Mepenzolate Bromide *(BAN, rINN)*

Bromuro de mepenzolato; Mepentsolaattibromidi; Mepenzolatbromid; Mépenzolate, Bromure de; Mepenzolate Methylbromide; Mepenzolati Bromidum; Mepenzolone Bromide. 3-Benziloyloxy-1,1-dimethylpiperidinium bromide.

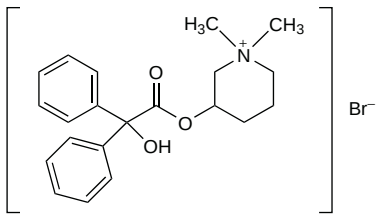
Мепензолата Бромид

$C_{21}H_{26}BrNO_3$ = 420.3.

CAS — 25990-43-6 (mepenzolate); 76-90-4 (mepenzolate bromide).

ATC — A03AB12.

ATC Vet — QA03AB12.



Pharmacopoeias. In *Jpn.*

Profile

Mepenzolate bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been used in the relief of gastrointestinal disorders associated with smooth muscle spasm and as an adjunct in the treatment of peptic ulcer disease. Up to 200 mg daily may be given orally in divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Trancolon†; ***Swed.:*** Cantil†; ***USA:*** Cantil.

Multi-ingredient: ***Jpn:*** Trancolon P†.

Mesalazine *(BAN, rINN)*

5-Aminosalicylic Acid; 5-ASA; Fisalamine; Mesalamine *(USAN)*; Mesalatsiini; Mesalazin; Mesalazina; Mesalazinas; Mésalazine; Mesalazinum. 5-Amino-2-salicylic acid.

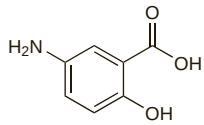
Месалазин

$C_7H_7NO_3$ = 153.1.

CAS — 89-57-6.

ATC — A07EC02.

ATC Vet — QA07EC02.



NOTE. Distinguish from 4-aminosalicylic acid (Aminosalicylic Acid, p.201) which is used in the treatment of tuberculosis.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.

Ph. Eur. 6.2 (Mesalazine). An almost white or light grey or light pink powder or crystals. Very slightly soluble in water; practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides and in dilute hydrochloric acid. Store in airtight containers. Protect from light.

USP 31 (Mesalamine). Light tan to pink needle-shaped crystals, odourless or with a slight characteristic odour. The colour may darken on exposure to air. Slightly soluble in water; very slightly soluble in dehydrated alcohol, in acetone, and in methyl alcohol; practically insoluble in butyl alcohol, in chloroform, in dichloromethane, in ether, in ethyl acetate, in *n*-hexane, and in propyl alcohol; soluble in dilute hydrochloric acid and in dilute alkali hydroxides. A 2.5% suspension in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

Adverse Effects and Precautions

Mesalazine may cause headache and gastrointestinal disturbances, such as nausea, diarrhoea, and abdominal pain. Hypersensitivity reactions may occasionally occur. Some patients may experience exacerbation of symptoms of colitis. There are some reports of myocarditis, pericarditis, pancreatitis, interstitial nephritis, nephrotic syndrome, allergic lung reaction, increased liver enzyme values, hepatitis, lupus-like syndrome, skin reactions, alopecia, peripheral neuropathy, myalgia, and arthralgia. There have been rare reports of blood disorders including aplastic anaemia, agranulocytosis, leucopenia, neutropenia, thrombocytopenia, and methaemoglobinaemia.

Mesalazine should not be given to patients with severe renal or hepatic impairment, or salicylate hypersensitivity. It should be used with caution in the elderly, and in mild to moderate renal or hepatic impairment, active peptic ulceration, or sulfasalazine allergy.

If a blood dyscrasia is suspected treatment should be stopped immediately and a blood count performed. Patients or their carers should be told how to recognise signs of blood toxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop. It is recommended that renal function is monitored before and during therapy (see Effects on the Kidneys, below).

◊ Many of the adverse effects associated with sulfasalazine (sulfapyridine linked to mesalazine) therapy have been attributed to the sulfapyridine moiety and most patients unable to tolerate sulfasalazine because of hypersensitivity or adverse reactions can be transferred to mesalazine without adverse effects occurring.[1-4] However, a small number of patients also have adverse effects while taking mesalazine and these are often very similar to those seen with sulfasalazine.[1-4] They may include nausea, abdominal discomfort or pain, exacerbation of diarrhoea, headache, fever, and rashes. Mesalazine is not generally associated with sulfasalazine's adverse effects on sperm (although there has been a case of reversible male infertility attributed to mesalazine—see under Sulfasalazine, p.1774). An analysis of adverse reactions reported to the UK CSM between 1991 and 1998 found no evidence of a significant difference in the frequency of serious adverse effects for mesalazine and sulfasalazine in the treatment of inflammatory bowel disease.[5] Reports of pancreatitis and interstitial nephritis (see Effects on the Kidneys, below), were more common with mesalazine. However, it has been pointed out that 80% of patients intolerant to sulfasalazine will tolerate mesalazine without problems.[6]

Mesalazine therapy should be started cautiously in patients with a history of sulfasalazine **hypersensitivity** and it should be withdrawn if signs of sensitivity develop or if there is diarrhoea or rectal bleeding. It has been suggested[2] that patients with a history of sulfasalazine hypersensitivity should be given test doses of mesalazine before starting a full course.

