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

Excipient with known effect: 152.75 mg lactose monohydrate see section 4.4

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified ReleaseTablets
Red-brown, oblong tablets marked ‘WC 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: 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.

4.3 Contraindications

A history of sensitivity to salicylates or any of the ingredients; renal sensitivity to sulfasalazine. Confirmed severe renal impairment (GFR less than 20 ml/min). 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

Mesalazine inhibits the thiopurine methyl-transferase (TPMT) activity *in vitro* and may therefore impair the metabolism of azathioprine, thioguanine 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.

Mesalazine has been implicated in the production of an acute intolerance syndrome characterized by cramping, acute abdominal pain and bloody diarrhoea, sometimes fever, headache and a rash; in such cases prompt withdrawal is required. The patient's history of sulfasalazine intolerance, if any, should be re-evaluated. If a rechallenge is performed later in order to validate the hypersensitivity, it should be carried out under close supervision and only if clearly needed, giving consideration to reduced dosage. The possibility of increased absorption of mesalazine and concomitant renal tubular damage as noted in the preclinical studies must be kept in mind. Patients on mesalazine 1000 mg, especially those on concurrent oral

products which contain or release mesalazine and those with pre-existing renal disease, should be carefully monitored with urinalysis, BUN and creatinine testing.

Renal disorders
Mesalazine may produce red-brown urine discoloration after contact with sodium hypochlorite bleach (e.g., in toilets cleaned with sodium hypochlorite contained in certain bleaches).

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

Nephrolithiasis
Cases of nephrolithiasis have been reported with the use of mesalazine, including stones of 100% mesalazine content. It is recommended to ensure adequate fluid intake during treatment.

Hepatic Failure
There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalazine. Evaluate the risk and benefits of using mesalazine in patients with known liver impairment.

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.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome

(SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment.
Mesalazine should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

Sensitivity/Hypersensitivity
Caution should be exercised when mesalazine (5-ASA) is initially used in patients known to be allergic to sulfasalazine. These patients should be instructed to discontinue therapy if signs of rash or fever become apparent. In case of an allergic reaction, appropriate measures (standard of care) should be taken.

Cardiac hypersensitivity reactions
Mesalazine-induced cardiac hypersensitivity reactions (myo- and pericarditis) have rarely been reported with mesalazine containing products. In case of previous mesalazine-induced cardiac hypersensitivity Asacol must not be reintroduced. Caution should be taken in patients with previous myo- or pericarditis of allergic background regardless of its origin.

Pulmonary disease
Patients with pulmonary disease, in particular asthma, should be very carefully monitored during treatment.

Idiopathic intracranial hypertension
Idiopathic intracranial hypertension (pseudotumor cerebri) has been reported in patients receiving mesalazine. Patients should be warned for signs and symptoms of idiopathic intracranial hypertension, including severe or recurrent headache, visual disturbances or tinnitus. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

Excipients with known effect warnings

Lactose
With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, i.e. is essentially "sodium-free".

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).
Monitor patients taking nephrotoxic drugs for changes in renal function and mesalazine-related adverse reactions.

The hypoglycaemic effect of sulfonylureas may be enhanced when administered with aminosalicylates (oral antidiabetics may be displaced from the binding sites of plasma proteins). 5- ASA was reported to inhibit coumarin anticoagulants, resulting in thrombosis.

Concomitant treatment with mesalazine may increase the risk of myelosuppression in patients receiving azathioprine, thioguanine or 6-mercaptopurine. The concurrent use of mesalazine with azathioprine, thioguanine or 6-mercaptopurine may increase the risk for blood dyscrasia. If concomitant use of mesalazine and azathioprine, thioguanine or 6-mercaptopurine cannot be avoided, monitor blood tests, including complete blood cell counts and platelet counts.

Several reports of possible interference with measurements, by liquid chromatography, of urinary normetanephrine have been observed in patients exposed to sulfasalazine or its metabolite, mesalazine.

4.6 Fertility, 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. If the infant develops diarrhoea breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

There are no data available on the effects of mesalazine on ability to drive and use machines.

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.

Undesirable effects reported from clinical studies and post marketing surveillance are listed below. Common, (≥1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (< 1/10,000), frequency not known (cannot be estimated from the available data).

System organ class	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**	**Frequency not known**

Blood and lymphatic system disorders			leucopenia, neutropenia, agranulocytosis, aplastic anaemia and thrombocytopenia *		
Immune system disorders					hypersensitivity reactions*
Nervous system disorders	headache		peripheral neuropathy, vertigo		Idiopathic intracranial hypertension *
Cardiac disorders			myocarditis, pericarditis*		
Respiratory thoracic and mediastinal disorders			bronchospasm, eosinophilic pneumonia	interstitial pneumonitis	Pleurisy, allergic and fibrotic lung reactions
Gastrointestinal disorders	nausea, vomiting, diarrhoea, abdominal pain		pancreatitis	exacerbation of the symptoms of colitis	Constipation
Hepato-biliary disorders			abnormalities of hepatic function (including hepatic failure) / abnormal liver function test, hepatitis		
Skin and subcutaneous tissue disorders			alopecia, lupus erythematosus-like reactions, rash (including urticaria), bullous skin reactions	erythema multiforme	Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)*
Musculoskeletal connective tissue and bone disorders	arthralgia/ myalgia				

Renal and urinary disorders			interstitial nephritis and nephrotic syndrome. Renal failure.*		nephrolithiasis*
Reproductive system and breast disorders				oligospermia (reversible)	
General disorders and administration site conditions:			Drug fever		mesalazine-induced acute intolerance syndrome*

*** See Section 4.4 for further information**

Severe cutaneous adverse reactions (SCARs), including Drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in association with mesalazine treatment (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

There have been no documented reports of serious toxicity in human resulting from massive overdosing with mesalazine. Under ordinary circumstances, mesalazine absorption from the colon is limited. 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 sebacate
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 oblong bottle with a child-resistant closure, cotton, and silica gel desiccant pouches. Pack-sizes of 12, 36 or 180 tablets.

HDPE round bottle with a child-resistant closure, cotton, and silica gel desiccant pouches. Pack-size of 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AbbVie Ltd.
Maidenhead
SL6 4UB
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 41042/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/02/2025

10 DATE OF REVISION OF THE TEXT

05/02/2025