

**ASACOL 800MG MR TABLETS
PL 00364/0083**

UKPAR

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**ASACOL 800MG MR TABLETS
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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 00364/0083). 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 00364/0083**

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 00364/0083) 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 application has been supplemented with additional clinical data.

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.

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.

PRECLINICAL 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.

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_{max} values in dogs and rats (at the NOAELs) were up to 9 fold greater than the mean human C_{max} , but the maximum C_{max} value obtained in humans was less than the mean rat C_{max} . The only figure available for systemic exposure to N-acetyl-5-aminosalicylic acid is a C_{max} value in rats. This is approximately 4.4 fold greater than the mean C_{max} value in humans, but similar to the maximum C_{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. The application has been supplemented with additional clinical data.

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 ulcerative colitis and 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

In addition to a review of the literature on the clinical pharmacology of mesalazine, the applicant provided the results of the following clinical studies.

Study 1

An open label, randomized, single dose study, 4-way cross-over study comparing 2 x 400mg Asacol tablets and 1 x 800mg Asacol tablets. This study compared the Asacol 400mg tablets with 3 developmental formulations (each with a different proportion of disintegrant in the formulation) of the 800mg tablets to determine a tablet formulation that had similar pharmacokinetic characteristics to that of the currently marketed 400mg tablet. Based on the results of this study and dissolution studies, a suitable formulation was determined.

Study 2

An open label study in 16 healthy male and female volunteers to determine the multiple dose pharmacokinetics of 5-ASA and N-acetyl 5-ASA following 7 days of dosing with Asacol 800mg tablets, at a dosage of 2 x 800mg tablets every 8 hours (4.8g/day). A single batch of product was used in this study.

Summary of Pharmacokinetic Parameters

Parameter	800mg tablet	
	5-ASA/ N-Ac-5-ASA	
AUC_τ (ng·h/ml)	20282.03	24864.04
C_{max} (ng·h/ml)	4972.08	4614.78
t_{max} (h)	2.63	3.13
t_{1/2z} (h)	11.89	19.56
%A_e (%)	9.28	19.01

Study 3

An open label, randomized single dose, two period cross-over study in 18 male and female subjects (16 completed) to determine the pharmacokinetics of 5-ASA and N-acetyl-5-ASA from Asacol 800mg tablets after fasting and after a high fat meal. A single batch of product has been used in this study.

Subjects received one 800mg Asacol tablet orally after an overnight fast of at least 10 hours (fasted state) or after an overnight fast of 10 hours followed by a high fat meal (fed state). Blood samples were collected pre-dosing and up to 72 hours after dosing. Total urinary output was collected over various intervals up to 48-72 hours after dosing.

Summary of Pharmacokinetic Parameters

Parameter	800mg tablet - Fed		800mg tablet - Fasted	
	5-ASA/ N-Ac-5-ASA	5-ASA/ N-Ac-5-ASA	5-ASA/ N-Ac-5-ASA	5-ASA/ N-Ac-5-ASA
AUC_{tlast} (ng·h/ml)	3651.7	19350.1	3913.6	21850.1
C_{max} (ng·h/ml)	175.7	837.43	294.0	1028.68
t_{max} (h)	23.78	25.62	9.61	11.13
t_{lag} (h)	15.32	15.15	6.20	5.39
t_{1/2z} (h)	15.15	15.35	13.41	13.62
%A_e (%)	0.20	11.29	0.21	12.04

The results from this study are consistent with that found in the literature.

For all three studies, 5-ASA and N-acetyl 5-ASA in human plasma and urine, with isotopically labelled internal standards are derivitised with propionic anhydride, and analysed using a validated HPLC method with MS detection. The LOQ in plasma was 10ng/ml for 5-ASA and 20ng/ml for the metabolite. In urine the LOQ were 0.05µg/ml and 0.15µg/ml respectively.

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

The efficacy of mesalazine at 2.4g/day has been well established and the applicant has provided a sufficient literature review to support the dose for use in mild acute exacerbation of ulcerative colitis and for maintenance of remission of ulcerative colitis and Crohn's ileocolitis. The applicant has also provided the results of two clinical studies to support a higher dose of 4.8g/day for use in moderate acute exacerbations of ulcerative colitis.

Study 1

A double blind, randomized, 6 week, parallel group design clinical study in patients with mild to moderately active ulcerative colitis (later amended to moderately active ulcerative colitis) assessing the safety and efficacy of Asacol 4.8g/day (800mg tablet) versus Asacol 2.4g/day (400mg tablet) for the treatment of mild to moderately active ulcerative colitis. Four batches of finished product of the proposed formulation were used in this study. Batch numbers for the 400mg and 800mg placebo batches and 400mg Asacol tablets are also given.