1. Dew MJ, *et al.* Treatment of ulcerative colitis with oral 5-aminosalicylic acid in patients unable to take sulphasalazine. *Lancet* 1983; **ii:** 801.
2. Campieri M, *et al.* 5-Aminosalicylic acid as rectal enema in ulcerative colitis patients unable to take sulphasalazine. *Lancet* 1984; **i:** 403.
3. Donald IP, Wilkinson SP. The value of 5-aminosalicylic acid in inflammatory bowel disease for patients intolerant or allergic to sulphasalazine. *Postgrad Med J* 1985; **61:** 1047–8.
4. Rao SS, *et al.* Clinical experience of the tolerance of mesalazine and olsalazine in patients intolerant of sulphasalazine. *Scand J Gastroenterol* 1987; **22:** 332–6.
5. Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002; **51:** 536–9.
6. D'Haens G, van Bodegraven AA. Mesalazine is safe for the treatment of IBD. *Gut* 2004; **53:** 155.

Breast feeding. The concentrations of mesalazine in maternal plasma and breast milk in a woman taking 500 mg three times daily, were 410 and 110 nanograms/mL respectively.[1] Although it was considered that the amount of mesalazine distributed into breast milk was small and that it was safe during breast feeding,[2,3] maternal use of mesalazine 500 mg suppositories twice daily has been associated with watery diarrhoea in a breast-fed infant[2] and for this reason the American Academy of Pediatrics considers that mesalazine should be given with caution to breast-feeding mothers.[4]

1. Jenss H, *et al.* 5-Aminosalicylic acid and its metabolite in breast milk during lactation. *Am J Gastroenterol* 1990; **85:** 331.
2. Nelis GF. Diarrhoea due to 5-aminosalicylic acid in breast milk. *Lancet* 1989; **i:** 383.
3. Klotz U, Harings-Kaim A. Negligible excretion of 5-aminosalicylic acid in breast milk. *Lancet* 1993; **342:** 618–19.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/02/06)

Effects on the blood. Although uncommon, mesalazine-associated adverse effects on the blood have been reported, including thrombocytopenia,[1,2] neutropenia,[3] severe aplastic anaemia,[4,5] and pancytopenia.[6] In July 1995 the UK CSM stated that it had been notified of 49 haematological reactions suspected of being associated with mesalazine,[7] including 5 reports of aplastic anaemia, 1 of agranulocytosis, 11 of leucopenia, and 17 of thrombocytopenia. There had been 3 fatalities. They recommended a blood count and immediate withdrawal of the drug if a dyscrasia was suspected. Intensive immunosuppressive treatment has been used in the management of mesalazine-associated aplastic anaemia.[5,8]

1. Daneshmend TK. Mesalazine-associated thrombocytopenia. *Lancet* 1991; **337:** 1297–8.
2. Farrell RJ, *et al.* Mesalamine-associated thrombocytopenia. *Am J Gastroenterol* 1999; **94:** 2304–6.
3. Wyatt S, *et al.* Filgrastim for mesalazine-associated neutropenia. *Lancet* 1993; **341:** 1476.
4. Abboudi ZH, *et al.* Fatal aplastic anaemia after mesalazine. *Lancet* 1994; **343:** 542.
5. Otsubo H, *et al.* Mesalazine-associated severe aplastic anemia successfully treated with antithymocyte globulin, cyclosporine and granulocyte colony-stimulating factor. *Int J Hematol* 1998; **68:** 445–8.
6. Kotanagi H, *et al.* Pancytopenia associated with 5-aminosalicylic acid use in a patient with Crohn's disease. *J Gastroenterol* 1998; **33:** 571–4.
7. Committee on Safety of Medicines/Medicines Control Agency. Blood dyscrasias and mesalazine. *Current Problems* 1995; **21:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 15/06/06)
8. Laidlaw ST, Reilly JT. Antilymphocyte globulin for mesalazine-associated aplastic anaemia. *Lancet* 1994; **343:** 981–2.

