asacol 800mg MR tablets are indicated for the maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis, and for the treatment of mild to moderate acute exacerbations of ulcerative colitis.

This product has been through a change of ownership procedure (CoA) from PL 00364/0083 to PL 10947/0012 on 25th May 2010.
PHARMACEUTICAL ASSESSMENT

COMPOSITION

The product is formulated as a delayed release, enteric-coated tablet containing 800mg of the active pharmaceutical ingredient mesalazine. The excipients present are lactose monohydrate, sodium starch glycolate type A, talc, povidone, magnesium stearate and colloidal anhydrous silica. Methacrylic acid-methyl methacrylate copolymer, talc, dibutyl phthalate, red ferric oxide, yellow ferric oxide and macrogol 6000 are present in the coating. Propylene glycol, black ferric oxide, ammonium hydroxide, ethanol and shellac glaze are present in the printing ink.

The tablets are presented in HDPE containers with child-resistant screw caps in packs of 12, 36 and 180 tablets.

DRUG SUBSTANCE

Mesalazine

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopeia specification is provided for mesalazine.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided for three batches and comply with the proposed specification.

Mesalazine is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 2 years when stored in double polyethylene bags in a cardboard box or fibre drum, protected from light.

DRUG PRODUCT

Other ingredients

All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the
production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

**Dissolution profiles**
Dissolution profiles of the drug product were carried out at various pH values. This was done to ensure that the product can withstand the increasing pH of the gastrointestinal tract until reaching the last portion of the small intestine in order to deliver a nominal amount of mesalazine to the terminal ileum and beyond for a topical action.

Batch to batch consistency was shown by dissolution testing.

**Manufacture**
A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Satisfactory process validation has been carried out.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

**Finished product specification**
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification.

The applicant has confirmed that primary reference standards are used and have provided the relevant certificates of analysis.

**Container Closure System**
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability data support the proposed shelf-life of 3 years with no special storage conditions; keep the bottle tightly closed.

**SPC, PIL and Labels**
The SPC, PIL and labels are pharmaceutically acceptable.

**CONCLUSION**
It is recommended that a Marketing Authorisation should be granted for this application.
NON-CLINICAL ASSESSMENT

INTRODUCTION

This is a National application for a delayed release, enteric-coated tablet containing 800mg mesalazine as the active ingredient. The application has been submitted according to article 10a (bibliographic application) of Directive 2001/83/EC.

Mesalazine (5-aminosalicylic acid – 5-ASA) is a non-steroidal, anti-inflammatory drug used for the treatment of ulcerative colitis. Its mechanism of action is not fully understood but appears to be topical. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease, and it is hypothesised that mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

The UK approved indications and dosing for Asacol 800mg MR tablets are:
- Mild acute exacerbations of ulcerative colitis: three tablets (2.4g) a day in divided doses.
- Moderate acute exacerbations of ulcerative colitis: six tablets (4.8g) a day in divided doses.
- Maintenance of remission of Crohn’s ileo-colitis: up to three tablets (2.4g) a day in divided doses.

The maximum daily therapeutic dose of 4.8g is equivalent to approximately 70mg/kg for a 70 kg adult.

A Marketing Authorisation has been granted via the Decentralised procedure for Asacol 1200mg gastro-resistant, prolonged release tablets which has the same maximum daily dose of 4.8g for short term use (induction of remission) in the UK.

PHARMACOKINETICS

The applicant reports that there is a paucity of non-clinical pharmacokinetic data on mesalazine in the literature and has conducted some additional single dose pharmacokinetic studies in mice, rats, dogs and humans. The studies were conducted with unformulated 5-aminosalicylic acid (5-ASA) which was shown to be completely absorbed from the small intestine. The safety margin is suggested to be somewhat small as indicated by the data for the AUC in dogs (administered an oral pressure controlled colon capsule) only being approximately twice that of the AUC in humans (administered Asacol 800mg MR Tablets) for a similar dose per kg. Although the use of unformulated 5-ASA will not model that of the modified release formulation of Asacol, the data obtained is useful to compare animal/human exposures.

In humans, mesalazine is better absorbed from the upper intestine than from the lower intestine, with absorption of orally-administered unformulated mesalazine from the upper GI tract in the region of 75%.
Moderate amounts of mesalazine and its metabolite, N-acetyl-5-aminosalicylic acid, are widely distributed to all tissues except the CNS following presystemic acetylation. Placental transfer can occur and there is evidence of fetal exposure in humans. The N-acetyl metabolite of mesalazine is considered to possess little pharmacological activity, although this has not been clearly demonstrated. Metabolism is reported to be primarily hepatic in both rats and humans, and the N-acetyl derivative appears to be the only metabolite of quantitative significance in these species. In dogs, which are poor acetylators, the drug is essentially unmetabolised.

Mesalazine is eliminated primarily as the N-acetyl metabolite. Elimination of both the parent compound and the main metabolite occurs primarily in the urine. Biliary excretion of mesalazine and its primary metabolite are low in humans. Low levels of mesalazine and its primary metabolite are excreted in breast milk.

No data on pharmacokinetic drug interactions are available in the literature nor were any provided by the company.

SAFETY PHARMACOLOGY

Good Laboratory Practice (GLP) safety pharmacology studies to investigate the potential effects of the product on QT interval have not been conducted as described in International Conference on Harmonisation (ICH) guidance S7B. However, a one year oral dosing toxicity study in beagle dogs was conducted in which no significant changes were observed in electrocardiograms of all animals.

The data provided from the study and as a summary of published data do not raise any additional safety concerns with regards to cardiovascular, CNS, respiratory or gastrointestinal pharmacology.

TOXICOLOGY

While mesalazine is a well known drug, the approved dose level for this product (when used to induce remission) is higher than previously marketed products.