A total of 386 patients were enrolled in the study, 268 with moderately active ulcerative colitis (139 of these patients were in the 2.4g/day group and 129 in the 4.8g/day group).

Study 2

A double blind, randomized, 6 week, parallel group design clinical trial in patients with mild to moderately active ulcerative colitis to assess the safety and efficacy of Asacol 4.8g/day (800mg tablet) versus Asacol 2.4g/day (400mg tablet) for the treatment of mild to moderately active ulcerative colitis. Three batches of finished product of the proposed formulation were used in this study. Batch numbers for the 400mg and 800mg placebo batches and 400mg Asacol tablets are also given.

A total of 301 patients were enrolled in the study (154 in the 2.4g/day group and 147 in the 4.8g/day group).

The positive control product used for pharmacokinetic, safety and efficacy studies is the US Asacol 400mg tablets and not the EU product.

Satisfactory certificates of analyses are included for all Asacol 800mg and 400mg tablets and placebo tablets used in these studies.

The design of both studies was the same. The chi-square test was used to determine the treatment effect. Adverse events and clinical laboratory evaluations were the safety parameters measured. The endpoints are listed below.

End points:

Primary Efficacy:

- Treatment outcome (success or failure) of patients with moderate disease at Week 6

Secondary Efficacy:

- Improvement in clinical assessment at Week 3 and Week 6
- Patient's assessment of efficacy

Whereas in patients with mild to moderately active ulcerative colitis no statistically significant differences were seen between the two treatment groups (2.4mg/day (Asacol 400mg MR tablets) or 4.8mg/day (Asacol 800mg MR tablets)), a statistically significant superiority of the higher dose was shown in patients with moderately active ulcerative colitis in primary efficacy endpoints, but not in all secondary efficacy endpoints. Both treatment groups showed an improvement from baseline scores.

There is a succinct and adequate overview of efficacy.

SAFETY

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. This has been supplemented by the results obtained from the clinical efficacy studies (see above). No new adverse events were observed for the higher dose used to treat moderate acute exacerbations of ulcerative colitis.

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 applicant provided sufficient data to support the use of a higher dose for the treatment of moderate acute exacerbations of ulcerative colitis.

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 00364/0083**

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the Marketing Authorisation application on 17 December 2004.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 18 January 2005.
3	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.
4	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.
5	The application was determined on 14 September 2007.

**ASACOL 800MG MR TABLETS
PL 00364/0083**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Asacol 800mg MR tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 800 mg of mesalazine (active substance) and 152.75 mg of lactose monohydrate (excipient).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified Release Tablets

Red-brown, oblong tablets marked 'PG 800'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 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 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.

4.3 Contraindications

A history of sensitivity to salicylates or renal sensitivity to sulfasalazine. Confirmed severe renal impairment (GFR less than 20 ml/min). Hypersensitivity to any of the ingredients. Severe hepatic impairment. Gastric or duodenal ulcer, haemorrhagic tendency.

4.4 Special warnings and precautions for use

Geriatric Use

Use in the elderly should be cautious and subject to patients having normal renal function

Intolerance

Discontinue treatment immediately if acute symptoms of intolerance occur including vomiting, abdominal pain or rash. This medicine contains lactose. Patients with the rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine because of the presence of lactose monohydrate.

Mesalazine inhibits the thiopurine methyl-transferase (TPMT) activity *in vitro* and may therefore impair the metabolism of azathioprine and 6-mercaptopurine. Standard haematological indices (including the white cell count) should be monitored repeatedly in patients taking azathioprine, especially at the beginning of such combination therapy, whether or not mesalazine is prescribed.

Renal disorder

Mesalazine is excreted rapidly by the kidney, mainly as its metabolite, N-acetyl-5-aminosalicylic acid. In rats, large doses of mesalazine injected intravenously produce tubular and glomerular toxicity. Asacol should be used with extreme caution in patients with confirmed mild to moderate renal impairment (see section 4.3). Patients on mesalazine should have renal function monitored, (with serum creatinine levels measured) prior to treatment start. Renal function should then be monitored periodically during treatment, for example every 3 months for the first year, then every 6 months for the next 4 years and annually thereafter, based on individual patient history. Physicians should take into account risk factors such as prior and concomitant medications, duration and severity of disease and concurrent illnesses. Treatment with mesalazine should be discontinued if renal function deteriorates. If dehydration develops, normal electrolyte and fluid balance should be restored as soon as possible.