Effects on the cardiovascular system. Myocarditis associated with chest pain and ECG abnormalities has been reported[1,2] in 2 patients taking mesalazine; 1 patient died in cardiogenic shock.[2] It has been suggested that mesalazine or sulfasalazine should be replaced by glucocorticoids if cardiac symptoms arise during treatment.[2] Pericarditis[3,4] with fever, rash, dyspnoea, pleural and pericardial effusions, and arthritis, has been described, and is considered to constitute a drug-induced lupus-like syndrome. Constrictive pericarditis with an absence of other lupus-like symptoms developed in a patient taking mesalazine for inflammatory bowel disease.[5] Based on reported cases of mesalazine-induced pericarditis, symptoms of this potentially life-threatening adverse effect have tended to arise 2 to 4 weeks after starting mesalazine, although symptom onset may be delayed by concurrent corticosteroid treatment.[6] Mesalazine cardiotoxicity presenting as an acute coronary syndrome, without myocarditis or pericarditis, has also been reported.[7]

1. Agnholt J, *et al.* Cardiac hypersensitivity to 5-aminosalicylic acid. *Lancet* 1989; **i:** 1135.
2. Kristensen KS, *et al.* Fatal myocarditis associated with mesalazine. *Lancet* 1990; **335:** 605.
3. Dent MT, *et al.* Mesalazine induced lupus-like syndrome. *BMJ* 1992; **305:** 159.
4. Lim AG, Hine KR. Fever, vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *BMJ* 1994; **308:** 113.
5. Oxentenko AS, *et al.* Constrictive pericarditis in chronic ulcerative colitis. *J Clin Gastroenterol* 2002; **34:** 247–51.
6. Waite RA, Malinowski JM. Possible mesalamine-induced pericarditis: case report and literature review. *Pharmacotherapy* 2002; **22:** 391–4.
7. Amin HE, *et al.* Mesalamine-induced chest pain: a case report. *Can J Cardiol* 2000; **16:** 667–9.

Effects on fertility. For a report of reversible male infertility occurring with mesalazine, see under Sulfasalazine, p.1774.

Effects on the hair. For a report of accelerated loss of scalp hair in 2 patients receiving mesalazine enemas, see under Sulfasalazine, p.1774.

Effects on the kidneys. Between February 1988 and December 1990 the UK CSM[1] received 9 reports of serious nephrotoxic reactions associated with the use of *Asacol*, a modified-release mesalazine preparation. The reactions included 4 cases of interstitial nephritis, 3 of severe renal failure, and 2 cases of nephrotic syndrome. A subsequent case report[2] indicated that by September 1998 the number of such reports for mesalazine totalled 104, including 35 cases of interstitial nephritis. The authors considered that monitoring of renal function was required in patients receiving mesalazine. A protocol for such monitoring was subsequently suggested,[3] and a similar protocol has been adopted in UK licensing information for mesalazine, with serum creatinine being estimated:

- before treatment
- every 3 months for the first year
- every 6 months for the next 4 years
- annually thereafter

The nephrotic syndrome[4] and interstitial nephritis[5] have also been reported with sulfasalazine, and interstitial nephritis with olsalazine (see p.1752). A large UK epidemiologic study found no difference in risk of renal disease between mesalazine and sulfasalazine. The study also concluded that the risk of renal disease associated with mesalazine and related compounds is low and may be partly attributable to the underlying disease.[6] Overall nephrotoxicity has been estimated to occur in about 1 in 4000 UK patients per year taking aminosalicylate-based therapy.[7]

1. Committee on Safety of Medicines. Nephrotoxicity associated with mesalazine (Asacol). *Current Problems 30* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024448&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
2. Popoola J, *et al.* Late onset interstitial nephritis associated with mesalazine treatment. *BMJ* 1998; **317:** 795–7.
3. Corrigan G, Stevens PE. Review article: interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2000; **14:** 1–6.
4. Barbour VM, Williams PF. Nephrotic syndrome associated with sulphasalazine. *BMJ* 1990; **301:** 818.
5. Dwarakanath AD, *et al.* Sulphasalazine induced renal failure. *Gut* 1992; **33:** 1006–1007.

6. Van Staa TP, *et al.* 5-Aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology* 2004; **126:** 1733–9.
7. Muller AF, *et al.* Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005; **21:** 1217–24.

Effects on the liver. A case of chronic hepatitis and liver fibrosis has been reported after prolonged use of mesalazine.[1] The authors considered that mesalazine should be stopped when liver dysfunction occurred.

1. Deltenre P, *et al.* Mesalazine (5-aminosalicylic acid) induced chronic hepatitis. *Gut* 1999; **44:** 886–8.

Effects on the nervous system. Peripheral neuropathy,[1] mainly affecting the legs, has occurred during mesalazine treatment. The symptoms resolved on stopping the drug. Mononeuritis multiplex was part of the presentation of an eosinophilic reaction attributed to mesalazine in an asthmatic patient;[2] Churg-Strauss syndrome developed after withdrawal of mesalazine, but the patient subsequently recovered without sequelae.

1. Woodward DK. Peripheral neuropathy and mesalazine. *BMJ* 1989; **299:** 1224.
2. Morice AH, *et al.* Mesalazine activation of eosinophil. *Lancet* 1997; **350:** 1105.

