For medical and financial media only

ASACOL® (MESALAZINE) 800mg MR TABLETS APPROVED FOR THE TREATMENT OF ACUTE ULCERATIVE COLITIS (UC), MAINTENANCE OF REMISSION OF UC AND CROHN'S ILEO-COLITIS

New Higher Dose Provides Faster Symptom Relief for Moderately Active UC Patients

Geneva Switzerland, 11 October 2007, Procter & Gamble Pharmaceuticals (NYSE: P&G) announced today that Asacol® (mesalazine) 800mg Modified Release (MR) tablets have been approved for the treatment of mild to moderate ulcerative colitis (UC) and maintenance of remission of UC and Crohn's ileo-colitis in the United Kingdom by the Medicines and Healthcare products Regulatory Agency (MHRA).

Asacol 800mg MR tablets have been approved for moderately active UC patients at the new high 4.8 grams per day dose based on the ASCEND (**A**ssessing the **S**afety and **C**linical **E**fficacy of a **N**ew **D**ose of 5-ASA) I and II clinical trials that demonstrated Asacol 800mg MR tablets given at 4.8g per day resulted in faster symptom relief compared to 2.4g per day in moderately active UC patients.[1] Median time to symptom resolution was 9 days for rectal bleeding and 12 days for resolution of abnormal stool frequency for moderately active UC patients receiving Asacol 800mg MR tablets given at 4.8g per day compared to 16 days and 15 days respectively, with those who received mesalazine 400mg tablets dosed at 2.4g per day.[1] Importantly, there were no significant differences in the overall serious side effect profile with Asacol 800mg MR tablets dosed at 4.8g per day compared to mesalazine 400mg dosed at 2.4g per day.[2]

"This is a clinically useful advance for patients with ulcerative colitis," said Simon Travis, DPhil, FRCP, Consultant Physician and Gastroenterologist at the John Radcliffe Hospital in Oxford. "Symptoms of rectal bleeding and diarrhoea resolve faster on higher dose Asacol, without increasing side effects for acute, moderately active UC patients."

"Procter & Gamble is delighted to bring this new option to ulcerative colitis patients," said Hans van Zoonen, Vice President Pharmaceuticals and Personal Healthcare, Europe. "We firmly believe that Asacol 800mg MR tablets will bring faster symptom relief to moderately active UC patients. The development of the 800mg tablet is part of our commitment to provide patients with more dosing choice and convenient options. Asacol is a key pillar to our growing GI franchise, one of three strategic focus areas within P&G Pharmaceuticals," he added.

Asacol 800mg MR tablets are indicated for the treatment of mild and moderate acute exacerbations of ulcerative colitis, to be administered at 2.4g/day and 4.8g/day, respectively, in divided doses. Asacol 800mg MR tablets, administered up to 2.4g/day, are also indicated for the maintenance of remission of ulcerative colitis and Crohn's ileo-colitis.

Procter & Gamble will advise healthcare professionals as soon as the new product is available for prescription to patients.

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References

1. Marion JF *et al.*, *Gut* 2006; **55**(Suppl II): Abstract 140
2. Hanauer SB *et al., Can J Gastroenterol* 2005; **19**(Supp C): Abstract R.0471

Notes to Editor

About Procter & Gamble Pharmaceuticals
Procter & Gamble has a rich heritage in health care that extends back more than 150 years. Then and now, P&G is driven by our mission to improve the lives of people around the world every day. P&G's health care products include prescription medicines, over-the-counter medications and oral care products. P&G began developing and marketing prescription products in the late 1960s.

Three billion times a day, P&G brands touch the lives of people around the world. The company has one of the strongest portfolios of trusted, quality, leadership brands, including Actonel®, Asacol®, Crest®, Fibresure®, Intrinsa®, Metamucil®, Oral-B®, Pepto-bismol®, Thermacare®, Vicks®, Pampers®, Ariel®, Always®, Pantene®, Herbal Essences®, Mach3®, Fairy®, Ace®, Lenor®, M. Propre®, Tampax®, Tempo®, Dash®, Pringles®, Iams®, Eukanuba®, Duracell®, Olay®, Head & Shoulders®, Wella, Gillette®, and Braun. The P&G community consists of 138,000 employees working in over 80 countries worldwide. Please visit http://www.pg.com for the latest news and in-depth information about P&G and its brands. For more information about P&G Pharmaceuticals, please visit www.pgpharma.com

About Asacol and Asacol 800mg MR Clinical Trials
Data analysis is from the combined results of two double-blind, randomised, multi-site, 6-week, controlled clinical trials designed to assess the safety and efficacy of 4.8 g/day modified-release mesalazine with an 800mg tablet compared to 2.4 g/day modified-release mesalazine with a 400mg tablet for the treatment of moderately active ulcerative colitis.

The two ASCEND (**A**ssessing the **S**afety and **C**linical **E**fficacy of a **N**ew **D**ose of 5-ASA) studies demonstrated that for patients with moderately active ulcerative colitis, beginning treatment with twice the standard dose of mesalazine, 4.8 grams per day with a new 800mg tablet rather than 2.4 grams per day using a 400mg mesalazine tablet for six weeks, resulted in faster symptom relief for moderately active UC patients with no increase in side effects. Treatment success was defined as improvement from baseline at week six with either complete response (remission) or partial response (improvement) to treatment.

Asacol 800mg MR tablets, at 4.8 g/day, demonstrated an overall incidence of adverse events comparable to mesalazine 400mg tablets dosed at 2.4 g/day. Reported adverse events were

generally mild and transient, and seldom resulted in discontinuation of treatment. Most commonly reported adverse events for Asacol 800mg MR tablets were nausea (6.1%), headache (5.4%), vomiting (4.1%) and flatulence (4.1%), while those for mesalazine 400mg tablets were headache (5.8%), abdominal pain (4.5%) and ulcerative colitis (3.9%). Patients should be made aware that ulcerative colitis rarely remits completely. Abrupt discontinuation of mesalazine therapy is not recommended and may result in relapse. Asacol 800mg MR tablets are contraindicated in patients with a history of sensitivity to salicylates or renal sensitivity to sulphasalazine, confirmed severe renal impairment (GFR less than 20 ml/min), hypersensitivity to any of the ingredients, severe hepatic impairment, gastric or duodenal ulcer and haemorrhagic tendency. Asacol 800mg MR tablets should be used with extreme caution in patients with confirmed mild to moderate renal impairment. It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol 800mg MR tablets and periodically while on Asacol 800mg MR tablet therapy. Please refer to the Asacol 800mg MR tablet Summary of Product Characteristics for a complete list of adverse events.

Asacol 800mg MR tablets are indicated for the treatment of mild acute exacerbations of ulcerative colitis, and for the treatment of moderate acute ulcerative colitis to be administered at 2.4g/day and 4.8g/day, respectively, in divided doses. Asacol 800mg MR tablets, administered at 2.4g/day, are also indicated for the maintenance of remission of ulcerative colitis and Crohn's ileo-colitis in divided doses.

Interchangeability between Asacol 800mg MR tablets and Asacol 400mg MR tablets has not been established.

For further information
Please contact Clare Pressney on 02073578187

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 ReleaseTablets

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 ≥ 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 (≥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 (≥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 (≥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 tmax 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 (t1/2) of mesalazine and N-Ac-5-ASA is seen following administration of Asacol 800mg MR tablets. The mean (t1/2) 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

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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