Blood Dyscrasias

Serious blood dyscrasias (some with fatal outcome) have been reported very rarely with mesalazine. Haematological investigations including a complete blood count may be performed prior to initiation and whilst on therapy according to the physician's judgement. Such tests should be done immediately if the patient develops unexplained bleeding, bruising, purpura, anaemia, fever or sore throat. Treatment should be stopped if there is suspicion or evidence of blood dyscrasia.

4.5 Interaction with other medicinal products and other forms of interaction

'Asacol' tablets should not be given with lactulose or similar preparations, which lower stool pH and may prevent release of mesalazine.

Concurrent use of other known nephrotoxic agents, such as NSAIDs and azathioprine, may increase the risk of renal reactions (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

Mesalazine is known to cross the placental barrier, but the limited data available on its use in pregnant women do not allow accurate assessment of possible adverse effects.

Mesalazine should therefore be used with caution during pregnancy and lactation when the potential benefit outweighs the possible hazards in the opinion of the physician.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Lactation

Low concentrations of mesalazine and higher concentrations of its N-acetyl metabolite have been detected in human milk. While the clinical significance of this has not been determined, caution should be exercised when mesalazine is administered to a nursing woman. Hypersensitivity reactions like diarrhoea cannot be excluded. Therefore, if the suckling neonate develops suspected adverse reactions consideration should be given to discontinuation of breast-feeding or discontinuation of treatment of the mother.

4.7 Effects on ability to drive and use machines

No influence.

4.8 Undesirable effects

In Phase III clinical studies in patients with moderate active ulcerative colitis, treated for 6 weeks with either 2.4g/day or 4.8g/day, there was no difference in the adverse event profiles between doses. The events are presented in the table below:

Adverse Events Reported in $\geq 2\%$ of Patients in Either Treatment Group

Adverse Event*	Asacol 800 mg (4.8 g/day) N = 213 (%)	Mesalazine 400 mg (2.4 g/day) N = 235 (%)
Headache	16 (7.5%)	14 (6.0%)
Abdominal pain	9 (4.2%)	12 (5.1%)
Diarrhoea	8 (3.8%)	9 (3.8%)
Nausea	8 (3.8%)	4 (1.7%)
Respiratory infection	7 (3.3%)	4 (1.7%)
Exacerbation of colitis	6 (2.8%)	6 (2.6%)
Dyspepsia	6 (2.8%)	5 (2.1%)
Vomiting	6 (2.8%)	2 (0.9%)
Flatulence	5 (2.3%)	7 (3.0%)
Rectal disorder	4 (1.9%)	6 (2.6%)
Flu syndrome	3 (1.4%)	8 (3.4%)
Rash	3 (1.4%)	5 (2.1%)
Increased cough	1 (0.5%)	9 (3.8%)
Sinusitis	1 (0.5%)	5 (2.1%)
Rhinitis	0 (0.0%)	7 (3.0%)

*Adverse events are listed by decreasing frequency as observed in the 4.8 g/day treatment group

Adverse events seen with oral mesalazine products are predominantly gastrointestinal, including nausea, vomiting, diarrhoea, and abdominal pain. Headache and arthralgia/myalgia have also been reported.

Blood and lymphatic system disorders:

Rare (<1/1,000): leucopenia, neutropenia, agranulocytosis, aplastic anaemia and thrombocytopenia.

Cardiac disorders:

Rare (<1/1,000): myocarditis, pericarditis

Nervous disorders:

Common ($\geq 1/100$ to $< 1/10$): headache

Rare ($< 1/1,000$): peripheral neuropathy, vertigo

Respiratory, thoracic and mediastinal disorders:

Rare ($< 1/1,000$): bronchospasm, eosinophilic pneumonia

Very rare ($< 1/10,000$): interstitial pneumonitis

Gastrointestinal disorders:

Common ($\geq 1/100$ to $< 1/10$): nausea, vomiting, diarrhoea, abdominal pain

Rare ($< 1/1,000$): pancreatitis

Very rare ($< 1/10,000$): exacerbation of the symptoms of colitis

Hepato-biliary disorders:

Rare ($< 1/1,000$): abnormalities of hepatic function / abnormal liver function test, hepatitis

Skin and subcutaneous tissue disorders:

Rare ($< 1/1,000$): alopecia, lupus erythematosus-like reactions, rash (including urticaria), bullous skin reactions,

Very rare ($< 1/10,000$): Stevens Johnson syndrome, erythema multiforme

Musculo-skeletal:

Common ($\geq 1/100$ to $< 1/10$): arthralgia/myalgia

Renal and urinary disorders

Rare ($< 1/1,000$): interstitial nephritis and nephrotic syndrome with oral mesalazine treatment, usually reversible on withdrawal. Renal failure has been reported.