Effects on the pancreas. Pancreatitis has been reported as an adverse effect of mesalazine.[1-4] In 2 patients,[1,2] with abdominal pain and raised amylase activity, this reaction to mesalazine was confirmed by rechallenge and symptoms resolved on mesalazine withdrawal. By February 1994 the UK CSM had received 15 reports[3] of pancreatitis associated with mesalazine therapy. However, a case control study suggested that inflammatory bowel disease, rather than the use of mesalazine, may be associated with an increased risk of acute pancreatitis (see under Sulfasalazine, p.1774)

1. Sachedina B, *et al.* Acute pancreatitis due to 5-aminosalicylate. *Ann Intern Med* 1989; **110:** 490–2.
2. Deprez P, *et al.* Pancreatitis induced by 5-aminosalicylic acid. *Lancet* 1989; **ii:** 445–6.
3. Committee on Safety of Medicines. Drug-induced pancreatitis. *Current Problems* 1994; **20:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 02/07/08)
4. Adachi E, *et al.* Acute pancreatitis secondary to 5-aminosalicylic acid therapy in a patient with ulcerative colitis. *Int J Pancreatol* 1999; **25:** 217–21.

Effects on the respiratory system. Pulmonary complications have been rarely reported with mesalazine. There have though been cases of interstitial lung disease, with features of hypersensitivity pneumonia.[1] Symptoms have included dyspnoea, cough, fever, and pleuritic chest pain, with the onset of symptoms varying from a few days to several years after starting mesalazine therapy. Although pulmonary complications can also be associated with inflammatory bowel disease itself, there has been a report[2] of eosinophilic pleural effusion in a patient who was given mesalazine in the absence of an established diagnosis of inflammatory bowel disease.

Pulmonary complications have also been reported with sulfasalazine (p.1774), and pulmonary symptoms may also manifest as part of a broader lupus-like syndrome (see Effects on the Cardiovascular System, above).

1. Foster RA, *et al.* Mesalamine-related lung disease: clinical, radiographic, and pathologic manifestations. *Inflamm Bowel Dis* 2003; **9:** 308–15.
2. Trisolini R, *et al.* Eosinophilic pleural effusion due to mesalamine: report of a rare occurrence. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; **17:** 288–91.

Lupus. A lupus-like syndrome has been reported in 4 patients receiving mesalazine who developed antinuclear antibody (ANA)-positivity with at least one clinical feature of lupus, such as arthropathy, skin rashes, or acute inflammation unrelated to the underlying condition.[1] In all 4 cases symptoms resolved upon stopping mesalazine. For similar reports, see Effects on the Cardiovascular System, above.

1. Kirkpatrick AW, *et al.* Lupus-like syndrome caused by 5-aminosalicylic acid in patients with inflammatory bowel disease. *Can J Gastroenterol* 1999; **13:** 159–62.

Pregnancy. Renal insufficiency in a neonate whose mother received mesalazine 2 to 4 g daily by mouth during the second trimester of pregnancy was suggested to be due to the drug,[1] although the proposed mechanism, inhibition of prostaglandin synthesis in the neonatal kidney, has been questioned.[2] A subsequent case-control study[3] found that use of oral mesalazine in 165 pregnant women with inflammatory bowel disease was not associated with a greater incidence of malformations. However, women treated with mesalazine were more likely to have preterm deliveries and newborns with decreased birth-weights, although the disease may have been a factor in this finding. A commentator on this study,[4] considered that active inflammatory bowel disease was a greater risk to pregnancy than drug treatment. In a further cohort of 123 pregnancies,[5] oral mesalazine at doses of 3 g daily or less did not increase the risk of fetal malformations or affect pregnancy outcome. The researchers concluded that further information was required on doses higher than 3 g daily. In another study,[6] all of 19 pregnancies in women receiving rectal mesalazine were full-term with no fetal abnormalities. A Danish cohort study[7] found an increased risk of still-birth and preterm birth in women who had been prescribed mesalazine or olsalazine during pregnancy, but no significant increased risk of malformations. The risk of still-birth was greatest in women with ulcerative colitis who were prescribed corticosteroids and either mesalazine or olsalazine, and the risk of preterm birth was greatest in women with ulcerative colitis who were prescribed either mesalazine or olsalazine alone. The authors acknowledged that it was difficult to distinguish between the increase in risk due to disease state, and the increase in risk due to medication.[7] For a discussion of sulfasalazine in pregnancy, see p.1774.

1. Colombel J-F, *et al.* Renal insufficiency in infant: side-effect of prenatal exposure to mesalazine? *Lancet* 1994; **344:** 620–1.
2. Marteau P, Devaux CB. Mesalazine during pregnancy. *Lancet* 1994; **344:** 1708–9.
3. Diav-Citrin O, *et al.* The safety of mesalamine in human pregnancy: a prospective controlled cohort study. *Gastroenterology* 1998; **114:** 23–8.
4. Sachar D. Exposure to mesalamine during pregnancy increased preterm deliveries (but not birth defects) and decreased birth weight. *Gut* 1998; **43:** 316.
5. Marteau P, *et al.* Foetal outcome in women with inflammatory bowel disease treated during pregnancy with oral mesalazine microgranules. *Aliment Pharmacol Ther* 1998; **12:** 1101–8.
6. Bell CM, Habal FM. Safety of topical 5-aminosalicylic acid in pregnancy. *Am J Gastroenterol* 1997; **92:** 2201–2.
7. Nørgård B, *et al.* Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish cohort study. *Gut* 2003; **52:** 243–7.