The kidney was the major target organ of toxicity in mice, rats and dogs, as evidenced by an increased incidence of renal pelvic dilation (mice), papillary inflammation, oedema and necrosis (rats) and chronic nephritis (dogs). Increased blood urea nitrogen and creatinine were also found in rats and dogs. The renal toxicity was observed in an acute oral toxicity study in dogs (bilateral renal papillary necrosis) at doses of 208-750mg/kg; in 14 day oral toxicity studies in rats and rabbits at doses of 1080mg/kg/day; in a 6 month oral toxicity study in rats (papillary necrosis) at 170mg/kg/day or higher; and in a 1 year oral toxicity study in dogs (chronic nephritis) at 80mg/kg/day or higher.

In a 52 week oral gavage study in dogs using unformulated mesalazine the NOAEL was reported as 40mg/kg/day, while in a 26 week dog study using Asacol delayed release tablets at approximate doses of up to 200mg/kg/day no renal or other histological mesalazine-related changes were detected.
Pharmacokinetic data submitted show that following a single dose of 4.8g mesalazine in humans, the degree of systemic exposure to mesalazine and N-acetyl-5-aminosalicylic acid was variable. The mean AUC at the NOAEL in dogs was approximately twice the mean human value but less than the maximum human value. Similarly, mean $C_{\text{max}}$ values in dogs and rats (at the NOAELs) were up to 9 fold greater than the mean human $C_{\text{max}}$, but the maximum $C_{\text{max}}$ value obtained in humans was less than the mean rat $C_{\text{max}}$. The only figure available for systemic exposure to N-acetyl-5-aminosalicylic acid is a $C_{\text{max}}$ value in rats. This is approximately 4.4 fold greater than the mean $C_{\text{max}}$ value in humans, but similar to the maximum $C_{\text{max}}$ value in humans.

A small safety margin is suggested as there is very limited pharmacokinetic data available. The AUC for mesalazine seen in dogs at the NOAEL was less than twice the AUC for mesalazine seen in healthy humans who were administered single 4.8g doses of the proposed product. This indicates that nephrotoxicity could be a concern.

As with other NSAIDs, mesalazine induced renal papillary necrosis in repeat-dose studies in mice, rats, dogs and in an acute cynomolgus monkey study. Though widely recognized in animals, this lesion is rare in man following treatment with NSAIDs. Thus, the small safety margin suggested by the limited pharmacokinetic data available is considered acceptable with the safety profile of mesalazine being known through 20 years of clinical experience.

**REPRODUCTIVE TOXICOLOGY**

Oral dosing reproductive studies have been conducted in two species (rats – Segment I, II and III; rabbits – Segment II only). Study results suggest no effects on male fertility in rats at oral doses up to 480mg/kg/day. There was no evidence of impaired embryo-fetal development at oral doses up to 480mg/kg/day in rats and rabbits, and no effect on pre and postnatal development in rats at doses of up to 400mg/kg/day. Reduced pup weight occurred at doses of 240 to 480mg/kg/day in rats. Maternal toxicity (indicated by reduced weight gain and mortality) was noted at doses of 360 and 480mg/kg/day in rats. No statistically significant differences were observed between dosing groups in rabbit teratogenicity studies.

**GENOTOXICITY**

No new non-clinical studies were conducted by the applicant for genotoxicity. There is appropriate data in the literature review provided for evidence of non-genotoxicity.
CARCINOGENICITY

Two year studies in mice (dietary ad-mix at doses of up to 2000mg/kg/day) and rats (dietary ad-mix at doses of up to 480mg/kg/day) did not reveal evidence of carcinogenic potential.

STUDIES ON IMPURITIES

All drug substance and finished product impurity levels are reported to comply with the relevant European Pharmacopeia monograph and/or the relevant ICH guidelines.

NONCLINICAL OVERVIEW

The nonclinical overview consisted of an acceptable review on the pharmacology and toxicology of mesalazine (5-aminosalicylic acid – 5-ASA).

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Sections 4.6 (Pregnancy and lactation) and 5.3 (Preclinical safety data) of the SPC are toxicologically acceptable.

ENVIRONMENTAL RISK ASSESSMENT

An Environmental Risk Assessment (ERA) has been provided and it is stated by the applicant that the draft guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00, 2003) has been consulted. The draft guideline has subsequently been re-drafted and finalised in 2005. However, the ERA submitted by the company is acceptable.

CONCLUSION

There are no preclinical objections to the grant of a Marketing Authorisation.
CLINICAL ASSESSMENT

INTRODUCTION

This is a bibliographic application by Procter & Gamble Pharmaceuticals UK Ltd for their own brand of modified release mesalazine.

Mesalazine is well established as an intestinal anti-inflammatory drug for the treatment of mild to moderate acute exacerbations of ulcerative colitis and for the maintenance of remission of Crohn’s ileo-colitis. It was first registered in the UK in 1985.

INDICATIONS

The proposed indications are:

Ulcerative colitis: For the treatment of mild to moderate acute exacerbations. For the maintenance of remission.

Crohn’s ileo-colitis: For the maintenance of remission.

These are considered to be satisfactory.

DOSE & DOSE SCHEDULE

The proposed dose and dose schedule for this product, for use in the above indications, is:

Swallow whole with water. Do not break, crush or chew the tablets before swallowing.

ADULTS:

Mild acute exacerbations of ulcerative colitis: Three tablets (2.4g) a day in divided doses.

Moderate acute exacerbations of ulcerative colitis: Six tablets (4.8g) a day in divided doses.

Maintenance of remission of ulcerative colitis and Crohn’s ileocolitis: Up to three tablets (2.4g) a day in divided doses.

ELDERLY: The normal adult dosage may be used unless renal function is impaired (see section 4.4).

CHILDREN: Not recommended.

This is considered to be satisfactory.
TOXICOLOGY
Refer to the pre-clinical assessment.

CLINICAL PHARMACOLOGY

General
No new data are presented and none are required for this application. In particular, no clinical studies to evaluate the pharmacokinetics of Asacol MR 800mg tablets have been conducted. In the original studies, levels of both mesalazine and its major metabolite N-AC-5-ASA were studied. Early studies were also undertaken to prove the validity of the delivery system. The site of drug release was demonstrated in several studies using a radiographic method.