Mesalazine-induced nephrotoxicity should be suspected in patients developing renal dysfunction during treatment.

General disorders and administration site conditions

Rare ($< 1/1,000$): Drug fever

4.9 Overdose

There is no clinical experience with overdose of Asacol 800 mg. Mesalazine is not metabolized to salicylate. There is no specific antidote for mesalazine overdose and treatment is symptomatic and supportive. It may include intravenous infusion of appropriate electrolytes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: A07EC02

Mesalazine is thought to have a topical anti-inflammatory effect on the intestinal mucosa, where it has been shown to inhibit prostaglandin and leukotriene synthesis, release of reactive oxygen species and other actions.

Moderately active ulcerative colitis:

Two active-controlled trials enrolled a total of 687 patients comparing Asacol 4.8 g/day (800 mg formulation) with mesalazine enteric coated tablets 2.4 g/day (400 mg formulation) in patients with mildly to moderately active ulcerative colitis. Both studies were of six weeks duration. Treatment success was defined on the basis of the Physician's Global Assessment (PGA), which took into consideration clinical assessments of rectal bleeding, stool frequency, and the patient's functional assessment and sigmoidoscopic examination. Across the two studies 4.8 g/day provided superior efficacy in patients with moderately active disease.

In the first study a total of 301 patients with mildly to moderately active UC were enrolled. Of these, 169 patients with moderately active disease were assessed for efficacy in a pre-defined subgroup analysis. In these patients, 4.8 g/day gave greater treatment success than 2.4 g/day (72% treatment success compared with 57%).

In the second study a total of 386 patients with mildly to moderately active ulcerative colitis were randomly assigned to treatment. In the 254 patients with moderately active disease, the pre-defined primary efficacy analysis showed that 4.8 g/day gave greater treatment success than 2.4 g/day (72% treatment success compared to 59%).

In both studies, more patients showed improvement on 4.8 g/day compared to 2.4 g/day across the clinical assessments (stool frequency, rectal bleeding, sigmoidoscopy and PGA). In combined studies, 4.8 g/day showed statistically significant superiority in the sigmoidoscopy and PGA scores.

At Week 3, more patients with moderately active disease achieved treatment success on 4.8 g/day compared with 2.4 g/day in each study and in the combined analysis (62% vs. 53%). These differences were not statistically significant.

In combined studies among patients with moderately active disease, the efficacy benefit of 4.8 g/day over 2.4 g/day was consistent across various subgroups including age, gender, race, ulcerative colitis disease history, prior medication usage and extent of disease (proctitis, proctosigmoiditis, left-sided colitis and pancolitis).

5.2 Pharmacokinetic properties

Asacol 800mg MR tablets are coated with an acrylic-based resin. Tablets coated with this specific resin have been shown to delay release of mesalazine until it reaches the terminal ileum and beyond.

Based on cumulative urinary recovery of 5-aminosalicylic acid and its metabolite, N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA) from single dose studies in healthy volunteers, approximately 20% of the orally administered mesalazine in Asacol 800mg MR tablets is systemically absorbed, leaving the remainder available for local action and elimination in the faeces. The absorbed mesalazine is rapidly acetylated in the gut mucosal wall and by the liver to N-Ac-5-ASA which is excreted mainly by the kidney.

The extent of systemic exposure to mesalazine, based on AUC and Ae%, following oral administration of Asacol 800mg MR tablets, is similar in fasted and fed subjects.

Pharmacokinetics studies for Asacol 800mg MR tablets indicated that the t_{max} for mesalazine and its metabolite, N-Ac-5-ASA, is prolonged, reflecting the modified release characteristics, and ranged from 4 to 12 hours. Large intersubject variability in the plasma concentrations and terminal exponential half-lives (t_{1/2}) of mesalazine and N-Ac-5-ASA is seen following administration of Asacol 800mg MR tablets. The mean (t_{1/2}) for mesalazine and N-Ac-5-ASA are usually about 12 hours, but may vary from 2 to 15 hours.

In patients with mildly to moderately active ulcerative colitis who participated in clinical safety and efficacy studies, the mean plasma concentrations of mesalazine and N-Ac-5-ASA following oral administration of 4.8g/day with the Asacol 800mg MR tablet for 6 weeks (N = 273) were 1931 ng/mL and 2951 ng/mL, respectively. In these studies, the mean plasma concentrations of mesalazine and N-Ac-5-ASA were 967 ng/mL and 1789 ng/mL, respectively, in patients with mildly to moderately active ulcerative colitis who were orally administered 2.4g/day with a mesalazine 400mg modified release tablet for 6 weeks (N = 275). The systemic exposure to mesalazine and N-Ac-5-ASA in patients with moderately active UC is similar to that observed in patients with mildly active UC.

5.3 Preclinical safety data

Apart from effects on the kidney (see section 4.4), preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. The latter was studied in rats and rabbits at oral doses up to 480 mg/kg/day and no evidence was detected for teratogenic effects or foetal toxicity due to mesalazine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core	lactose monohydrate sodium starch glycolate talc povidone magnesium stearate colloidal anhydrous silica
Coating	methacrylic acid – methyl methacrylate copolymer (1:2) talc dibutyl phthalate ferric oxide red (E172) methacrylic acid – methyl methacrylate copolymer (1:1) ferric oxide yellow (E172) macrogol
Black ink containing	propylene glycol ferric oxide black (E172) ammonium hydroxide ethanol shellac glaze (bleached, de-waxed)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Keep the bottle tightly closed.

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure, cotton, and silica gel desiccant pouches. Pack-sizes of 12, 36 or 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Procter & Gamble Pharmaceuticals UK Ltd

Rusham Park

Whitehall Lane

Egham

Surrey

TW20 9NW

8 MARKETING AUTHORISATION NUMBER(S)

PL00364/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/09/2007

10 DATE OF REVISION OF THE TEXT

14/09/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Asacol® (mesalazine) 800mg MR tablets

1. What you should know about Asacol® 800mg MR tablets.

This leaflet contains important information about your Asacol® 800mg MR tablets. Please read this information carefully before you start taking this medication. If you have any questions or are unsure about anything, please ask your doctor or pharmacist. Keep this leaflet until you have finished this pack of Asacol® 800mg MR as you may want to read it again.

Remember that this product has been prescribed for you personally and you should not give this medication to anyone else as it may harm them.

2. What is Asacol® 800mg MR and what is it used for?

The active ingredient in Asacol is called mesalazine. Mesalazine is one of a group anti-inflammatory medicines called salicylates. They are used for the treatment of inflammatory bowel disease (IBD).

Asacol has been shown to reduce the symptoms of IBD in men and women with ulcerative colitis. These symptoms can include rectal bleeding, frequent diarrhoea and abdominal pain.

Asacol has also been shown to help prevent the return of symptoms (also called a flare) in people with ulcerative colitis and another type of IBD called Crohn's ileo-colitis.

Your tablets are available in packs of 12, 36 and 180. Not all pack sizes may be marketed.

3. What do Asacol® 800mg MR tablets contain?

The active ingredient of Asacol is called mesalazine. Each tablet contains 800mg of mesalazine.

Each tablet also contains lactose monohydrate, sodium starch glycolate, talc, povidone, magnesium stearate, colloidal anhydrous silica, methacrylic acid – methyl methacrylate copolymer (1:2), dibutyl phthalate, ferric oxide red (E172), methacrylic acid – methyl methacrylate copolymer (1:1), ferric oxide yellow (E172), macrogol, propylene glycol, ferric oxide black (E172), ammonium hydroxide, ethanol, shellac glaze (bleached, de-waxed).

4. Who makes Asacol® 800mg MR tablets?

The manufacturer is:
Procter & Gamble Pharmaceuticals
Germany GmbH
Dr.-Otto-Röhm-Str. 2-4
64331 Weiterstadt, Germany

The marketing authorisation is held by:
Procter & Gamble Pharmaceuticals UK Ltd
Rusham Park Technical Centre
Whitehall Lane, Egham
Surrey, TW20 9NW

5. Important information before taking

Asacol® 800mg MR tablets

Do not take Asacol

- If you are allergic to any of the ingredients listed in section 3 above.
- If you have previously found that you are allergic to aspirin or any other salicylate.
- If you have ever had serious kidney or liver problems.
- If you have stomach ulcers with or without bleeding.

This medicine should not be taken by children unless directed by a doctor.

Take special care with Asacol

Before taking this medicinal product it is important to tell your doctor if any of the conditions listed below apply to you. If they do, you may need check-ups more often or your doctor may decide not to prescribe Asacol for you:

- If you have ever had any kidney problems, especially if you are elderly.
- If you have ever had any blood disorders, especially while taking medicines such as sulphasalazine.
- If you are pregnant, think you may be, or intend to become pregnant.
- If you are breast-feeding.
- If you have been told by your doctor that you have an intolerance to some sugars.
- If you are taking any of the following types of medications:
 - Lactulose, or similar medicines which change the pH of the stool (poo)
 - Azathioprine, affecting the immune system (your doctor may need to do blood tests)
 - Medicines called NSAIDs (non-steroidal anti-inflammatory medicines) which includes ibuprofen, aspirin and Cox-II inhibitors.

When you start taking the tablet, your doctor may test your blood from time to time.

6. Taking Asacol® 800mg MR tablets

You should take Asacol tablets exactly as instructed by your doctor.

For the treatment of ulcerative colitis

The usual dosage is up to six tablets every day. Your doctor will tell you when to take the tablets.

To prevent a flare of ulcerative colitis or Crohn's ileocolitis

The usual dosage is up to three tablets every day. Your doctor will tell you when to take the tablets.

In addition:

- You can take your tablets at any time of the day with or without meals.
- Swallow the tablets whole. **Do not break, chew or crush them.**
- Take your tablets for as long as your doctor tells you to.

The aim of Asacol treatment is to bring the symptoms of your IBD under control and then keep your IBD in remission. It is important that you take the right number of tablets every day exactly as instructed by your doctor. Remember to make an appointment for a repeat prescription at the right time so that you don't miss a day of treatment.

If you have any questions about your medicine you should speak to your doctor or pharmacist.

If you take more Asacol® 800mg MR tablets than you should

You should only take as many tablets as your doctor or pharmacist has told you. If you take too many tell your doctor or hospital casualty department straight away. Take your tablet pack with you.

If you have forgotten to take your tablets

If you forget to take a dose, take it as soon as possible after you remember and then take your next dose as normal. Do not take two doses together; if it is almost time to take the next dose, wait until then and carry on as before. If you have any doubts, or are concerned that you may experience a relapse of your IBD symptoms, speak to your doctor or pharmacist for advice.

7. Possible Side Effects

Like all medicines, mesalazine can cause side effects.

The most common side effects seen with mesalazine are gastrointestinal symptoms, including nausea, vomiting, diarrhoea, flatulence and abdominal pain. Headache, aches and pains in the muscles or joints have also been reported.

Other side effects have been reported rarely and usually improve after stopping Asacol. These are hair loss, chest pain, rashes (itchy, red or raised rashes), chest infections, flu-like symptoms, sinusitis / rhinitis, cough inflammation of the pancreas leading to stomach pain, changes in liver or kidney function, inflammation of the liver or kidney, unexplained wheezing or shortness of breath, a worsening of the symptoms of colitis, and a very rare and severe type of allergic reaction called Stevens Johnson Syndrome, which causes a red blistering rash which may spread all over the body.

You should tell your doctor if you have a lot of infections, develop fever, sore throat or mouth ulcers, or if you bruise more easily, become very pale, have any unusual bleeding (e.g. nose bleeds, bleeding gums) or develop spots under the skin.

You must speak to your doctor or pharmacist if you experience these or any other effects which are not listed in this leaflet. You should speak to your doctor or pharmacist before stopping treatment.

8. Storing Asacol® 800mg MR tablets

- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage condition.
- Do not remove the moisture absorbing pouches from the bottle. Keep the bottle tightly closed. The sachets are not part of your medicine and are marked DO NOT EAT.
- Do not use after the expiry date stated on the bottle.

9. Further information

If you have any questions about your medication speak to your doctor or pharmacist.

For more information on Inflammatory Bowel Disease contact:

The National Association for Colitis and Crohn's Disease (NACC)
4 Beaumont House
Sutton Road
St Albans
Herts
AL1 5HH

Telephone Information Line: 0845 130 2233
(Weekdays: 10am – 1pm)

NACC-in-Contact Support Line: 0845 130 3344
(Monday to Thursday: 6.30pm -9pm)

Website: www.nacc.org.uk

Marketing authorisation number

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Leaflet prepared in September 2006

A159220

95473417

800mg

Asacol[®] 800mg
MR tablets
(MESALAZINE)

Each modified release tablet
contains 800 mg mesalazine

180 Tablets

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 (1:2), 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, ethanol, shellac glaze (bleached, de-waxed)

POM

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