Interactions

Preparations formulated to release mesalazine in the colon should not be given with drugs, such as lactulose, that lower colonic pH as they may prevent the release of mesalazine (but see Gastrointestinal Drugs below).

Anticoagulants. For reference to a case of mesalazine reducing the effect of *warfarin*, see Gastrointestinal Drugs, p.1430.

Antineoplastics. For mention of 5-aminosalicylates such as mesalazine inhibiting the metabolism of thiopurine antineoplastics, and increasing their toxicity, see Mercaptopurine, p.744.

Gastrointestinal drugs. Although it has been suggested that *lactulose* could delay the intestinal release of mesalazine from modified-release preparations, a study found no evidence that lactulose influenced the release or disposition of mesalazine.[1] Similarly, *omeprazole* did not appear to increase the likelihood of premature mesalazine release.

1. Hussain FN, *et al.* Mesalazine release from a pH dependent formulation: effects of omeprazole and lactulose co-administration. *Br J Clin Pharmacol* 1998; **46:** 173–5.

Pharmacokinetics

If given orally as conventional formulations, mesalazine would be extensively absorbed from the upper gastrointestinal tract, with little of the drug reaching the colon. Oral preparations are therefore generally formulated to release the drug in the terminal ileum and colon, where it is thought to exert a mainly local action. The specific release characteristics differ somewhat between formulations and this, together with interindividual variation, makes comparison of pharmacokinetic data between studies difficult. Even with modified-release preparations some 30 to 50% of an oral dose is thought to be lost to absorption in healthy subjects. Absorption from rectal dosage forms has also varied widely, with factors such as the dose, the formulation, and the pH also playing a role, but mean absorption of around 10 to 30% of a rectal dose has been reported.

The absorbed portion of mesalazine is almost completely acetylated in the gut wall and in the liver to acetyl-5-aminosalicylic acid. The rate of acetylation, and hence the concentration of parent drug and metabolite in the systemic circulation, may be dose dependent and subject to saturation. The acetylated metabolite is excreted mainly in urine by tubular secretion, with traces of the parent compound.

The plasma half-life of mesalazine is reported to be about 40 minutes and it is 40 to 50% bound to plasma proteins; the acetylated metabolite has a plasma half-life of 70 minutes and is about 80% bound to plasma proteins.

Only negligible quantities of mesalazine cross the placenta. Amounts distributed into breast milk are very small.

◊ Reviews.

1. De Vos M. Clinical pharmacokinetics of slow release mesalazine. *Clin Pharmacokinet* 2000; **39:** 85–97.
2. Sandborn WJ, *et al.* Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003; **17:** 29–42.

Uses and Administration

Mesalazine is an anti-inflammatory drug structurally related to the salicylates and active in inflammatory bowel disease (p.1697); it is considered to be the active moiety of sulfasalazine (p.1773). Mesalazine is thought to act locally on the inflamed intestinal tissue, rather than systemically. Although its precise mechanism of action is uncertain, it may be due to inhibition of prostaglandin and leukotriene synthesis in the gastrointestinal mucosa.

Mesalazine is given orally or rectally in the treatment of *acute attacks* of mild to moderate ulcerative colitis, or the *maintenance of remission* of ulcerative colitis. Some products are also used for the *maintenance of remission* of Crohn's ileo-colitis.

There are several differently formulated oral preparations of mesalazine available, and dosage recommendations vary. Recommended doses for some UK preparations are as follows:

- *Asacol 400 mg* tablets (*Procter and Gamble, UK*), *Ipocol* tablets (*Sandoz, UK*), *Mesren* tablets (*IVAX, UK*): acute attack, initially 2.4 g daily in divided doses; maintenance of remission, 1.2 to 2.4 g daily in divided doses. The *BNFC* includes similar doses for children aged 12 to 18 years
- *Asacol 800 mg* tablets (*Procter and Gamble, UK*): mild acute exacerbations, 2.4 g daily in divided doses; moderate acute exacerbations, 4.8 g daily in divided doses; maintenance of remission, up to 2.4 g daily in divided doses
- *Mezavant* tablets (*Shire, UK*): acute attack, initially 2.4 to 4.8 g once daily; maintenance of remission, 2.4 g once daily
- *Pentasa* tablets (*Ferring, UK*): acute attack, initially up to 4 g daily in 2 or 3 divided doses; maintenance of remission, adjusted individually from an initial dose of 1.5 g daily in 2 or 3 divided doses. The *BNFC* includes the same doses for children aged 15 to 18 years. For children aged 5 to 15 years: acute attack, 15 to 20 mg/kg (maximum 1 g) 3 times daily; maintenance of remission, 10 mg/kg (maximum 500 mg) 2 or 3 times daily
- *Pentasa* granules (*Ferring, UK*): acute attack, initially, up to 4 g daily in 2 to 4 divided doses; maintenance of remission, 2 g daily in 2 divided doses. The *BNFC* includes the same dose for acute attack in children aged 12 to 18 years, and 0.5 to 1 g twice daily for maintenance of remission. For children aged 5 to 12 years: acute attack, 15 to 20 mg/kg (maximum 1 g) 3 times daily; maintenance of remission, 10 mg/kg (maximum 500 mg) 2 or 3 times daily
- *Salofalk* tablets (*Falk, UK*): acute attack, initially 1.5 g daily in 3 divided doses; maintenance of remission, 0.75 to 1.5 g daily in divided doses. The *BNFC* includes the same dose for acute attack in children aged 12 to 18 years, and 250 to 500 mg given 2 or 3 times daily for maintenance of remission
- *Salofalk* granules (*Falk, UK*): acute attack, initially 1.5 to 3 g daily, either once daily, or in 3 divided doses; maintenance of remission, 1.5 g daily in 3 divided doses. The *BNFC* includes similar doses for children aged 12 to 18 years. For children aged 6 to 12 years: acute attack, 10 to 15 mg/kg (maximum 1 g) 3 times daily; maintenance of remission, 7.5 to 15 mg/kg (maximum 500 mg) twice daily (or 250 mg given 3 times daily for those weighing less than 40 kg)