The pharmacodynamics of mesalazine are well-known as a result of numerous studies. It is effective topically.

A satisfactory overview of clinical pharmacology has been provided.

EFFICACY
No new data are presented and none are required for this application. There is a succinct and adequate overview of efficacy.

SAFETY
No new data are presented and none are required for this application. The safety profile of mesalazine is well-known, as the drug has been on the market for 20 years. A succinct and adequate overview has been provided.

EXPERT REPORT
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

CONCLUSIONS
A Marketing Authorisation should be granted for this product.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Asacol 800mg MR tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
Results of the toxicology studies did not identify any properties likely to cause toxicity in humans when the product is used as directed in the SPC.

EFFICACY
No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with mesalazine is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
ASACOL 800MG MR TABLETS
PL 10947/0012

STEPS TAKEN FOR ASSESSMENT

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 17 December 2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 18 January 2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the clinical dossier on 22 July 2005, and further information relating to the quality dossier on 05 January 2006 and 12 June 2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 08 December 2005 for the clinical section, and again on 13 March 2006 and 08 June 2007 for the quality section.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 14 September 2007.</td>
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</tbody>
</table>
Module 6

Asacol 800 mg MR Tablets

PL 10947/0012

**STEPS TAKEN AFTER ASSESSMENT**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Description</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/12/2012</td>
<td>Type II variation</td>
<td>To update section 4.2 (Posology and method of administration) of the SPC and consequentially the leaflet by adding ‘once daily option’ in dosage regimen of the product.</td>
<td>Variation granted 21/03/2013</td>
</tr>
</tbody>
</table>
ANNEX 1 – CLINICAL VARIATION ASSESSMENT REPORT

Our Reference: PL 10947/0012 - 0013
Product: Asacol MR Tablets 800 mg
Marketing Authorisation Holder: WARNER CHILCOTT UK LIMITED
Active Ingredient(s): MESALAZINE.
Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard

Reason:
To update section 4.2 (Posology and method of administration) of the SmPC and consequently the leaflet by adding ‘once daily option’ in dosage regimen of the product.

Supporting Evidence
Clinical Overview
SmPC tracked and clean
Mock up leaflet

Evaluation
Asacol 800 mg MR is currently indicated in patients with ulcerative colitis (UC) for the treatment of mild to moderate acute exacerbations and for the maintenance of remission; and in patients with Crohn’s disease, it is indicated for the maintenance of remission. For the maintenance of remission, up to 2.4 g is taken per day in divided doses. Following a similar Type II variation being granted with Octasa, a similar product to Asacol, the Marketing Authorisation Holder (MAH) is seeking a once-daily dosing for their product, Asacol 800 mg MR tablets. The MAH argues that the issue of non-adherence to prescribed regimen of mesalazine could be improved by providing patients with simpler and more convenient dose regimens.

To support this change to dosage regimen, the clinical overview provides a summary of pharmacokinetic studies and clinical therapeutic studies comparing once daily dosing with divided dosing. The MAH has not supplied the articles they refer to.

The MAH refers to 8 studies which have been identified following a data search for controlled clinical trials comparing once daily dosing of mesalazine with divided dosing. This search included different types of mesalazine products and one study which used Asacol 800 mg MR tablets.

Pharmacokinetics:
Mesalazine acts locally on the colonic epithelium rather than systemically. As a result, systemic bioavailability of the mesalazine does not equate to its efficacy and therefore pharmacodynamic or comparative clinical studies are required to demonstrate clinical equivalence.
As supportive evidence, the MAH summarises a dynamic model to simulate the distribution of 5-ASA in the colon using computer software (STELLA). The simulated distribution of 5-ASA in the total colon and four colonic compartments (right colon, transverse colon, descending colon and sigmoid colon) was examined for the administration of Asacol 800 mg MR tablets either as one 2.4 g dose or three 800 mg doses. The model was run 100 times to simulate administration of Asacol 800 mg MR tablets for 100 days. Results from this study showed that the maximum, average and distribution of model-predicted colonic 5-ASA, both under healthy and simulated disease conditions, are similar when Asacol tablets are dosed at 2.4 g once-daily compared to 800 mg three-times daily.

<table>
<thead>
<tr>
<th>Table 2: Maximum, average and distribution of model-predicted Asacol (mg) in segments of the colon under healthy conditions and conditions characterizing ulcerative colitis.</th>
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<tbody>
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<tr>
<td></td>
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<tr>
<td>Max</td>
</tr>
<tr>
<td>Healthy patient</td>
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<tr>
<td>Right colon</td>
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<tr>
<td>Transverse</td>
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<tr>
<td>Descending</td>
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<tr>
<td>Sigmoid</td>
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<tr>
<td>Total colon</td>
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<tr>
<td>Patient with reduced motility</td>
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<tr>
<td>Right colon</td>
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<tr>
<td>Transverse</td>
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<tr>
<td>Descending</td>
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<tr>
<td>Sigmoid</td>
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<tr>
<td>Total colon</td>
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<tr>
<td>Patient with increased motility</td>
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<tr>
<td>Right colon</td>
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<tr>
<td>Transverse</td>
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<tr>
<td>Descending</td>
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<tr>
<td>Sigmoid</td>
</tr>
<tr>
<td>Total colon</td>
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<tr>
<td>Patient with frequent bowel movements (5 daily)</td>
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<tr>
<td>Right colon</td>
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<tr>
<td>Transverse</td>
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<tr>
<td>Descending</td>
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<tr>
<td>Sigmoid</td>
</tr>
<tr>
<td>Total colon</td>
</tr>
<tr>
<td>Patient with frequent bowel movements (12 daily)</td>
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<tr>
<td>Right colon</td>
</tr>
<tr>
<td>Transverse</td>
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<tr>
<td>Descending</td>
</tr>
<tr>
<td>Sigmoid</td>
</tr>
<tr>
<td>Total colon</td>
</tr>
</tbody>
</table>

There was no discussion on statistical significance of these findings, although the MAH argues there is no clinically significant difference.

Assessor’s comment: It is not clear what the purpose of this study was if it was not to identify if firstly there is any difference between the two groups and then to consider if this difference is clinically significant.

Efficacy Studies:
The MAH provided a summary of the eight studies identified in the search described earlier:
The main study the applicant refers to as the most relevant is the CODA study (Colitis Once Daily Asacol) Hawthorn 2012. The summary as provided by the applicant in the Clinical Overview is as below:

<table>
<thead>
<tr>
<th>Study</th>
<th>Country and Number of Centres</th>
<th>Key Eligibility Criteria</th>
<th>Criteria Used to Define Response Endpoint</th>
<th>Number of Patients</th>
<th>Medications used</th>
<th>Duration of Therapy</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al. (2003) Investigator Initiated Study</td>
<td>USA, 1 site</td>
<td>Adults: UC in clinical remission for 4 months, receiving mesalazine maintenance therapy</td>
<td>Harvey-Bradshaw Index &gt;3</td>
<td>22</td>
<td>Asacol 400mg MR tablets, average dose 2.5g/day once-daily vs. 2.7g/day twice or three-times daily</td>
<td>12 Months</td>
<td>1:1 Randomisation Investigator-blind Superiority design</td>
</tr>
<tr>
<td>Kamm et al. (2009) Phase 3 Safety Study</td>
<td>Multinational, 101 sites</td>
<td>Adults; Participation in one of two parent studies +/- 8 week extension study; UC in remission</td>
<td>Clinical or endoscopic relapse</td>
<td>401</td>
<td>Mezavant 2.4g once-daily, vs. 1.2g twice-daily</td>
<td>12 Months</td>
<td>1:1 Randomisation Open label Exploratory design</td>
</tr>
<tr>
<td>Kane et al. (2009) Investigator Initiated Study</td>
<td>USA, 2 sites</td>
<td>Age &gt;18 years; UC in clinical remission for 4 months and maintained on Asacol 400mg MR tablets</td>
<td>UCDAI score &gt;3 or an increase &gt;3</td>
<td>20</td>
<td>Asacol 400mg MR tablets 1.8-3.2g/day one-daily vs. twice-daily dosing</td>
<td>12 Months</td>
<td>1:1 Randomisation Investigator-blind Superiority design</td>
</tr>
<tr>
<td>Dignass et al. (2009) PODIUM Phase 3 Study</td>
<td>Multinational (6 European Countries), 69 sites</td>
<td>Age &gt;18 years; UC in remission: clinical relapse within 12 months of study entry; on maintenance therapy with 5-ASA at enrollment or during 12 months prior to study entry</td>
<td>UCDAI score &gt;3</td>
<td>382</td>
<td>Pentasa 3g once-daily vs. 1g twice daily</td>
<td>12 Months</td>
<td>1:1 Randomisation Investigator-blind Non-inferiority design</td>
</tr>
<tr>
<td>Prantera et al. (2009) Investigator Initiated Study</td>
<td>Italy, Poland, and Ukraine, 47 sites</td>
<td>Age 18-75 years; Left-sided UC in remission for ≥1 month prior to study entry: experienced at least 1 relapse during 12 months prior to study entry</td>
<td>UCDAI score &gt;3 or endoscopic evidence of active disease</td>
<td>331</td>
<td>Mezavant 2.4g once-daily vs. Asacol 400mg MR tablets 1.3g morning and 880mg evening</td>
<td>12 Months</td>
<td>1:1 Randomisation Double-blind Superiority design</td>
</tr>
<tr>
<td>Sandborn et al. (2010) GOEM Phase 4 Study</td>
<td>USA, Canada, and Puerto Rico, 193 sites</td>
<td>Age &gt;18 years; UC in remission for ≥3 months maintained on Asacol 400mg MR tablets at a stable dose from 1.6 to 2.4 g/day; at least one relapse within previous 18 months</td>
<td>SCCAI &gt;4</td>
<td>1,023</td>
<td>Asacol 400mg MR tablets 1.0-2.4g/day one-daily vs. twice-daily</td>
<td>12 Months</td>
<td>1:1 Randomisation Investigator-blind Non-inferiority design</td>
</tr>
<tr>
<td>Krus et al. (2011) Phase 3 Dose-Finding Study</td>
<td>Multinational (12 countries), 65 sites</td>
<td>Age 18-75 years; UC in remission; last acute UC episode offset within 3 months prior to study entry</td>
<td>GAI score &gt;4 and an increase of ≥3 from baseline</td>
<td>647</td>
<td>Salofalk granules 3g once-daily vs. 1.5g once-daily vs. 500mg three-times daily</td>
<td>12 Months</td>
<td>1:1 Randomisation Double-blind Non-inferiority design</td>
</tr>
<tr>
<td>Hawthorne et al. (2012) CODA Investigator Initiated Study</td>
<td>UK, 32 sites</td>
<td>Age &gt;18 years; UC in remission on maintenance therapy with a 5-ASA for at least 4 weeks prior to study entry; at least one relapse within previous 2 years</td>
<td>Symptoms of relapse with a Barore score &gt;1</td>
<td>213</td>
<td>Asacol 800mg MR Tablets 2.4g once-daily vs. 800mg three-times daily</td>
<td>12 Months</td>
<td>1:1 Randomisation Investigator-blind Non-inferiority design</td>
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</tbody>
</table>
This study was conducted in 32 centres in the UK between 2006 and 2009 and was an investigator-blind, randomised, non-inferiority study comparing once-daily (OD) Asacol (3 x Asacol 800 mg MR Tablets) versus 800 mg (1 x Asacol 800 mg MR tablet) three-times daily (TDS) for the maintenance of remission of UC. Patients aged over 18 years whose ulcerative colitis had been in remission for at least 4 weeks (but who had experienced at least one relapse within the previous 2 years) and who were receiving maintenance therapy with either mesalazine, sulfasalazine, olsalazine or balsalazide were recruited and followed-up for 12 months. The primary endpoint was relapse rate and non-inferiority would be concluded if the lower limit of the two-sided 95% confidence interval of the difference in proportions relapsing (TDS-OD) exceeded -10%. Relapse was defined as symptoms of active disease (bloody diarrhoea or rectal bleeding for 3 days or more) with a sigmoidoscopic appearance of grade 2 or 3 using the modified Baron score.

Secondary outcomes included time until confirmed relapse and a multivariate analysis of various factors known to affect the likelihood of relapse as effect modifiers. Analysis of adverse events and adherence to treatment was also performed. Adherence was measured by tablet counts and self-reported adherence. A subgroup of patients used a bottle cap device for study medication that recorded all bottle opening events. Adverse events were assessed during follow-up clinic visits at 6-weeks, 6-months and 12-months (final) or in the event of suspected relapse. In addition to the clinic visits, telephone follow-up was carried out at 3-months and 9-months to record adverse events and changes to concomitant medication.

213 patients were randomised to either the OD (n=103) or TDS (n=110) group using a 1:1 randomisation ratio and represent the Intention To Treat (ITT) population. 94 patients in each arm completed the study and the Per Protocol (PP) population contained 79 patients in the OD group and 72 patients in the TDS group.

Primary analysis confirmed non-inferiority of once-daily dosing. In the ITT population, relapse rates were 31% [95% CI 22-40"] in the OD group and 45% [95% CI 35-54"] in the TDS group. In the PP population relapse rates were 20% (95% CI 11-29") in the OD and 36% (95% CI 25-47") in the TDS group. The difference between relapse rates (TDS – OD) was 14% (95% CI 1-26") for the ITT population and 16% (95% CI 2-30") for the PP population. As the lower limit of the confidence interval was not less than -10% in any population, non-inferiority of once-daily dosing compared with conventional TDS dosing was confirmed. In pre-specified secondary analysis, the ITT and PP populations also showed potential superiority of once-daily dosing.

All measures of adherence were significantly better in the OD group compared to the TDS group. In the adherence sub-study, treatment adherence was significantly better in the OD group (n=28), with median days adherent (opening cap once or more) of 96.6% (IQR 92.7%-98%) versus a median of 54.8% (IQR 34.4%-85.7%) days in the TDS group (n=30) when the cap was opened at least three times (P < 0.001). Multivariate analysis showed once-daily dosing was associated with lower relapse risk for UC independently of adherence.
This study therefore demonstrates that once-daily dosing with Asacol 800 mg MR Tablets dosed at 2.4 g/day is as effective as three-times daily dosing and pre-specified secondary analysis suggested significantly reduced relapse rates with once-daily dosing. The benefit was, however, of borderline clinical significance and may relate in part to the significantly improved adherence seen in those patients receiving a once-daily regimen. These findings of this comparative clinical study also demonstrate the bioequivalence of Asacol 800 mg MR Tablets dosed at 2.4 g once-daily compared with 800 mg three-times daily (as currently licensed).

Assessor’s Comment: It appears from what has been described by the applicant that the two different treatment regimen were comparable. However, it is likely that the once daily dosing appears better than the divided dosing due to a better compliance with this regime. The MAH should provide the article referred to for review.

The applicant provided a summary of the key findings from the other studies as below:
<table>
<thead>
<tr>
<th>Study</th>
<th>Mesalazine used</th>
<th>Disease distribution</th>
<th>Number of patients (ITT)</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kane et al. (2005)</td>
<td>Asacol 400mg MR Tablets, average dose 2.5mg/day once-daily vs. 2.7g/day three-times daily</td>
<td>Not reported</td>
<td>n=22</td>
<td>In the ITT population, maintenance of remission at 8 months was seen in: 62% in OD group, 60% in BD/TG group (P=0.76)</td>
<td>Treatments adherence was seen in: 75% in OD group, 74% in BD/TG group (P=0.8) Amount of medication taken was: 60% in OD group, 74% in BD/TG group (P=0.07)</td>
</tr>
<tr>
<td>Kamm et al. (2005)</td>
<td>Mezavant 2.4g once-daily vs. 1.2g twice-daily</td>
<td>77.3% left-sided colitis; 0.7% upper limit in transverse colon; 18.8% pancolitis (reported for safety population only)</td>
<td>n=451</td>
<td>In the safety population (n=459) 174 patients (37.7%) experienced 384 adverse events, the majority of which were mild or moderate in intensity. 15 patients (3.3%), nine in each group, experienced a total of 22 serious adverse events (10 in the OD and 12 in BD group). Most SAEs were asthenorexia, experienced by 5 patients in the OD group and 4 patients in the BD group. Mezavant 2.4g/day administered as once-daily or twice-daily demonstrated a good safety profile and was well tolerated.</td>
<td>In efficacy population, maintenance of remission at 12 months seen in: 74.4% in OD group, 68.8% in BD group (P=0.381) In PP population, maintenance of remission at 12 months seen in: 67.8% in OD group, 72.2% in BD group (P=0.359) Treatment compliance (&gt;80% of study medication taken) was seen in: 93.3% of OD group, 86.6% of BD group (p-value not reported) Mezavant 2.4g/day administered as once-daily or twice-daily was effective as maintenance treatment</td>
</tr>
<tr>
<td>Kane et al. (2005)</td>
<td>Asacol 400mg MR Tablets, 1.6-3.2g/day once-daily vs. twice-daily dosing</td>
<td>75% pancolitis; 20% left-sided colitis; 5% proctitis</td>
<td>n=20</td>
<td>In ITT population, maintenance of remission at 12 months seen in: 50% of OD group, 37.6% of BD group (P=0.31) Study failed to demonstrate superiority of 1.0-2.4g OD compared with 1.3-2.4g BD regimen</td>
<td>Treatment adherence was seen in: 42% of OD group, 37.7% of BD group (P=0.05) Median amount of study medication consumed was: 41% in OD group, 55% in BD group (P=0.5)</td>
</tr>
<tr>
<td>Dignass et al. (2005)</td>
<td>Pentasa 2g once-daily vs. 1g twice daily</td>
<td>28.5% pancolitis; 71.5% left-sided colitis, patients with disease &lt;15 cm from the anal verge excluded</td>
<td>n=302</td>
<td>In ITT population, maintenance of remission at 12 months seen in: 70.0% of OD group, 58.0% of BD group (P=0.024) In PP population, maintenance of remission at 12 months seen in: 72.8% of OD group, 69.5% of BD group (P=0.251) Study demonstrated non-inferiority and superiority of Pentasa 2g OD vs. 1g BD</td>
<td>Median time to relapse: 232 days in OD group, 146 days in BD group (P=0.06) Self-reported adherence to therapy (VAS score) after 6, 9, and 12 months was significantly greater in the OD group vs. BD group at all but 1 study visit (P&lt;0.05) Compliance measured by medication taken was not significantly different between the groups</td>
</tr>
</tbody>
</table>
Meta-Analyses:

The applicant also refers to four meta-analyses published which have been performed on some or all of the studies shown above. The MAH has summarised the key findings from these meta-analyses.
The MAH concludes that based on this data, patients are more likely to adhere to a regimen of once daily dosing than to one where mesalazine is taken in divided doses throughout the day. In addition, it is also concluded that once daily dosing is as effective as conventional dosing for the maintenance of remission in quiescent UC.
Safety
The MAH refers to the data from the CODA study as this was the only study which used Asacol MR 800 mg tablets. Only 103 patients were exposed to once-daily dosing. It is concluded that the adverse event profile associated with single daily dose for up to 12 months is consistent with that found in the group using the conventional dosing regime.

Conclusion
The applicant has referred to published articles which could support their proposal of once daily dosing for Asacol 800 mg MR tablets. However, a full review of these articles is required prior to any conclusion being drawn on the efficacy and safety of this dosing regime.

Decision - Request for Further Information

OUTSTANDING POINTS
1. The MAH refers to published clinical data to support this Type II variation but these have not been submitted for assessment. The applicant is requested to submit the articles referred to in their Clinical Overview for a full assessment of the data.

Response received 22 February 2013

1. The MAH refers to published clinical data to support this Type II variation but these have not been submitted for assessment. The applicant is requested to submit the articles referred to in their Clinical Overview for a full assessment of the data.

These have been provided by the applicant and the relevant ones, relating to Asacol 400 mg and 800 mg tablets are discussed below:

Kane et al 2003
A pilot study to assess the short-term outcomes of once-daily dosing versus conventional dosing of mesalazine in maintaining quiescent ulcerative colitis and to assess adherence rates with both regimens.

Adult patients with documented diagnosis of UC required to have been in clinical remission for at least 4 months and receiving mesalazine for maintenance of quiescent disease were recruited. Subjects were randomised to receive either once daily dosing or continued conventional dosing. The dose of mesalazine remained unchanged throughout the course of the study. Each patient knew the regimen they were receiving but instructed not to discuss study personnel. Patients were assessed at 3 and
6 months after enrolment. Relapse was defined as a score of 3 on the Harvey-Bradshaw index. The study endpoint was the presence or absence of disease activity at the end of 6 months. At study end, an investigator blinded to individual patient treatment regimens assessed the outcomes and medication consumption rates for each group.

22 patients were enrolled in the study. 12 in the OD group and 10 in the CD group (3 receiving tds and 7 receiving bd dosing). Similar degree of compliance was found in both groups. At 6 months, 1 patient in each group experienced a clinical disease relapse. Both patients were found to be non-compliant to the dosing regimen they were assigned.

**Assessor’s Comment:**
This was a small study and no meaningful conclusions can be drawn on the efficacy and safety of OD dosing over conventional dosing.

**Kane et al 2008**
This study aimed to examine the efficacy and tolerability of Asacol for long-term maintenance and compare the rates of medication consumption between groups over a prolonged period.

Patients with ulcerative colitis in remission for at least 4 months before study entry were enrolled in the study. Patients were randomised into one of 2 groups: once daily dosing or conventional dosing (twice daily or three times daily). This was an investigator-blind study. Patients were then followed and assessed at 3 month intervals up to month 12. Disease assessment was carried out using the modified Ulcerative Colitis Disease Activity Index (UCDAI). Remission was defined as a score of 3 or less. Disease activity, or flare of disease, was defined as a score >3 or an increase of more than 3 points during the preceding time interval. Medication consumption rates at months 3, 6, 9 and 12 were calculated. The endpoint of the study was disease relapse or the 12-month study period.

20 patients were randomised. Study was discontinued due to a decision to conduct a larger multi-centre study. Not all subjects as per the sample size calculation were recruited. 12 subjects were randomised to once daily mesalazine for 12 months and 8 to the conventional dosing group. All patients in the CD group had been taking their medication BD and this was continued in the study. 6 out of 12 patients (50%) in the OD group experienced a flare of disease activity during the study period compared with 5 out of 8 (62.5%) in the CD group. 5/12 (42%) in the OD group were adherent to their regimen compared to 3/8 (37.5%) in the CD group. None of those in the OD group adherent to their regimen experienced a flare while 6/7 who were non-adherent experienced a flare of disease. In the CD group, 1/3 adherent patients experienced a flare compared with 4/5 in the non-adherent group.

The report concludes that no reported adverse events were felt to be associated directly with once daily therapy. One patient was reported to have died in the study. The patient was in remission but the regimen the patient was on is not reported, although investigators reported this did not contribute to his death, which was secondary to an MI.
Assessor’s Comment:
Again, given the small size of the study, no conclusions can be drawn on the efficacy or safety of this regimen, although this does not suggest a significant difference in both regimens exists. However, it can be seen that subject adherence to study regime is more likely to influence disease activity.

This study was conducted to determine the efficacy and safety of once-daily dosing of Asacol 400 mg tablets compared with twice daily dosing for maintaining remission in UC patients. It was a multicentre, randomised, investigator-blinded, active control trial. Patients with UC maintained in clinical remission (defined as a Simple Clinical Colitis Activity Index (SCCAI) of 2 points or fewer) for at least 3 months on Asacol, at a stable dose between 1.6 g – 2.4 g/day.

Patients were randomised in a 1:1 ratio to receive either once daily or twice daily dosing regimen of Asacol at the same total daily dose they were receiving at baseline. Patients were assessed at screening and at 3, 6, 9 and 12 months. SCCAI score was used for assessment of disease severity and efficacy. Relapse was defined as any SCCAI score of 5 points or higher. Adherence to treatment was also assessed. The primary endpoint was maintenance of clinical remission at month 6.

A total of 1027 patients were randomised and 1023 were dosed (512 OD, 511 BD). Patient characteristics at baseline are reported to be similar including disease activity, except for baseline extracolonic features, which there were more cases (with arthritis) in the OD group than in the BD group. 4% of patients were receiving an OD dosing regimen at baseline, 62% were receiving a BD regimen, 33% were receiving a TDS dosing regimen and 1% were receiving ‘other’ dosing regimen.

At month 6, 90.5% (428 of 473) of patients dosed once daily had maintained clinical remission compared with 91.8% (435 of 474) of those dosed twice daily. No significant differences were seen between the 2 dosing regimens in the rates of clinical remission at months 3 and 12. Time-to-relapse also was similar at month 6 and month 12. Medication adherence was high in both treatment groups but a difference in MARS questionnaire scores between the two groups was only observed at month 3. Patients who relapsed had similar MARS questionnaire scores as compared with those who did not relapse.

Incidence of SAEs was higher in the once-daily group. There were 18 patients (3.5%) with SAEs in the once daily group and 9 patients (1.8%) in the twice daily group. There were some cardiovascular related events (Atrial Fibrillation, cardiac failure congestive, TIA, Myocardial infarction) which only occurred in the once daily group but only one event of each was reported. The events were considered by the investigator to be doubtfully related to study medication. 9 patients were withdrawn from the study due to AEs (2 from OD group and 7 from BD group).

Assessor’s Comment:
This larger study supports the efficacy and safety of the OD dosing. The relapse rate in this study is however considerably low compared to other similar trials. Asacol 400 mg tablets was used in this study which has been shown not be bioequivalent to the 800 mg. This was a comparison between BD dosing and OD dosing. However, 33%
of patients in the study had been on TDS dosing prior to the study. The incidence of SAEs in the OD group is higher than in the BD group although these events were only single events and reported by the investigators as doubtfully related to the study medication.

Hawthorne et al 2012
The CODA study’s objective was to evaluate if OD mesalazine given as 3 x 800 mg Asacol tablets was as effective and safe as 1 x 800 mg TDS, as maintenance therapy for UC over 1 year. The study was an investigator-blind multicentre trial.

Patients with UC in remission on maintenance therapy with mesalazine, sulfasalazine, olsalazine or balsalazide for at least 4 weeks but with at least one relapse within the previous 2 years were recruited. At screening, subjects were consented, blood and urine were taken and flexible or rigid sigmoidoscopy was performed. Symptoms of disease activity were assessed using the Mayo score, with the full score incorporating the modified sigmoidoscopy score. Patients were randomised to OD or TDS in a 1:1 ratio. The study was investigator-blind and subjects were instructed not to reveal to either the research nurse or doctor which treatment group they were in. Disease was assessed at 6-week, 6-month, 12-month (final) clinic visits using the stool frequency and rectal bleeding component of the Mayo Clinic score. At months 3, and 9, telephone follow-up to record adverse events and any changes to concomitant medications were carried out. At final visit, rigid or flexible sigmoidoscopy was done and a Mayo score was calculated. The primary endpoint was relapse rate during the 12 month follow-up. Secondary outcomes included time (in weeks) until confirmed relapse and analysis of factors as effect modifiers. A subgroup of patients participated in the adherence sub-study using the Medication Event Monitoring System (MEMS).

213 patients were randomised (103 to the OD group, 110 to the TDS group). 9 patients in the OD group and 16 in the TDS group were withdrawn for reasons other than relapse. In the OD group, 15 patients had protocol violations - 14 had adherence less than 75%. In the TDS group 22 were not included, 20 due to adherence less than 75%. Relapse rates were 31% in the OD group (95% CI 22% - 40%), and 45% in the TDS group (95% CI 35 – 54%). A similarly consistent difference was seen between the two groups in relapse rate in the PP population and complete case population. Non-inferiority of the OD regimen was confirmed as the lower limit of the CI was not less than -10%. 95.2% of patients were more than 75% adherent in the OD group compared to 92.5 % in the TDS group. (p = 0.46). Adherence was not found to be an independent predictor of relapse.

Overall 83 events were reported in the OD group and 84 in the TDS group. Serious adverse events in the OD group were abdominal pain, five admissions for surgery, and one worsening of UC. In the TDS group, there were 2 hospital admissions, unrelated to UC or trial medication.

Assessor’s Comment:
The results of this study support the outcome of the study by Sandborn. This was also conducted in patients on 800 mg Asacol. The relapse rate is similar to what’s been observed in other similar studies.
Meta-analysis has also been conducted evaluating the efficacy of once daily dosing of mesalazine compared with bd or tds. These are summarised below:

Feagan and Macdonald 2012 Cochrane Review:
A systematic review and meta-analysis of once-daily oral mesalazine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis.

Literature search identified 11 randomised studies. Three of these were induction of remission studies and 8 assessed maintenance of remission. The studies investigating maintenance of remission included some or all of the studies discussed above.

At 6 months, the pooled analysis of the ITT population included 1045 patients (two studies – Kane 2003 and Sandborn 2010). 16.2% (85/524) patients who received OD dosing regime relapsed compared to 14.8% (77/521) patients in the conventional dosing group. Pooled relative risk (RR) was 1.10 (95% CI 0.83 – 1.46) showing no statistically significant difference between OD dosing and conventional dosing for relapse at 6 months (p=0.51).

At 12 months, the pooled analysis of the ITT group included 2826 patients (7 studies – including Kane 2003, 2008, Sandborn 2010, Hawthorne 2012). 28.7% (400/1394) of patients in the OD group relapsed compared to 31.1% of patients in the CD group. The pooled RR was 0.92 (95% CI 0.83 – 1.03), showing no statistically significant difference between OD dosing and CD for relapse at 12 months (p=0.17).

No statistically significant difference was seen in the incidence of adverse events.

The authors concluded that OD oral dosing of mesalazine is as effective and safe as conventional dosing for the treatment of mild to moderately active UC and for maintenance of remission in quiescent UC.

Ford et all 2011
A systematic review and meta-analysis investigating once daily dosing compared to conventional dosing schedule of mesalazine and relapse of quiescent ulcerative colitis.

A literature search identified seven randomised controlled trials (RCTs) (including Kane 2008, Hawthorne 2011, Sandborn 2010) containing 2745 patients which used mesalazine. 1349 of these patients were randomised to receive once-daily mesalazine and 1396 to a CD schedule.

In total 423 (31.4%) patients allocated to once daily mesalazine relapsed compared with 461 (33%) patients assigned to a CD schedule. The RR of relapse with once-daily dosing compared with a CD schedule was 0.94 (95% CI 0.82 – 1.08).

No statistically significant difference was detected between OD and CD schedules in terms of the incidence of total adverse events (RR 1.08; 95% CI 0.97 – 1.20).

The authors concluded an OD dosing schedule for administration of oral mesalazine in UC is likely to be equally as effective as a conventional dosing schedule over 12 months of therapy, in terms of preventing relapse of quiescent disease.
Tong et al 2012
Meta-analysis investigating the efficacy and safety of once-daily versus multiple daily mesalazine for patients with ulcerative colitis.

9 published studies and one abstract were identified (including Kane 2003, 2008, Sandborn 2010 and Hawthorne 2011). Data for reporting relapse rates with OD vs MD mesalazine after 6 to 12 months of therapy were available from 8 RCTs, including a total of 2860 patients with quiescent UC. By ITT analysis, 372 (26.3%) of patients with OD dosing relapsed compared with 384 (26.5%) of patients on multiple dosing (RR 1.00 95% CI 0.89 – 1.12). After data was pooled, there was no significant increased risk of relapse within a year in quiescent UC patients (RR = 0.97 95% CI 0.74 – 1.27). Subgroup analysis of the eight studies using different formulations revealed there was no significant difference for relapse rates between OD and MD dosing in Asacol (RR=0.93, 95% CI 0.72 – 1.19).

No statistically significant differences were observed in the incidence of total AE (RR of experiencing any adverse event = 1.06, 95% CI 0.93 – 1.20), serious AE (RR = 1.48, 95% CI 0.92 – 2.41) and discontinuations due to AE (RR = 1.00 95% CI 0.99 – 1.02) with OD vs MD mesalazine.

Assessor’s Comment:
The overall conclusions from the meta-analyses support the efficacy and safety of the OD daily dosing of Asacol when compared with CD.

The applicant proposes the following changes to section 4.2 of the SmPC:

Posology and method of administration
Swallow whole with water. Do not break, crush or chew the tablets before swallowing.
ADULTS:
Mild acute exacerbations of ulcerative colitis: Three tablets (2.4g) a day in divided doses.

Moderate acute exacerbations of ulcerative colitis: Six tablets (4.8g) a day in divided doses.

Maintenance of remission of ulcerative colitis: Up to three tablets (2.4g) a day once daily or in divided doses.

Maintenance of remission of Crohn’s ileocolitis: Up to three tablets (2.4g) a day in divided doses.

ELDERLY: The normal adult dosage may be used unless renal function is impaired (see section 4.4).

CHILDREN: Not recommended.

The following is proposed in the PIL:
The usual dose is:

- *Treating ulcerative colitis* – up to 6 tablets each day divided throughout the day (as advised by your doctor).
- *Preventing a flare of ulcerative colitis* – up to 3 tablets each day once daily or divided throughout the day (as advised by your doctor).
- *Preventing a flare of Crohn’s ileo-colitis* – up to 3 tablets each day divided throughout the day (as advised by your doctor).

**Overall Conclusion:**
Based on the evidence provided, this Type II variation is approvable.
SUMMARY OF PRODUCT CHARACTERISTICS

Following approval of the variation on 21st April 2013 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET (PIL)

Following approval of the variation on 21st April 2013 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
UKPAR Asacol 800mg MR tablets

PL 10947/0012

LABELLING
KEEP OUT OF REACH AND SIGHT OF CHILDREN.

This medicine contains lactose. See leaflet for further information.

This medicinal product does not require any special storage conditions. Do not remove desiccant pouches from the bottle.

Keep the bottle tightly closed.

For oral administration to be taken as directed by your doctor. Please read the Patient Information Leaflet before you begin taking "Asacol®" 800 mg MR tablets.

Do not break, crush, or chew the tablet.

Swallow whole with water.

Each tablet also contains:

Core: Lactose monohydrate, sodium starch glycolate, talc, povidone, magnesium stearate, colloidal anhydrous silica

Coating: Methacrylic acid – methyl methacrylate copolymer (1:1), talc, dibutyl phthalate, ferric oxide red (E172), methacrylic acid – methyl methacrylate copolymer (1:1), ferric oxide yellow (E172), macrogol

Black Ink: Propylene glycol, ferric oxide black (E172), ammonium hydroxide, shellac.