Mesalazine may be given rectally, particularly when disease affects the sigmoid colon and rectum. Various formulations are available and the dose is usually given at night, but preparations do vary. Recommended doses for some UK preparations are as follows (the *BNFC* also suggests that these doses are suitable for children aged 12 to 18 years):

- *Asacol* suppositories (*Procter and Gamble, UK*): 0.75 to 1.5 g daily in divided doses
- *Asacol* foam enema (*Procter and Gamble, UK*): 1 g daily for disease affecting the rectosigmoid region; 2 g daily for disease involving the descending colon
- *Pentasa* suppositories and suspension enema (*Ferring, UK*): 1 g daily
- *Salofalk* suppositories (*Falk, UK*): 0.5 to 1 g given 2 or 3 times daily
- *Salofalk* foam enema and suspension enema (*Falk, UK*): 2 g daily

Similar preparations are available in other countries, and in the USA a suspension enema containing 4 g of mesalazine has been used.

◊ References.

1. Clemett D, Markham A. Prolonged-release mesalazine: a review of its therapeutic potential in ulcerative colitis and Crohn's disease. *Drugs* 2000; **59:** 929–56.
2. Hanauer SB, Strömberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004; **2:** 379–88.
3. Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 01/06/07).
4. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
5. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 01/06/07).
6. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **23:** 841–55.
7. van Bodegraven AA, Mulder CJ. Indications for 5-aminosalicylate in inflammatory bowel disease: is the body of evidence complete? *World J Gastroenterol* 2006; **12:** 6115–23.
8. Anonymous. Once-daily mesalamine (Lialda) for ulcerative colitis. *Med Lett Drugs Ther* 2007; **49:** 25–6.
9. McCormack PL, *et al.* Delayed-release Multi Matrix System (MMX) mesalazine: in ulcerative colitis. *Drugs* 2007; **67:** 2635–42.
10. Kale-Pradhan PB, *et al.* Multi-Matrix System Mesalamine: to use or not to use. *Ann Pharmacother* 2008; **42:** 265–9.

Administration. Because the release characteristics of different formulations of mesalazine vary, they should not be regarded as interchangeable.[1] This applies even to those formulations where the dosage is apparently similar.[2] However, a study established that an oral once-daily regimen was bioequivalent to a twice-daily regimen of the same product (*Pentasa (Ferring, France)*).[3]

1. Forbes A, Chadwick C. Mesalazine preparations. *Lancet* 1997; **350:** 1329.
2. Benbow AG, Gould I. Mesalazine preparations. *Lancet* 1998; **351:** 68.
3. Gandia P, *et al.* Is once-daily mesalazine equivalent to the currently used twice-daily regimen? A study performed in 30 healthy volunteers. *J Clin Pharmacol* 2007; **47:** 334–42.

Diverticular disease. In a study involving 218 patients with a history of recurrent attacks of acute diverticulitis (p.1695), half were assigned to treatment with oral rifaximin 400 mg twice daily for 7 days, and half received rifaximin plus a modified-release formulation of mesalazine 800 mg three times daily, again for 7 days. Courses were then repeated, with rifaximin at the same dose and mesalazine at 800 mg twice daily, for 7 days in each month, and patients followed for 12 months. The combination of rifaximin and mesalazine was significantly more effective in reducing symptomatic episodes and normalisation of bowel habit than rifaximin alone: 89 of 107 patients given the combination were symptom-free at 12 months, compared with 44 of 105 given just the antibacterial.[1] Similarly, the same group found that in patients with uncomplicated diverticular disease given 10 days of treatment with rifaximin and mesalazine (*Pentacol; Sofar, Ital.*) in the doses above, followed by mesalazine 1.6 g daily for 8 weeks, 70 of 86 completing the study were completely asymptomatic, suggesting that daily mesalazine alone was an effective maintenance therapy, although longer-term studies were needed.[2] Mesalazine has also been investigated in combination with a probiotic preparation of lactic-acid-producing organisms.[3]

1. Tursi A, *et al.* Long-term treatment with mesalazine and rifaximin versus rifaximin alone for patients with recurrent attacks of acute diverticulitis of colon. *Dig Liver Dis* 2002; **34:** 510–15.
2. Brandimarte G, Tursi A. Rifaximin plus mesalazine followed by mesalazine alone is highly effective in obtaining remission of symptomatic uncomplicated diverticular disease. *Med Sci Monit* 2004; **10:** PI70–PI73.
3. Tursi A, *et al.* Mesalazine and/or Lactobacillus casei in preventing recurrence of symptomatic uncomplicated diverticular disease of the colon: a prospective, randomized, open-label study. *J Clin Gastroenterol* 2006; **40:** 312–16.

Preparations

USP 31: Mesalamine Delayed-Release Tablets; Mesalamine Extended-Release Capsules; Mesalamine Rectal Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Bufexan; Pentasa; Salofalk; Suprimal; Xalazina; Yolecol; ***Austral.:*** Mesasal; Pentasa; Salofalk; ***Austria:*** Claversal; Pentasa; Salofalk; ***Belg.:*** Asacol†; Claversal; Colitofalk; Pentasa; ***Braz.:*** Asalit; Chron-ASA; Mesacol; Pentasa†; ***Canad.:*** Asacol; Mesasal; Pentasa; Salofalk; ***Chile:*** Pentasa; Salofalk; ***Cz.:*** Asacol; Pentasa; Salofalk; Samezil; ***Denm.:*** Asacol; Mesasal; Pentasa; ***Fin.:*** Asacol; Pentasa; Salofalk; ***Fr.:*** Fivasa; Pentasa; Rowasa; ***Ger.:*** Asacolitin; Claversal; Pentasa; Salofalk; ***Gr.:*** Asacol; Asalazin†; Crohnezine; Ectospasmol; Empenox; Enterin; Favorat; Laboxantryl; Mesagin†; Pentasa; Prozylex†; Salofalk; ***Hong Kong:*** Asacol; Pentasa; Salofalk; ***Hung.:*** Asacol; Huma-Col-Asa; Pentasa; Salofalk; Xalazin; ***India:*** Asacol; Mesacol; ***Indon.:*** Salofalk; ***Irl.:*** Asacolon; Pentasa; Salofalk; ***Israel:*** Asacol; Pentasa; Rafassal; ***Ital.:*** Asacol; Asalex; Asamax; Asavixin; Claversal; Enteraproct; Enterasin; Lextrasa; Mesaflor; Pentacol; Pentasa; Plimage; Quota; Salofalk†; Xalazin†; ***Jpn:*** Pentasa; ***Malaysia:*** Pentasa; Salofalk; ***Mex.:*** Asacol; Kenzomyl†; Pentasa; Salofalk; Seramine; ***Neth.:*** Asacol; Asamax; Claversal; Pentasa; Salofalk; ***Norw.:*** Asacol; Mesasal; Pentasa; ***NZ:*** Asacol; Pentasa; ***Philipp.:*** Pentasa; Salofalk; ***Pol.:*** Asamax; Colitan; Jucolon; Pentasa; Salofalk; ***Port.:*** Asacol; Claversal; Pentasa; Salofalk; ***Rus.:*** Mesacol (Месакол); Pentasa (Пентаса); Samezil (Самезил); ***S.Afr.:*** Asacol; Mesasal; Pentasa; ***Singapore:*** Asacol; Pentasa; Salofalk; ***Spain:*** Claversal; Lixacol; Pentasa; Salofalk; ***Swed.:*** Asacol; Mesasal; Pentasa; Salofalk; ***Switz.:*** Asacol; Asazine; Mesazine; Pentasa; Salofalk; ***Thai.:*** Asacol†; Mesacol; Salofalk; ***Turk.:*** Asacol; Salofalk; ***UK:*** Asacol; Ipocol; Mesren; Mezavant; Pentasa; Salofalk; ***USA:*** Asacol; Canasa; Lialda; Pentasa; Rowasa.

Methanthelinium Bromide *(BAN, pINN)*

Bromuro de metantelinio; Dixamonum Bromidum; Methantheline Bromide; Methanthelinii Bromidum; Méthanthélinium, Bromure de; MTB-51; SC-2910. Diethylmethyl[2-(xanthen-9-ylcarbonyloxy)ethyl]ammonium bromide.

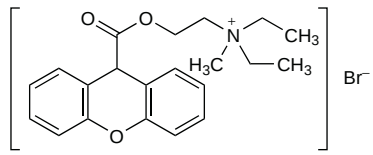
Метантелиния Бромид

$C_{21}H_{26}BrNO_3$ = 420.3.

CAS — 5818-17-7 (methanthelinium); 53-46-3 (methanthelinium bromide).

ATC — A03AB07.

ATC Vet — QA03AB07.



Profile
Methanthelinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease, in gastrointestinal disorders associated with smooth muscle spasm, and in the management of urinary incontinence. A usual oral dose in gastrointestinal disorders is 50 mg three times daily.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Vagantin.

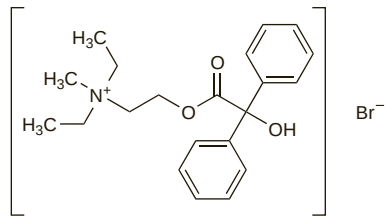
Methylbenactyzium Bromide *(rINN)*

Benactyzine Methobromide; Bromuro de metilbenacticio; Methylbenactyzii Bromidum; Méthylbénactyzium, Bromure de. Diethyl(2-hydroxyethyl)methylammonium bromide benzilate.

Метилбенактизия Бромид

$C_{21}H_{28}BrNO_3$ = 422.4.

CAS — 3166-62-9.



Pharmacopoeias. In *Jpn.*

Profile
Methylbenactyzium bromide, a derivative of benactyzine (p.383), is an antimuscarinic with effects similar to those of atropine (p.1219). It has been given orally for the treatment of gastrointestinal spasm and nocturnal enuresis.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Anxiolit plus.

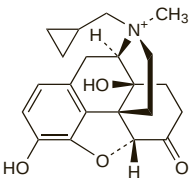
Methylnaltrexone Bromide *(USAN, rINN)*

Bromure de Méthylnaltrexone; Bromuro de Metilnaltrexona; Methylnaltrexonii Bromidum; MRZ-2663BR; Naltrexone Methobromide. (17*RS*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide.

Метинальтрексон Бромид

$C_{21}H_{26}BrNO_4$ = 436.3.

CAS — 83387-25-1 (methylnaltrexone); 73232-52-7 (methylnaltrexone bromide).



Br⁻ and epimer at N^+

Profile
Methylnaltrexone bromide is a selective peripherally acting antagonist of opioid μ-receptors that is used for the treatment of opioid-induced constipation in patients receiving palliative care for advanced illness, when response to usual laxative therapy is insufficient. It is also being studied for treatment of opioid-induced urinary retention and postoperative ileus.

For the treatment of opioid-induced constipation methylnaltrexone bromide may be given once every 48 hours by subcutaneous injection in the following doses according to body-weight: patients less than 38 kg in weight, 150 micrograms/kg; 38 to 62 kg, 8 mg; 62 to 114 kg, 12 mg; more than 114 kg, 150 micrograms/kg.

◊ References.

1. Yuan CS. Methylnaltrexone mechanisms of action and effects on opioid bowel dysfunction and other opioid adverse effects. *Ann Pharmacother* 2007; **41:** 984–93.
2. Reichle FM, Conzen PF. Methylnaltrexone, a new peripheral μ-receptor antagonist for the prevention and treatment of opioid-induced extracerebral side effects. *Curr Opin Investig Drugs* 2008; **9:** 90–100.
3. Thomas J, *et al.* Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008; **358:** 2332–43.

Preparations
Proprietary Preparations (details are given in Part 3)
UK: Relistor; ***USA:*** Relistor.

Metoclopramide *(BAN, rINN)*

Metoclopramida; Métoclopramide; Metoclopramidum; Metoklopramid; Metoklopramidas; Metoklopramidi. 4-Amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide.

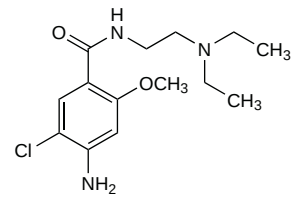
Метоклопрамид

$C_{14}H_{22}ClN_3O_2$ = 299.8.

CAS — 364-62-5.

ATC — A03FA01.

ATC Vet — QA03FA01.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *Jpn.*

Ph. Eur. 6.2 (Metoclopramide). A white or almost white, fine powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble to slightly soluble in alcohol; slightly soluble in dichloromethane.

Metoclopramide Hydrochloride *(BANM, USAN, rINNM)*

AHR-3070-C; DEL-1267; Hidrocloruro de metoclopramida; Métoclopramide, chlorhydrate de; Metoclopramidi hydrochloridum; Metoclopramidi Hydrochloridum Monohydricum; Metoklopramid Hidroklorür; Metoklopramid-hidroklorid; Metoklopramid-hydrochlorid monohydrát; Metoklopramidhydroklorid; Metoklopramidihydrokloridi; Metoklopramido hidrochloridas; Metoklopramidu chlorowodorek; MK-745.

Метоклопрамида Гидрохлорид

$C_{14}H_{22}ClN_3O_2$,HCl,H_2O = 354.3.

CAS — 7232-21-5 (anhydrous metoclopramide hydrochloride); 54143-57-6 (metoclopramide hydrochloride monohydrate); 2576-84-3 (anhydrous metoclopramide dihydrochloride).

ATC — A03FA01.

ATC Vet — QA03FA01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, and *US.*

Ph. Eur. 6.2 (Metoclopramide Hydrochloride). A white or almost white, crystalline powder or crystals. Very soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. A 10% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Metoclopramide Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder.