mothorax but the treatment is associated with pain and a high frequency of toxic effects.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Maladin.

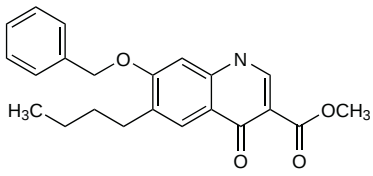
Methyl Benzoquate *(BAN)*

Nequinate *(USAN, pINN)*; AY-20385; ICI-55052; Néquinate; Nequinato; Nequinatum. Methyl 7-benzyloxy-6-butyl-1,4-dihydro-4-oxoquinoline-3-carboxylate.

Нехинат

$C_{22}H_{23}NO_4$ = 365.4.

CAS — 13997-19-8.



Profile

Methyl benzoquate is an antiprotozoal used in veterinary practice with clopidol (p.831) for the prevention of coccidiosis in poultry.

Metronidazole *(BAN, USAN, rINN)*

Bayer-5360; Metronidatsoli; Metronidazol; Metronidazolas; Métronidazole; Metronidazolum; NSC-50364; RP-8823; SC-10295. 2-(2-Methyl-5-nitroimidazol-1-yl)ethanol.

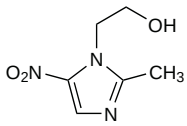
Метронидазол

$C_6H_9N_3O_3$ = 171.2.

CAS — 443-48-1.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.



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

Ph. Eur. 6.2 (Metronidazole). A white or yellowish, crystalline powder. Slightly soluble in water, in alcohol, in acetone, and in dichloromethane. Protect from light.

USP 31 (Metronidazole). White to pale yellow, odourless crystals or crystalline powder. It darkens on exposure to light. Sparingly soluble in water and in alcohol; slightly soluble in chloroform and in ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. See below.

Metronidazole Benzoate *(BAN, rINNM)*

Benzoato de metronidazol; Benzoyl Metronidazole; Metronidatsolibentsoaatti; Metronidazolbensoat; Metronidazol-benzoát; Métronidazole, benzoate de; Metronidazoli benzoas; Metronidazolo benzoatas; RP-9712. 2-(2-Methyl-5-nitroimidazol-1-yl)ethyl benzoate.

Метронидазола Бензоат

$C_{13}H_{13}N_3O_4$ = 275.3.

CAS — 13182-89-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

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

Ph. Eur. 6.2 (Metronidazole Benzoate). White or slightly yellowish, crystalline powder or flakes. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

USP 31 (Metronidazole Benzoate). A white to slightly yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; very slightly soluble in solvent ether. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Metronidazole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de metronidazol; Métronidazole, Chlorhydrate de; Metronidazoli Hydrochloridum; SC-32642.

Метронидазола Гидрохлорид

$C_6H_9N_3O_3$,HCl = 207.6.

CAS — 69198-10-3.

ATC — A01AB17; D06BX01; G01AF01; J01XD01; P01AB01.

ATC Vet — QA01AB17; QD06BX01; QG01AF01; QJ01XD01; QP51AA01.

Incompatibility. Solutions of metronidazole hydrochloride have a low pH, usually of less than 2.0, before dilution and neutralisation for intravenous use. These undiluted solutions react with aluminium in equipment such as needles to produce reddish-brown discoloration, and a precipitate has been reported with ready-to-use preparations of metronidazole hydrochloride, although this occurred after contact for 6 hours or more.[1,2]

Several studies have assessed the compatibility of antibacterial injections and other drugs when added to metronidazole solution for intravenous infusion.[3-7] Results have varied according to the criteria applied and the preparations and conditions used. Physical incompatibilities due to the low pH of metronidazole injections appear to be more of a problem than chemical incompatibility. Regardless of these studies, it is generally recommended that other drugs should not be added to intravenous solutions of metronidazole or its hydrochloride. Specific information on the compatibility of individual formulations may be found in the manufacturers' literature.

1. Schell KH, Copeland JR. Metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 1040, 1042.
2. Struthers BJ, Parr RJ. Clarifying the metronidazole hydrochloride-aluminum interaction. *Am J Hosp Pharm* 1985; **42:** 2660.
3. Bisaillon S, Sarrazin R. Compatibility of several antibiotics or hydrocortisone when added to metronidazole solution for intravenous infusion. *J Parenter Sci Technol* 1983; **37:** 129–32.
4. Gupta VD, Stewart KR. Chemical stabilities of hydrocortisone sodium succinate and several antibiotics when mixed with metronidazole injection for intravenous infusion. *J Parenter Sci Technol* 1985; **39:** 145–8.
5. Gupta VD, *et al.* Chemical stabilities of cefamandole nafate and metronidazole when mixed together for intravenous infusion. *J Clin Hosp Pharm* 1985; **10:** 379–83.
6. Barnes AR. Chemical stabilities of cefuroxime sodium and metronidazole in an admixture for intravenous infusion. *J Clin Pharm Ther* 1990; **15:** 187–96.
7. Nahata MC, *et al.* Stability of metronidazole and ceftizoxime sodium in ready-to-use metronidazole bags stored at 4 and 25° C. *Am J Health-Syst Pharm* 1996; **53:** 1046–8.

Adverse Effects

The adverse effects of metronidazole are generally dose-related. The most common are gastrointestinal disturbances, especially nausea and an unpleasant metallic taste. Vomiting, and diarrhoea or constipation may also occur. A furred tongue, glossitis, and stomatitis may be associated with an overgrowth of *Candida*. There have been rare reports of antibiotic-associated colitis associated with metronidazole, although it is also used in the treatment of this condition.

Weakness, dizziness, ataxia, headache, drowsiness, insomnia, and changes in mood or mental state such as depression or confusion have also been reported. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures have been associated with high doses of metronidazole or prolonged treatment.

Temporary moderate leucopenia and thrombocytopenia may occur in some patients receiving metronidazole. Skin rashes, urticaria, and pruritus occur occasionally and erythema multiforme, angioedema, and anaphylaxis have been reported rarely. Other adverse effects include urethral discomfort and darkening of the urine. Raised liver enzyme values, cholestatic hepatitis, and jaundice have occasionally been reported. Thrombophlebitis may follow intravenous use of metronidazole.

Studies have shown metronidazole to be mutagenic in bacteria and carcinogenic in some *animals*.

Carcinogenicity and mutagenicity. Metronidazole is mutagenic in bacterial assays, and its hydroxy metabolite even more so, but studies of mammalian cells *in vitro* and *in vivo* have not consistently demonstrated a mutagenic effect. Similarly, there is no uniformity in the limited data concerning genotoxicity in humans,[1] and although metronidazole has been classified as a carcinogen in *animals*, the evidence of human carcinogenicity is ambiguous. There was no appreciable increase in the incidence of cancer in a retrospective study of 771 patients given metronidazole for vaginal trichomoniasis,[2] nor in another similar study of 2460 patients.[3] The first study[2] did show an excess of cases of lung cancer, although all 4 were in women who were smokers. Subsequent follow-up[4] to 1984, covering a period of 15 to 25 years, still showed an excess of lung cancer cases even after allowing for smoking status. However, this follow-up also continued to show no significant increase overall in cancer-related morbidity or mortality. Follow-up[5] of the patients from the second study for 11 to 15 years to 1984 also showed no increase in the overall incidence of cancers nor did it confirm any increase in lung cancer.

Risks to the fetus are discussed under Pregnancy in Precautions, below.

1. Bendesky A, *et al.* Is metronidazole carcinogenic? *Mutat Res* 2002; **511:** 133–44.
2. Beard CM, *et al.* Lack of evidence for cancer due to use of metronidazole. *N Engl J Med* 1979; **301:** 519–22.
3. Friedman GD. Cancer after metronidazole. *N Engl J Med* 1980; **302:** 519.
4. Beard CM, *et al.* Cancer after exposure to metronidazole. *Mayo Clin Proc* 1988; **63:** 147–53.
5. Friedman GD, Selby JV. Metronidazole and cancer. *JAMA* 1989; **261:** 866.

Effects on the blood. Adverse haematological effects associated with metronidazole therapy include a report of bone marrow aplasia, with leucopenia and markedly reduced erythropoiesis and granulopoiesis,[1] aplastic anaemia,[2] and the haemolytic-uraemic syndrome.[3]

1. White CM, *et al.* Bone marrow aplasia associated with metronidazole. *BMJ* 1980; **280:** 647.
2. Raman R, *et al.* Metronidazole induced aplastic anaemia. *Clinician* 1982; **46:** 464–8.
3. Powell HR, *et al.* Haemolytic-uraemic syndrome after treatment with metronidazole. *Med J Aust* 1988; **149:** 222–3.

Effects on the ears. A review of reports of ototoxicity notified to the Australian Adverse Drug Reactions Advisory Committee revealed a number of cases of deafness associated with the use of metronidazole.[1]

1. Anonymous. Drug-induced ototoxicity. *WHO Drug Inf* 1991; **5:** 12.

Effects on the eyes. Myopia which developed in a patient after 11 days of oral metronidazole for trichomoniasis had resolved 4 days after withdrawal of treatment, but recurred when she resumed treatment.[1]

Optic neuropathies have also occurred.[2,3] In one report, retrobulbar or optic neuritis was seen in 7 patients given oral metronidazole.[2] Dosage varied from 0.75 to 1 g daily and duration of treatment from 7 days to a year. Abnormalities included defects in colour vision, decreased vision, and scotomas. Vision improved on withdrawal of metronidazole, although there was a residual deficit in 2 patients.

1. Grinbaum A, *et al.* Transient myopia following metronidazole treatment for Trichomonas vaginalis. *JAMA* 1992; **267:** 511–12.
2. Putnam D, *et al.* Metronidazole and optic neuritis. *Am J Ophthalmol* 1991; **112:** 737.
3. McGrath NM, *et al.* Reversible optic neuropathy due to metronidazole. *Clin Experiment Ophthalmol* 2007; **35:** 585–6.

Effects on the gastrointestinal tract. ***ANTIBIOTIC-ASSOCIATED COLITIS.*** Reports of pseudomembranous colitis associated with the use of metronidazole.

1. Thomson G, *et al.* Pseudomembranous colitis after treatment with metronidazole. *BMJ* 1981; **282:** 864–5.
2. Daly JJ, Chowdary KVS. Pseudomembranous colitis secondary to metronidazole. *Dig Dis Sci* 1983; **28:** 573–4.

Effects on the liver. Severely elevated liver enzyme values, consistent with a drug-induced hepatitis, occurred in a patient given metronidazole hydrochloride 500 mg every 6 hours intravenously for 4 days. He was also receiving cefapirin sodium and tobramycin sulfate.[1] A case of reversible hepatotoxicity caused by an overdose of metronidazole 12.5 g has also been reported.[2]

1. Appleby DH, Vogtland HD. Suspected metronidazole toxicity. *Clin Pharm* 1983; **2:** 373–4.
2. Lam S, Bank S. Hepatotoxicity caused by metronidazole overdose. *Ann Intern Med* 1995; **122:** 803.

Effects on the nervous system. ***ASEPTIC MENINGITIS.*** A 42-year-old man had 3 episodes of aseptic meningitis during treatment with oral metronidazole as part of an eradication regimen for *Helicobacter pylori* infection.[1] On each occasion his symptoms resolved spontaneously when eradication treatment was stopped and recurred when treatment was restarted. The aseptic meningitis was attributed to the metronidazole and the patient later tolerated an eradication treatment regimen containing a proton-pump inhibitor and a macrolide.

1. Khan S, *et al.* Metronidazole-induced aseptic meningitis during Helicobacter pylori eradication therapy. *Ann Intern Med* 2007; **146:** 395–6.

CEREBELLAR TOXICITY. Ataxia and dysarthria have been reported in 2 patients taking oral metronidazole plus intravenous cefepime or oral levofloxacin.[1] Symptoms occurred about one month after starting treatment and resolved 2 to 5 weeks after stopping metronidazole.

1. Woodruff BK, *et al.* Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med* 2002; **346:** 68–9.

CONVULSIONS. Reports of convulsions associated with metronidazole therapy (usually in high doses or in patients with renal impairment).

1. Halloran TJ. Convulsions associated with high cumulative doses of metronidazole. *Drug Intell Clin Pharm* 1982; **16:** 409.

2. Wienbren M, *et al.* Convulsions and encephalopathy in a patient with leukemia after treatment with metronidazole. *J Clin Pathol* 1985; **38:** 1076.
3. Ferroir JP, *et al.* Polynévrite, crises convulsives et syndrome cérébelleux, complications d'un traitement par le métronidazole. *Presse Med* 1985; **14:** 2108.
4. Moulin B, *et al.* Risque neurotoxique du métronidazole (MN) au cours de l'insuffisance rénale sévère. *Ann Med Interne (Paris)* 1988; **139:** 369.
5. Sopena B, *et al.* Convulsiones inducidas por la asociación de metronidazol y cloroquina. *Med Clin (Barc)* 1990; **95:** 675.
6. Beloosesky Y, *et al.* Convulsions induced by metronidazole treatment for Clostridium difficile-associated disease in chronic renal failure. *Am J Med Sci* 2000; **319:** 338–9.

EFFECTS ON MENTAL FUNCTION. Although metronidazole is sometimes used to reduce colonic flora in the treatment of hepatic encephalopathy, impaired metabolism of metronidazole in such patients can result in elevated plasma concentrations and consequent toxicity. Psychosis and manic behaviour were reported in one such patient during treatment for hepatic encephalopathy with metronidazole and lactulose, although plasma-metronidazole concentrations were not found to be raised (24 micrograms/mL).[1] Symptoms resolved when metronidazole was stopped. Acute psychosis has also been reported in a patient following a 5-day course of intravenous metronidazole 1 g daily for a gynaecological disorder.[2]

1. Uhl MD, Riely CA. Metronidazole in treating portosystemic encephalopathy. *Ann Intern Med* 1996; **124:** 455.
2. Schreiber W, Spernal J. Metronidazole-induced psychotic disorder. *Am J Psychiatry* 1997; **154:** 1170–1.

PERIPHERAL NEUROPATHY. Peripheral neuropathy has been reported in patients receiving prolonged treatment with metronidazole.[1-4] Stopping metronidazole or lowering the dose usually results in complete resolution or improvement of the neuropathy but in some patients it may persist despite these measures. For reports of retrobulbar or optic neuritis associated with metronidazole, see Effects on the Eyes, above.

1. Duffy LF, *et al.* Peripheral neuropathy in Crohn's disease patients treated with metronidazole. *Gastroenterology* 1985; **88:** 681–4.
2. Boyce EG, *et al.* Persistent metronidazole-induced peripheral neuropathy. *DICP Ann Pharmacother* 1990; **24:** 19–21.
3. Learned-Coughlin S. Peripheral neuropathy induced by metronidazole. *Ann Pharmacother* 1994; **28:** 536.
4. Dreger LM, *et al.* Intermittent-dose metronidazole-induced peripheral neuropathy. *Ann Pharmacother* 1998; **32:** 267–8.

Effects on the pancreas. A small number of cases of acute pancreatitis associated with metronidazole, in some cases recurrent on rechallenge, have been reported.[1-4] No cases were found in a retrospective study of about 6500 patients who had received metronidazole.[5]

1. Plotnick BH, *et al.* Metronidazole-induced pancreatitis. *Ann Intern Med* 1985; **103:** 891–2.
2. Sanford KA, *et al.* Metronidazole-associated pancreatitis. *Ann Intern Med* 1988; **109:** 756–7.
3. Sura ME, *et al.* Metronidazole-associated pancreatitis. *Ann Pharmacother* 2000; **34:** 1152–5.
4. Tsesmeli NE, *et al.* Acute pancreatitis as a possible consequence of metronidazole during a relapse of ulcerative colitis. *Eur J Gastroenterol Hepatol* 2007; **19:** 805–6.
5. Friedman G, Selby JV. How often does metronidazole induce pancreatitis? *Gastroenterology* 1990; **98:** 1702–3.

Gynaecomastia. Gynaecomastia occurred in a 36-year-old man with ulcerative colitis after taking metronidazole for about a month.[1]

1. Fagan TC, *et al.* Metronidazole-induced gynecomastia. *JAMA* 1985; **254:** 3217.

Hypersensitivity. A hypersensitivity reaction with chills, fever, generalised erythema, and a maculopapular rash developed after a single dose of metronidazole in a patient who had previously developed a rash during treatment with intravaginal metronidazole.[1]

1. Knowles S, *et al.* Metronidazole hypersensitivity. *Ann Pharmacother* 1994; **28:** 325–6.

Precautions

Peripheral neuropathy, transient epileptiform seizures, and leucopenia have sometimes been associated with prolonged or intensive treatment with metronidazole (see Adverse Effects, above). Clinical and laboratory monitoring is advised in patients given metronidazole for more than 10 days. Doses should be reduced in patients with severe hepatic impairment.

It is suggested that the use of metronidazole should be avoided during pregnancy, and this caution applies especially to use during the first trimester and to the use of high-dose regimens (see also below).

Patients are advised not to drink alcoholic beverages while taking metronidazole (see under Interactions, below).

Breast feeding. Metronidazole is distributed into breast milk giving it a bitter taste which may impair feeding.[1] The American Academy of Pediatrics considers that although the effects of metronidazole on breast-fed infants are unknown they may be of concern. It recommends that breast feeding should be stopped for 12 to 24 hours when single-dose therapy is used;[2] no specific recommendations are given for long-term treatment.

1. Rubin PC. Prescribing in pregnancy: general principles. *BMJ* 1986; **293:** 1415–17.
2. 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 03/02/04)

Pregnancy. Metronidazole is mutagenic in bacteria and carcinogenic in *rodents*. It readily crosses the placenta achieving similar concentrations in the placental cord and maternal plasma and its use in pregnancy is controversial. Meta-analyses of studies involving the use of metronidazole in the first trimester of pregnancy[1,2] concluded that there did not appear to be an increased risk of teratogenicity. However, in the USA licensed product information considers metronidazole to be contra-indicated during the first trimester in patients with trichomoniasis; use for trichomoniasis during the second and third trimesters may be acceptable. For other indications the risks and benefits of treatment with metronidazole should be weighed carefully, especially in the first trimester.

1. Burtin P, *et al.* Safety of metronidazole in pregnancy: a meta-analysis. *Am J Obstet Gynecol* 1995; **172:** 525–9.
2. Caro-Patón T, *et al.* Is metronidazole teratogenic? A meta-analysis. *Br J Clin Pharmacol* 1997; **44:** 179–82.

Interactions

When given with alcohol, metronidazole may provoke a disulfiram-like reaction in some patients. Acute psychoses or confusion have been associated with the use of metronidazole and disulfiram together.

Metronidazole is reported to impair the metabolism or excretion of several drugs including warfarin (p.1429), phenytoin (p.499), lithium (see Antimicrobials, p.404), ciclosporin, and fluorouracil (p.723), with the consequent potential for an increased incidence of adverse effects. There is some evidence that phenytoin might accelerate the metabolism of metronidazole. Plasma concentrations of metronidazole are decreased by phenobarbital, with a consequent reduction in the effectiveness of metronidazole. Cimetidine has increased plasma concentrations of metronidazole and might increase the risk of neurological adverse effects. For references to some of these interactions, see below.

For incompatibilities between metronidazole and other drugs in solutions for injection, see above.

Alcohol. Metronidazole may provoke a disulfiram-like reaction in some individuals when given with alcohol; reactions have occurred after the use of preparations formulated with alcohol, including injections, as well as after drinking alcohol.[1] Acute psychosis or confusional state was reported in 6 of 29 alcoholic patients who were also taking disulfiram.[2] However, an analysis of published reports[3] and a study in healthy subjects[4] both found that there was no convincing evidence of a disulfiram-like reaction between metronidazole and alcohol although caution was still advised.

1. Edwards DL, *et al.* Disulfiram-like reaction associated with intravenous trimethoprim-sulfamethoxazole and metronidazole. *Clin Pharm* 1986; **5:** 999–1000.
2. Rothstein E, Clancy DD. Toxicity of disulfiram combined with metronidazole. *N Engl J Med* 1969; **280:** 1006–7.
3. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother* 2000; **34:** 255–7.
4. Visapää J-P, *et al.* Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother* 2002; **36:** 971–4.

Antineoplastics. For reference to the effect of metronidazole on busulfan, see p.691.

Carbamazepine. For a report of a possible interaction between metronidazole and carbamazepine, see p.475.

Cimetidine. In a study in 6 healthy subjects metronidazole plasma concentrations were increased by twice-daily doses of cimetidine. The effect was presumed to be due to inhibition of cytochrome P450 isoenzymes responsible for metronidazole metabolism.[1] However, cimetidine was not found to affect the pharmacokinetics of metronidazole in a study in patients with Crohn's disease[2] nor in a single-dose study in healthy subjects.[3]

1. Gugler R, Jansen JC. Interaction between cimetidine and metronidazole. *N Engl J Med* 1983; **309:** 1518–19.
2. Eradiri O, *et al.* Interaction of metronidazole with cimetidine and phenobarbital in Crohn's disease. *Clin Pharmacol Ther* 1987; **41:** 235.
3. Loft S, *et al.* Lack of effect of cimetidine on the pharmacokinetics and metabolism of a single oral dose of metronidazole. *Eur J Clin Pharmacol* 1988; **35:** 65–8.

Disulfiram. For a report of acute psychosis or confusional state following metronidazole treatment in alcoholic patients receiving disulfiram, see under Alcohol, above.

Mycophenolate mofetil. For details of a pharmacokinetic study reporting reduced exposure to mycophenolate mofetil when given with metronidazole or metronidazole plus norfloxacin, see Antibacterials, p.1837.

Omeprazole. Although concentrations in plasma and saliva of metronidazole and its hydroxy metabolite were unaffected by omeprazole in healthy subjects, those in gastric juice were substantially lowered, possibly as a result of a reduction in transfer from the plasma.[1] However, this may be of limited clinical significance during treatment of *Helicobacter pylori* infections.

1. Jessa MJ, *et al.* The effect of omeprazole on the pharmacokinetics of metronidazole and hydroxymetronidazole in human plasma, saliva and gastric juice. *Br J Clin Pharmacol* 1997; **44:** 245–53.

Phenobarbital. An increase in the rate of metabolism of metronidazole, resulting in treatment failure, was reported in a patient taking phenobarbital.[1] In a retrospective survey of patients who had not responded to treatment with metronidazole, 80% were found to be on long-term phenobarbital therapy.[2] It was found that up to 3 times the usual dose was required to produce a parasitological cure of giardiasis in such patients.

1. Mead PB, *et al.* Possible alteration of metronidazole metabolism by phenobarbital. *N Engl J Med* 1982; **306:** 1490.
2. Gupte S. Phenobarbital and metabolism of metronidazole. *N Engl J Med* 1983; **308:** 529.

Phenytoin. In addition to conflicting reports on the effects of metronidazole on the metabolism of phenytoin (p.499), increased metabolism of metronidazole was reported in a patient during treatment with phenytoin.[1]

1. Wheeler LA, *et al.* Use of high-pressure liquid chromatography to determine plasma levels of metronidazole and metabolites after intravenous administration. *Antimicrob Agents Chemother* 1978; **13:** 205–9.

Antimicrobial Action

Metronidazole is active against several protozoa including *Balantidium coli*, *Blastocystis hominis*, *Entamoeba histolytica*, *Giardia intestinalis* (*Giardia lamblia*), and *Trichomonas vaginalis*. Most obligate anaerobic bacteria, including *Bacteroides* and *Clostridium* spp., are sensitive *in vitro* to metronidazole. It is bactericidal. It also has activity against the facultative anaerobes *Gardnerella vaginalis* and *Helicobacter pylori* and against some spirochaetes. Resistance to metronidazole has been reported and cross-resistance to other nitroimidazoles, such as tinidazole, may occur.

◊ Metronidazole has well-established bactericidal activity against obligate anaerobic bacteria *in vitro*, including the Gram-negative organisms *Bacteroides fragilis* and other *Bacteroides* spp., *Fusobacterium* spp., and *Veillonella* spp., and the Gram-positive organisms *Clostridium difficile, Cl. perfringens*, and other *Clostridium* spp., *Eubacterium* spp., *Peptococcus* spp., and *Peptostreptococcus* spp.; *Propionibacterium* and *Actinomyces* spp. are often resistant.[1-6] It also has activity against the facultative anaerobe *Gardnerella vaginalis*, although its bactericidal effect is reported to be much slower than against obligate anaerobes,[7] against some strains of *Campylobacter* spp. including *C. fetus* subsp. *jejuni*,[8,9] and against *Helicobacter pylori*.[10,11]

The oxidative metabolites of metronidazole also have antibacterial activity; the hydroxy metabolite has been reported to be consistently more active than metronidazole against strains of *G. vaginalis*.[12,13]

The mode of action of metronidazole is not entirely clear, but is thought to involve reduction by bacterial 'nitroreductases' to an unstable intermediate which interacts with DNA, effectively preventing further replication.[14] A number of factors affect the sensitivity of micro-organisms to metronidazole *in vitro*. Anaerobic conditions are important for optimal activity. Interactions between micro-organisms and metronidazole have been described, including inhibition of *Escherichia coli* by metronidazole in the presence of *B. fragilis* and enhancement of the rate of killing of *B. fragilis* by metronidazole in the presence of *E. coli*.

Resistance to metronidazole has developed in sensitive species. Although no resistance among the *B. fragilis* group was observed over several years,[15,16] there have been occasional reports of resistance in this group[17-22] and in other *Bacteroides* spp.[23-25] now known as *Prevotella* spp. Nitroimidazole resistance in *Helicobacter pylori* has been increasing and may be associated with reduced response rates to anti-*Helicobacter* therapy for peptic ulcer disease in some populations (see Peptic Ulcer Disease under Uses, below).

1. Wüst J. Susceptibility of anaerobic bacteria to metronidazole, ornidazole, and tinidazole and routine susceptibility testing by standardized methods. *Antimicrob Agents Chemother* 1977; **11:** 631–7.
2. Dubreuil L, *et al.* Susceptibility of anaerobic bacteria from several French hospitals to three major antibiotics. *Antimicrob Agents Chemother* 1984; **25:** 764–6.
3. Hill GB, Ayers OM. Antimicrobial susceptibilities of anaerobic bacteria isolated from female genital tract infections. *Antimicrob Agents Chemother* 1985; **27:** 324–31.

4. Chow AW, *et al.* In vitro susceptibility of Clostridium difficile to new β-lactam and quinolone antibiotics. *Antimicrob Agents Chemother* 1985; **28:** 842–4.
5. Brazier JS, *et al.* Antibiotic susceptibility of clinical isolates of clostridia. *J Antimicrob Chemother* 1985; **15:** 181–5.
6. Van der Auwera P, *et al.* Comparative serum bactericidal activity against test anaerobes in volunteers receiving imipenem, clindamycin, latamoxef and metronidazole. *J Antimicrob Chemother* 1987; **19:** 205–10.
7. Ralph ED, Amatnieks YE. Metronidazole in treatment against Haemophilus vaginalis (Corynebacterium vaginale). *Antimicrob Agents Chemother* 1980; **18:** 101–4.
8. Hof H, *et al.* Comparative in vitro activities of niridazole and metronidazole against anaerobic and microaerophilic bacteria. *Antimicrob Agents Chemother* 1982; **22:** 332–3.
9. Freydière AM, *et al.* In vitro susceptibilities of 40 Campylobacter fetus subsp jejuni strains to niridazole and metronidazole. *Antimicrob Agents Chemother* 1984; **25:** 145–6.
10. Marshall BJ, *et al.* Pyloric campylobacter infection and gastroduodenal disease. *Med J Aust* 1985; **142:** 439–44.
11. Howden A, *et al.* In-vitro sensitivity of Campylobacter pyloridis to furazolidone. *Lancet* 1986; **ii:** 1035.
12. Ralph ED, Amatnieks YE. Relative susceptibilities of Gardnerella vaginalis (Haemophilus vaginalis), Neisseria gonorrhoeae, and Bacteroides fragilis to metronidazole and its two major metabolites. *Sex Transm Dis* 1980; **7:** 157–60.
13. Shanker S, Munro R. Sensitivity of Gardnerella vaginalis to metabolites of metronidazole and tinidazole. *Lancet* 1982; **i:** 167.
14. Ingham HR, *et al.* Interactions between micro-organisms and metronidazole. *J Antimicrob Chemother* 1982; **10:** 84–7.
15. Tally FP, *et al.* Susceptibility of the Bacteroides fragilis group in the United States in 1981. *Antimicrob Agents Chemother* 1983; **23:** 536–40.
16. Tally FP, *et al.* Nationwide study of the susceptibility of the Bacteroides fragilis group in the United States. *Antimicrob Agents Chemother* 1985; **28:** 675–7.
17. Ingham HR, *et al.* Bacteroides fragilis resistance to metronidazole after long-term therapy. *Lancet* 1978; **i:** 214.
18. Eme A, *et al.* Bacteroides fragilis resistant to metronidazole. *J Antimicrob Chemother* 1983; **12:** 523–5.
19. Lamothe F, *et al.* Bacteroides fragilis resistant to both metronidazole and imipenem. *J Antimicrob Chemother* 1986; **18:** 642–3.
20. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; **23:** 660–2.
21. Hickey MM, *et al.* Metronidazole resistant Bacteroides fragilis infection of a prosthetic hip joint. *J Infect* 1990; **20:** 129–33.
22. Turner P, *et al.* Simultaneous resistance to metronidazole, co-amoxiclav, and imipenem in clinical isolate of Bacteroides fragilis. *Lancet* 1995; **345:** 1275–7.
23. Sprott MS, *et al.* Metronidazole-resistant anaerobes. *Lancet* 1983; **i:** 1220.
24. McWalter PW, Baird DR. Metronidazole-resistant anaerobes. *Lancet* 1983; **i:** 1220.
25. Sprott MS, Kearns AM. Metronidazole-resistant Bacteroides melaninogenicus. *J Antimicrob Chemother* 1988; **22:** 951–2.

Pharmacokinetics

Metronidazole is readily and almost completely absorbed after oral doses. Peak plasma concentrations of about 6 and 12 micrograms/mL are achieved, usually within 1 to 2 hours, after single doses of 250 and 500 mg respectively. Some accumulation occurs and consequently there are higher concentrations when multiple doses are given. Absorption may be delayed, but is not reduced overall by food. Metronidazole benzoate given orally is hydrolysed in the gastrointestinal tract to release metronidazole, which in turn is then absorbed.

Peak steady-state plasma concentrations of about 25 micrograms/mL with trough concentrations of about 18 micrograms/mL have been reported in patients given an intravenous loading dose of 15 mg/kg followed by 7.5 mg/kg every 6 hours. The bioavailability of metronidazole from rectal suppositories is 60 to 80%; peak plasma concentrations are half those achieved with equivalent oral doses and effective concentrations occur after about 5 to 12 hours. Absorption from vaginal pessaries is poor with a reported bioavailability of about 20 to 25%; absorption is gradual producing peak plasma concentrations of about 2 micrograms/mL after a dose of 500 mg. An intravaginal gel formulation providing a dose of 37.5 mg metronidazole produced peak plasma concentrations of 0.3 micrograms/mL at 8 hours, with a bioavailability of 56%.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast milk, cerebral abscesses, CSF, liver and liver abscesses, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma. It also crosses the placenta and rapidly enters the fetal circulation. No more than 20% is bound to plasma proteins.

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The principal oxidative metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the hydroxy metabolite), which has antibacterial activity and is detected in plasma and urine, and 2-methyl-5-nitroimidazole-1-acetic acid (the acid metabolite), which has virtually no antibacterial activity and is often not detected in plasma, but is excreted in urine. Small amounts of reduced metabolites, acetamide and *N*-(2-hydroxyethyl)oxamic acid (HOA), have also been detected in urine and are probably formed by the intestinal flora.

The elimination half-life of metronidazole is about 8 hours; that of the hydroxy metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe hepatic impairment; that of the hydroxy metabolite is prolonged in patients with substantial renal impairment.

The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces.

◊ References.

1. Cunningham FE, *et al.* Pharmacokinetics of intravaginal metronidazole gel. *J Clin Pharmacol* 1994; **34:** 1060–5.
2. Lamp KC, *et al.* Pharmacokinetics and pharmacodynamics of the nitroimidazole antimicrobials. *Clin Pharmacokinet* 1999; **36:** 353–73.

Hepatic impairment. There have been differing results from pharmacokinetic studies of the elimination of metronidazole in patients with hepatic impairment. No marked difference was reported[1] between patients with cirrhosis or hepatosplenic schistosomiasis given a single 500-mg oral dose of metronidazole when compared with healthy subjects; this suggested that, in the absence of renal impairment, dosage adjustment was not needed in patients with hepatic impairment. However, others found[2] that elimination of metronidazole, given intravenously, was considerably impaired in a study of 10 patients with alcoholic liver disease or chronic active hepatitis, 7 of whom also had reduced creatinine clearance. Responding to the comment[3] that these differing results were probably due to impaired renal elimination, the authors suggested[4] that impaired elimination of metronidazole was due to impaired hepatic metabolism rather than decreased renal clearance; other studies have shown metronidazole clearance to be normal in renal impairment. They nevertheless agreed that reduction in the dosage of metronidazole is required only when hepatic function is very poor, particularly when renal function is impaired. A study in 10 severely ill patients with or without impaired hepatic and/or renal function[5] also suggested that hepatic function is a very important determinant of metronidazole elimination.

1. Daneshmend TK, *et al.* Disposition of oral metronidazole in hepatic cirrhosis and in hepatosplenic schistosomiasis. *Gut* 1982; **23:** 807–13.
2. Farrell G, *et al.* Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1983; **287:** 1845.
3. Daneshmend TK, Roberts CJC. Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984; **288:** 405.
4. Farrell G, *et al.* Impaired elimination of metronidazole in decompensated chronic liver disease. *BMJ* 1984, **288:** 1009.
5. Ljungberg B, *et al.* Metronidazole: pharmacokinetic observations in severely ill patients. *J Antimicrob Chemother* 1984; **14:** 275–83.

Infants and children. A single intravenous dose of 15 mg/kg has been suggested for neonates[1] which would produce therapeutic concentrations of metronidazole for around 24 hours in term neonates and 48 hours in preterm neonates. Renal and hepatic function is incompletely developed in newborn infants and consequently the elimination half-life of metronidazole is prolonged and has been reported to range from 25 to 109 hours.[1] Elimination half-life is inversely proportional to gestational age[1,2] and as the infant matures half-life is reduced to values closer to those in adults.[1,3]

1. Jager-Roman E, *et al.* Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr* 1982; **100:** 651–4.
2. Hall P, *et al.* Intravenous metronidazole in the newborn. *Arch Dis Child* 1983; **58:** 529–31.
3. Amon I, *et al.* Disposition kinetics of metronidazole in children. *Eur J Clin Pharmacol* 1983; **24:** 113–19.

Renal impairment. Pharmacokinetic studies have indicated that doses of metronidazole need not be altered in patients with renal impairment,[1] although adjustments might be required in patients undergoing haemodialysis, since metronidazole and its hydroxy metabolite are efficiently cleared and extensively removed in such patients.[2] However, in another study[3] the amount of metronidazole and its hydroxy metabolite cleared was found to depend on the type of dialysis membrane used; the authors concluded that dosage supplementation may be needed only for seriously ill patients undergoing haemodialysis with a membrane having high metronidazole clearance.

Routine adjustment of dosage was not considered necessary in patients undergoing peritoneal dialysis.[4] However, the potential for metabolites to accumulate was noted in patients on continuous ambulatory peritoneal dialysis[5] and it was suggested that dosage reduction may be necessary if excessive concentrations of metabolites are found to be toxic.

1. Houghton GW, *et al.* Pharmacokinetics of metronidazole in patients with varying degrees of renal failure. *Br J Clin Pharmacol* 1985; **19:** 203–9.
2. Somogyi A, *et al.* Disposition and removal of metronidazole in patients undergoing haemodialysis. *Eur J Clin Pharmacol* 1983; **25:** 683–7.
3. Lau AH, *et al.* Hemodialysis clearance of metronidazole and its metabolites. *Antimicrob Agents Chemother* 1986; **29:** 235–8.
4. Cassey JG, *et al.* Pharmacokinetics of metronidazole in patients undergoing peritoneal dialysis. *Antimicrob Agents Chemother* 1983; **24:** 950–1.
5. Guay DR, *et al.* Pharmacokinetics of metronidazole in patients undergoing continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother* 1984; **25:** 306–10.

Uses and Administration

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa (see Antimicrobial Action, above); it also has a radiosensitising effect on hypoxic tumour cells. Its mechanism of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced.

Metronidazole is used in the treatment of susceptible protozoal infections such as amoebiasis, balantidiasis, *Blastocystis hominis* infections, giardiasis, and trichomoniasis; it has also been tried in leishmaniasis and microsporidiosis. For details of these infections and their treatment see under Choice of Antiprotozoal, p.822. Metronidazole is also used in the treatment and prophylaxis of anaerobic bacterial infections. Specific bacterial infections treated with metronidazole include bacterial vaginosis, acute necrotising ulcerative gingivitis, pelvic inflammatory disease, tetanus, and antibiotic-associated colitis. For details of these infections and their treatment see under Choice of Antibacterial, p.162.

Metronidazole is used to eradicate *Helicobacter pylori* in peptic ulcer disease (with other antimicrobials, and either bismuth compounds or proton pump inhibitors) and in the management of malodorous tumours and ulcers where there is anaerobic infection. It is also used in the treatment of rosacea and of dracunculiasis (guinea-worm infection) and has been given in the treatment of perianal Crohn's disease and hepatic encephalopathy. It has also been tried as an adjunct to the radiotherapy of malignant neoplasms. See also below for these miscellaneous uses.

ADMINISTRATION AND DOSAGE. Metronidazole is given orally in tablets or, as metronidazole benzoate, in oral suspension; the tablets are taken with or after food and the suspension at least 1 hour before food. Metronidazole is also given rectally in suppositories, applied topically as a cream or gel, or given by intravenous infusion of metronidazole or metronidazole hydrochloride. Doses are expressed in terms of metronidazole base.

In **amoebiasis**, metronidazole acts as an amoebicide at all sites of infection with *Entamoeba histolytica*. Because of its rapid absorption it is probably less effective against parasites in the bowel lumen and is therefore used with a luminal amoebicide such as diloxanide furoate or diiodohydroxyquinoline in the treatment of invasive amoebiasis. Metronidazole is given in oral doses of 400 to 800 mg three times daily for 5 to 10 days. Children aged 1 to 3 years may be given one-quarter, those aged 3 to 7 years one-third, and those aged 7 to 10 years one-half the total adult daily dose; alternatively 35 to 50 mg/kg daily in divided doses has been used. An alternative adult dose is 1.5 to 2.5 g as a single daily dose for 2 or 3 days.

In **balantidiasis** and ***Blastocystis hominis* infection**, metronidazole has been given orally in a dose of 750 mg three times daily for 5 and 10 days, respectively.

In **giardiasis**, the usual oral dose of metronidazole is 2 g once daily for 3 successive days, or 400 mg three times daily for 5 days, or 500 mg twice daily for 7 to 10

days. Dosage for children is proportional, as for amoebiasis (above). An alternative schedule for children is 15 mg/kg daily in divided doses.

In **trichomoniasis**, metronidazole is given orally either as a single 2-g dose, as a 2-day course of 800 mg in the morning and 1.2 g in the evening, or as a 7-day course of 600 mg to 1 g daily in two or three divided doses. Sexual partners should also be treated. If treatment needs to be repeated, an interval of 4 to 6 weeks between courses has been recommended. Vaginal preparations containing metronidazole are available for the treatment of vaginal trichomoniasis in some countries. Children with trichomoniasis may be given a 7-day course of metronidazole by mouth as follows: 1 to 3 years, 50 mg three times daily; 3 to 7 years, 100 mg twice daily, and 7 to 10 years, 100 mg three times daily. An alternative children's dose is 15 mg/kg daily in 3 divided doses for 7 days.

Bacterial vaginosis is treated similarly to vaginal trichomoniasis with which it may co-exist; metronidazole is usually given orally as a single 2-g dose or as a 5 to 7-day course of 400 or 500 mg twice daily. Alternatively it may be applied locally as 5 g of a 0.75% gel once or twice daily for 5 days.

In **acute necrotising ulcerative gingivitis**, metronidazole 200 mg three times daily is given orally for 3 days; similar doses are used in acute dental infections. A 25% dental gel has also been used as an adjunct to the treatment of chronic periodontal infections.

For the treatment of most **anaerobic bacterial infections**, metronidazole is given orally in an initial dose of 800 mg followed by 400 mg every 8 hours, usually for about 7 days. A regimen of 500 mg every 8 hours is alternatively used. When oral therapy is precluded metronidazole may be given intravenously, 500 mg being infused as 100 mL of a 5 mg/mL solution at a rate of 5 mL/minute every 8 hours, or rectally as a 1-g suppository every 8 hours for 3 days, then every 12 hours; oral therapy should be substituted as soon as possible. Suppositories may be unsuitable for beginning therapy in serious infections because of the slower absorption of metronidazole. Children may be given 7.5 mg/kg every 8 hours by mouth or by intravenous infusion; recommended rectal doses for children, to be given every 8 hours for 3 days, then every 12 hours thereafter, are: for those aged under 1 year, 125 mg; 1 to 5 years, 250 mg; 5 to 10 years, 500 mg. In the USA recommended adult doses of metronidazole are 7.5 mg/kg every 6 hours by mouth or 15 mg/kg by intravenous infusion followed by 7.5 mg/kg every 6 hours, doses being infused over 1 hour; by either route a total dose of 4 g in 24 hours should not be exceeded. In mixed anaerobic and aerobic infections metronidazole is given with the appropriate antibacterials.

For the **prevention of postoperative anaerobic bacterial infections**, especially in patients undergoing abdominal or gynaecological surgery, metronidazole is given orally, intravenously, or rectally in doses similar to those used for treatment, usually with a beta-lactam or an aminoglycoside antibacterial. Various schedules have been employed. In the UK, licensed doses for adults are:

- orally 400 mg every 8 hours in the 24 hours before surgery followed postoperatively by intravenous or rectal dosage until oral therapy is possible
- by intravenous infusion, 500 mg shortly before operation and repeated every 8 hours, oral doses of 200 or 400 mg every 8 hours being substituted as soon as possible
- by rectum, 1 g every 8 hours starting 2 hours before surgery.

The *BNF*, however, recommends that oral doses should be started only 2 hours before the operation and that the number of doses for all dose routes be limited to a total of four. In the USA the recommended schedule for adults undergoing colorectal surgery is metronidazole 15 mg/kg by intravenous infusion over 30 to 60 minutes, completed about 1 hour before surgery, followed by two further intravenous doses of 7.5 mg/kg infused at 6 and 12 hours after the initial dose.

In **peptic ulcer disease**, metronidazole is used in combination therapy to eradicate *Helicobacter pylori*. Typical regimens include metronidazole plus another antibacterial (clarithromycin or amoxicillin) given with either a proton pump inhibitor (omeprazole or lansoprazole) or with ranitidine bismuth citrate. The usual dose of metronidazole is 400 mg twice daily except when given with omeprazole and amoxicillin, when metronidazole 400 mg three times daily is used. Treatment is continued for 1 week.

For **leg ulcers** and **pressure sores** infected with anaerobic bacteria, oral metronidazole 400 mg may be given three times daily for 7 days. Metronidazole is also applied topically as a 0.75% or 0.8% gel to reduce the odour associated with anaerobic infection in **fungating tumours**.

In the treatment of **rosacea** metronidazole is given orally or applied topically.

Administration in hepatic impairment. Since metronidazole is mainly metabolised by hepatic oxidation, accumulation of metronidazole and its metabolites is likely in patients with severely impaired hepatic function. Metronidazole should therefore be given with caution and at reduced doses to patients with severe hepatic impairment, and especially hepatic encephalopathy when adverse affects of metronidazole can add to the symptoms of the disease. One-third of the usual daily dose may be given once daily in these patients. For patients with lesser degrees of hepatic impairment, pharmacokinetic studies have not produced consistent results (see under Pharmacokinetics, above) and no recommendations about dosage reduction have been made by licensed product information.

Administration in renal impairment. The elimination of metronidazole is largely unchanged in patients with renal impairment, although metabolites may accumulate in patients with end-stage renal disease on dialysis (see under Pharmacokinetics, above). Dosage reductions are therefore not usually recommended for patients with renal impairment although, since both metronidazole and its metabolites are removed by haemodialysis, doses need to be given immediately after haemodialysis.

Dracunculiasis. Metronidazole may be beneficial in the management of dracunculiasis (p.136). It provides symptomatic relief and is also thought to weaken the anchorage of the worms within subcutaneous tissue, thus allowing them to be removed more quickly.

Metronidazole has been given in a variety of regimens, including doses of 400 mg three times daily for 5 days,[1] 40 mg/kg daily in three divided doses (to a maximum daily dose of 2.4 g) for 3 days,[2] and 400 mg daily for 10 to 20 days.[3] WHO recommends 25 mg/kg daily for 10 days;[4] a dose of 250 mg three times daily for 10 days has also been recommended.

1. Padonu KO. A controlled trial of metronidazole in the treatment of dracontiasis in Nigeria. *Am J Trop Med Hyg* 1973; **22:** 42–4.
2. Kale OO. A controlled field trial of the treatment of dracontiasis with metronidazole and niridazole. *Ann Trop Med Parasitol* 1974; **68:** 91–5.
3. Muller R. Guinea worm disease: epidemiology, control, and treatment. *Bull WHO* 1979; **57:** 683–9.
4. WHO. *WHO model formulary.* Geneva: WHO, 2004.

Hepatic encephalopathy. The treatment of hepatic encephalopathy is discussed on p.1697. It includes the use of an antimicrobial such as metronidazole to reduce the intestinal flora.

Inflammatory bowel disease. Metronidazole is used in the treatment of perineal Crohn's disease (see Inflammatory Bowel Disease, p.1697) and may also be used in colonic Crohn's disease, when it has been tried with ciprofloxacin. It has also proved effective for the prevention of postsurgical recurrence. Duration of therapy is usually limited to 3 months.

References.

1. Bernstein LH, *et al.* Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980; **79:** 357–65.
2. Brandt LJ, *et al.* Metronidazole therapy for perineal Crohn's disease: a follow-up study. *Gastroenterology* 1982; **83:** 383–7.
3. Ursing B, *et al.* A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. *Gastroenterology* 1982; **83:** 550–62.
4. Sutherland L, *et al.* Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991; **32:** 1071–5.
5. Rutgeerts P, *et al.* Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995; **108:** 1617–21.
6. Prantera C, *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91:** 328–32.

Metabolic disorders. Children with excesses of methylmalonic[1,2] and propionic[3] acid in their blood or urine have shown clinical improvement when given metronidazole, which reduced the excretion of faecal propionate and urinary methylmalonate. Metronidazole is considered to act through its antimicrobial effect on gut anaerobes that are involved in propionate production; such propionate cannot be handled by these children who are deficient in the relevant enzyme.

1. Bain MD, *et al.* Contribution of gut bacterial metabolism to human metabolic disease. *Lancet* 1988; **i:** 1078–9.
2. Koletzko B, *et al.* Antibiotic therapy for improvement of metabolic control in methylmalonic aciduria. *J Pediatr* 1990; **117:** 99–101.
3. Mellon AF, *et al.* Effect of oral antibiotics on intestinal production of propionic acid. *Arch Dis Child* 2000; **82:** 169–72.

Mouth disorders and infections. Ciclosporin-induced gingival hyperplasia resolved in 4 patients after treatment with metronidazole.[1]

Metronidazole is considered to be effective for the treatment of acute necrotising ulcerative gingivitis and is an alternative to penicillin in other dental infections (see Mouth Infections, p.180).

1. Wong W, *et al.* Resolution of cyclosporin-induced gingival hypertrophy with metronidazole. *Lancet* 1994; **343:** 986.

Peptic ulcer disease. The use of metronidazole is well established in regimens for eradicating *Helicobacter pylori* (see Peptic Ulcer Disease, p.1702). However, the emergence of metronidazole-resistant strains of *H. pylori* has been associated with an increased rate of treatment failures with some regimens.[1-4] Difficulties arise in assessing metronidazole resistance and in correlating *in-vitro* results with clinical response.[5] In populations in which the incidence of resistance is high, it may become necessary to use alternative regimens,[6] but in other areas, such as the UK, regimens including metronidazole continue to be among the standard alternatives (although the *BNF* recommends that they should not be used for initial treatment in patients who have been given metronidazole for other infections).

1. Buckley MJM, *et al.* Metronidazole resistance reduces efficacy of triple therapy and leads to secondary clarithromycin resistance. *Dig Dis Sci* 1997; **42:** 2111–15.
2. Lerang F, *et al.* Highly effective twice-daily triple therapies for Helicobacter pylori infection and peptic ulcer disease: does in vitro metronidazole resistance have any clinical relevance? *Am J Gastroenterol* 1997; **92:** 248–53.
3. Misiewicz JJ, *et al.* One week triple therapy for Helicobacter pylori: a multicentre comparative study. *Gut* 1997; **41:** 735–9.
4. van Zanten SV, *et al.* Adding once-daily omeprazole 20 mg to metronidazole/amoxicillin treatment for Helicobacter pylori gastritis: a randomized, double-blind trial showing the importance of metronidazole resistance. *Am J Gastroenterol* 1998; **93:** 5–10.
5. Goddard AF, Logan RPH. Antimicrobial resistance and Helicobacter pylori. *J Antimicrob Chemother* 1996; **37:** 639–43.
6. Fennerty MB. Should we abandon metronidazole containing Helicobacter pylori treatment regimens? The clinical relevance of metronidazole resistance. *Am J Gastroenterol* 1998; **93:** 2–3.

Skin disorders. Metronidazole may be effective in the management of malodorous anaerobic skin infections associated with ulceration (p.194), including *pressure sores* and *fungating tumours*. Both the oral and topical routes have been employed but the evidence in favour of its use is largely anecdotal as few randomised controlled studies have yet been performed.[1,2]

Metronidazole has also been used[3] in the treatment of *rosacea* (p.1583). Metronidazole 200 mg twice daily by mouth was more effective than placebo[4] and as effective as oral oxytetracycline.[5] Similarly, topical preparations (for example, 0.75% cream, gel, or lotion or 1% cream) have been found to be better than placebo and as effective as oral oxytetracycline.[6,7]

1. Clark J. Metronidazole gel in managing malodorous fungating wounds. *Br J Nurs* 2002 **11** (suppl): S54–S60.
2. Paul JC, Pieper BA. Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy Wound Manage* 2008; **54:** 18–27.
3. Conde JF, *et al.* Managing rosacea: a review of the use of metronidazole alone and in combination with oral antibiotics. *J Drugs Dermatol* 2007; **6:** 495–8.
4. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet* 1976; **i:** 1211–12.
5. Saihan EM, Burton JL. A double-blind trial of metronidazole versus oxytetracycline therapy for rosacea. *Br J Dermatol* 1980; **102:** 443–5.
6. McClellan KJ, Noble S. Topical metronidazole: a review of its use in rosacea. *Am J Clin Dermatol* 2000; **1:** 191–9.
7. Dahl MV, *et al.* Once-daily topical metronidazole cream formulations in the treatment of the papules and pustules of rosacea. *J Am Acad Dermatol* 2001; **45:** 723–30.

Surgical infection. Metronidazole and related nitroimidazoles are used in surgical infection prophylaxis (p.195) to reduce the rate of wound infection.

Haemorrhoidectomy. Prophylactic metronidazole reduced pain following haemorrhoidectomy in a small study.[1]

1. Carapeti EA, *et al.* Double-blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy. *Lancet* 1998; **351:** 169–72.

African trypanosomiasis. Although there is no established alternative treatment for *Trypanosoma brucei rhodesiense* infections that are resistant to melarsoprol (see p.827), metronidazole and suramin were effective in 1 patient.[1]

1. Foulkes JR. Metronidazole and suramin combination in the treatment of arsenical refractory rhodesian sleeping sickness—a case study. *Trans R Soc Trop Med Hyg* 1996; **90:** 422.

Preparations

BP 2008: Metronidazole Gel; Metronidazole Intravenous Infusion; Metronidazole Oral Suspension; Metronidazole Suppositories; Metronidazole Tablets;

USP 31: Metronidazole Gel; Metronidazole Injection; Metronidazole Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Bexon; Colpofilin; Dazotron; Epaq†; Etronil; Flagyl; Format; Ginkan; Gynotran; Metral; Metrocev; Metrolocal; Nalox; Noritate†; Padet; Repligen; Rozex; Taremis; Tolbin; Tricofin; Trimstat†; ***Austral.:*** Flagyl; Metrogyl; Metronide; Rozex; ***Austria:*** Acsacea; Anaerobex; Elyzol; Rozex; Trichex; ***Belg.:*** Anaeromet†; Flagyl; Pharmaflex†; Rosaced; Rozex; ***Braz.:*** Ambrosil†; Amebil†; Astergyl†; Canderm; Dalzolston; Flagyl; Flanizol; Helmizol; Metrizol†; Metrodax†; Metrogyl†; Metronib†; Metronide; Metroniflex; Metronil; Metronin; Metronix; Metrotix†; Metroval; Metrozol; Minegyl†; Neo Metrodazol; Odonid; Rozex; ***Canad.:*** Flagyl; Florazole; Metrocream; Metrogel; Metrolotion; NidaGel; Noritate; Novo-Nidazol†; Trikacide; ***Chile:*** Deprocid; Flagyl; Geloderm; Kabizol; Medazol; Metrocream; Metrogel; Metropast; Noritate†; ***Cz.:*** Deflamon†; Efloran; Entizol; Klion†; Medazol†; Rosalox; Rozex; ***Denm.:*** Elyzol; Flagyl; Metrogel†; Rozex; Zidoval; ***Fin.:*** Elyzol; Flagyl; Rosazol; Rozex; Trikozol; Zidoval; ***Fr.:*** Elyzol; Flagyl; Rosiced; Rozacreme; Rozagel; Rozex; ***Ger.:*** Arilin; Clont; Elyzol; Flagyl; Fossyol†; Infectoclont; Metrocreme; Metrogel; Metronid-Puren†; Metronimerck; Metronour; Metront†; Rosiced; Vagimid; ***Gr.:*** Colpocin-T; Elyzol Dental; Emedal; Flagolin; Flagyl; Gnostol; Metrazol; Metrogyl; Periotret; Robaz; Rosiced; Trichovagil; Tricodazole; Unitrim; ***Hong Kong:*** Elyzol; Flagyl; Gynoplix; Marphazole; Metole; Metrogyl; Noritate; Qualigyl; Rozex; Unigo; ***Hung.:*** Klion; Rozex; Supplin; ***India:*** Aristogyl; Flagyl; Giardyl†; Metrogyl; Monizole; Unimezol†; ***Indon.:*** Anmerob; Biatron; Corsagyl; Dumozol; Farnat; Fladex; Flagyl; Flametia; Fortagyl; Metrofusin; Molazol; Nidazole; Promuba; Supplin; Tismazol; Trichodazol; Trogiar; Trogyl; Vagizol; ***Irl.:*** Anabact†; Flagyl; Metronide; Metrotop; Rozex; ***Israel:*** Elyzol; Flagyl; Metrogyl; Noritate; Rozex; Venogyl; Zidoval; ***Ital.:*** Deflamon; Elyzol; Flagyl; Rosased†; Rozex; Vagilen; Zidoval; ***Malaysia:*** Flagyl; Frotin; Protogyl†; Ranigyl†; Rozex; Setrozole†; ***Mex.:*** Ameblin; Antral†; Biomona; Biotazol; Dasmetrol; Dualizol; Elyzol; Epaq; Fagizol; Fartricon; Flagenase; Flagenol; Flagepat; Flagyl; Flamin†; Flaxtec; Fresenizol; Hemestal; Lagylan; Lamblit; Lozad; Medazol; Medizol; Messeldazol; Metosan†; Metricom; Metrizol; Metrobendizol; Metrocream; Metrogel; Metroson; Milezzol; Nidralon-V; Nidrozol; Nitromidager; Ortrizol; Otrozol; Ovazol-V; Planizol; Promibasol; Prozolin; Retofar†; Samonil; Selegil†; Servizol; Solumidazol; Stomffler; Valpar; Vanestrin-V; Vertisal; ***Neth.:*** Flagyl; Metrogel; Rosiced; Rozex; ***Norw.:*** Elyzol; Flagyl; Rozex; Zidoval; ***NZ:*** Flagyl; Rozex; Trichozole; ***Philipp.:*** Ameryl; Anerobia; Flagyl; Metrinox; Metrodal; Norstene; Patryl; Robaz; Rodazid; Servizol; Tricomycin; Triconex; Tridel; Vamogyl; Zol; ***Pol.:*** Metrosept; Rozex; ***Port.:*** Dumozol; Flagyl; Metroderme; Norstene; Rodermil; Roseless; Rosiced; ***Rus.:*** Efloran (Эфлоран); Flagyl (Флагил); Klion (Клион); Metrogyl (Метрогил); Metroseptol (Метросептол); Rosamet (Розамет); Trichopol (Трихопол); ***S.Afr.:*** Bemetrazole; Flagyl; Medamet; Metagyl†; Metazol; Metrazole; Metrostat; Narobic; Rozex; Trichazole; Zagyl; Zobacide; ***Singapore:*** Fladex; Flagyl; Medazole; Metrozole†; MND†; Nizole; Rozex; ***Spain:*** Amotein; Flagyl; Rozex; Tricowas B; Zidoval; ***Swed.:*** Elyzol†; Flagyl; Rozex; Zidoval; ***Switz.:*** Arilin; Elyzol; Flagyl; Metrolag; Perilox; Rivozol†; Rosalox; Rozex; ***Thai.:*** Asiazole; Biogyl; Elyzol†; Flagyl; Med-Tricocide†; Medazyl†; Mefiron; Menisole; Mepagyl†; Mesolex†; Metrazole; Metrocide; Metrogyl; Metrolex; Metrovid; Milanidazole; Robaz; Tricomed; Unigo; Vagil†; Vagyl; ***Turk.:*** Flagyl; Metrajil; Metrazol; Metrosel; Nidazol; Roza; ***UAE:*** Negazole; ***UK:*** Acea; Anabact; Elyzol; Flagyl; Metrogel; Metrolyl; Metrosa; Metrotop; Metrozol; Noritate; Norzol; Rozex; Vaginyl; Zidoval; Zyomet; ***USA:*** Flagyl; Metrocream; Metrogel; Metrogel Vaginal; Noritate; Protostat; Vandazole; ***Venez.:*** Bactrizol; Flegyl; Menizol; Metren; Metris; Metrogyl; Metrovax; Rozek.

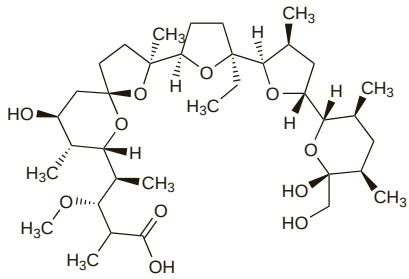
Multi-ingredient: ***Arg.:*** Bexon; Ciprocort; Estilomicin; Farm-X Duo; Farm-X Ginecologico; Flagystatin; Ginal Cent; Ginkan; Linfol; Linfol Cicatrizante; Mailen; Monizol Cort; Naxo TV; Neocolpoben†; Ovumix; Pelvicillin NF; Pentol; Septigyn; Tratomax; Vagicural Plus; ***Austral.:*** Somac-MA; ***Austria:*** Helicocin; ***Braz.:*** Bio-Vagin; Colpatrin; Colpist; Colpistar; Colpistatin; Donnagel; Flagyl Nistatina; Fungimax; Ginestatin; Minegyl C/Nistatina†; Nistazol†; Periodontil; Profargil†; Tricolpex; Tricomax; Vagi Biotic; Vagimax; ***Canad.:*** Flagystatin; Losec 1-2-3 M; Rosasol; ***Cz.:*** Klion-D; Rodogyl†; ***Fin.:*** Flagyl Comp; Helipak A; Helipak T; Losec Heliral†; ***Fr.:*** Birodogyl; Missilor; Rodogyl; Tergynan; ***Hung.:*** Klion-D; ***India:*** Aristogyl Plus; Aristogyl-F; Bacigyl-N†; Dyrade-M; Dysfur-M†; Entamizole; Flagyl-F†; Kaltin MF; Metrogyl-F†; Neocip M; NM Powder; Okaflox M; Powergyl; Qugyl; ***Indon.:*** Fladystin; Flagystatin; Trichostatic; Vagistin; ***Ital.:*** Meclon; ***Malaysia:*** Neo-Penotran; Rodogyl; ***Mex.:*** Acenil; Amebyl; Diodolina; Eskapar Compuesto; Flagenase 400; Flagocil; Flagystatin V; Gynotran; Lambliquin; Madecassol C; Metodine; Metrodiyod; Metrofur; Metroviform†; Norecil; Nysmosons-V; Promibasol-Plus; Rodogyl; Stomffler Plus; Vagitrol-V; ***Philipp.:*** Flagystatin; Neo-Penotran; ***Pol.:*** Gynalgin; ***Rus.:*** Gynalgin (Гиналгин); Klion-D (Клион-Д); Metrogyl Denta (Метрогил Дента); Metrogyl Plus (Метрогил Плюс); Neo-Penotran (Нео-Пенотран); ***Singapore:*** Flagystatin; Neo-Penotran; ***Spain:*** Blastoestimulina; Rhodogil; ***Turk.:*** Neo-Penotran; Nidazol-M; ***UK:*** HeliMet†; ***USA:*** Helidac; Pylera.

Monensin *(BAN, USAN, rINN)*

Lilly-67314; Monensina; Monensinum. 4-{2-[2-Ethyl-3′-methyl-5′-(tetrahydro-6-hydroxy-6-hydroxymethyl-3,5-dimethylpyran-2-yl)perhydro-2,2′-bifuran-5-yl]-9-hydroxy-2,8-dimethyl-1,6-dioxaspiro[4.5]dec-7-yl}3-methoxy-2-methylpentanoic acid.

Монензин

$C_{36}H_{62}O_{11}$ = 670.9.
CAS — 17090-79-8.
ATC Vet — QP51AH03.



Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Monensin). A mixture of antibiotic substances produced by *Streptomyces cinnamonensis*.

Monensin Sodium *(BANM, rINNM)*

Monensin Sodique; Monensina sódica; Natrii Monensinum.

Натрий Монензин

$C_{36}H_{61}NaO_{11}$ = 692.9.
CAS — 22373-78-0.

Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Monensin Sodium). An off-white to tan crystalline powder. Slightly soluble in water; soluble in chloroform and in methyl alcohol; practically insoluble in petroleum spirit. Avoid moisture and excessive heat.

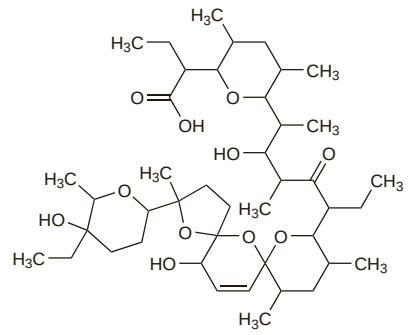
Profile
Monensin is an antiprotozoal used as the sodium salt in veterinary practice for the prevention of coccidiosis in poultry and as a growth promotor for cattle.

Narasin *(BAN, USAN, rINN)*

Compound 79891; Lilly-79891; Narasina; Narasine; Narasinum. 2-(6-{5-[2-(5-Ethyltetrahydro-5-hydroxy-6-methylpyran-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl}tetrahydro-3,5-dimethylpyran-2-yl)butyric acid.

Наразин

$C_{43}H_{72}O_{11}$ = 765.0.
CAS — 55134-13-9.
ATC Vet — QP51AH04.



Pharmacopoeias. In *US* for veterinary use only.
USP 31 (Narasin Granular). It contains narasin mixed with suitable carriers and inactive ingredients prepared in a granular form that is free-flowing and free of aggregates. Narasin is a white to off-white crystalline powder. Soluble in water and in methyl alcohol.

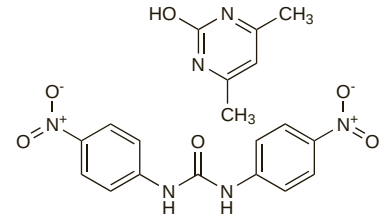
Profile
Narasin, an antibiotic produced by *Streptomyces aureofaciens*, is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in chickens.

Nicarbazin *(BAN)*

Nicarbazina. An equimolecular complex of 1,3-bis(4-nitrophenyl)urea ($C_{13}H_{10}N_4O_5$) and 4,6-dimethylpyrimidin-2-ol ($C_6H_8N_2O$).

Никарбазин

$C_{19}H_{18}N_6O_6$ = 426.4.
CAS — 330-95-0.
ATC Vet — QP51AE03.



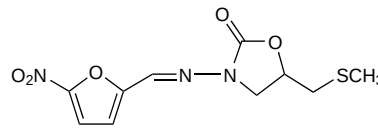
Profile
Nicarbazin is an antiprotozoal used in veterinary practice for the prevention of coccidiosis in poultry.

Nifuratel *(BAN, USAN, rINN)*

Methylmercadone; Nifurateeli; Nifuratelum. 5-Methylthiomethyl-3-(5-nitrofurfurylideneamino)-2-oxazolidone.

Нифурател

$C_{10}H_{11}N_3O_5S$ = 285.3.
CAS — 4936-47-4.
ATC — G01AX05.
ATC Vet — QG01AX05.



Adverse Effects
Adverse effects associated with nifuratel include gastrointestinal disturbances, peripheral neuropathy, and thrombocytopenic purpura. Allergic reactions, hepatotoxicity, blood dyscrasias, and pulmonary reactions similar to those seen with the structurally related drug nitrofurantoin have been reported rarely. Haemolytic anaemia may occur in patients with G6PD deficiency given nifuratel.

Hypersensitivity. There have been several reports of contact dermatitis associated with nifuratel, including a report after only one application of nifuratel ointment in a man whose wife was undergoing treatment with nifuratel vaginal pessaries.[1]

1. Bedello PG, *et al*. Contact dermatitis from nifuratel. *Contact Dermatitis* 1983; **9:** 166.

Precautions
Nifuratel should not be given to patients with renal impairment, neuropathies, or G6PD deficiency.

Interactions
A disulfiram-like reaction may occur in patients taking alcohol while on nifuratel therapy.

Pharmacokinetics
When taken orally nifuratel is absorbed from the gastrointestinal tract. A metabolite, with activity against bacteria but not against trichomonads, is excreted in the urine.

Uses and Administration
Nifuratel is a nitrofuran derivative with a broad antimicrobial spectrum. It is active against the protozoan *Trichomonas vaginalis* and has an antibacterial spectrum similar to that of nitrofurantoin and some antifungal activity against *Candida albicans*. Although other drugs are preferred, nifuratel has been used to treat susceptible infections of the genito-urinary tract in oral doses of 200 to 400 mg three times daily. It has also been given vaginally.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Macmiror; ***Cz.:*** Macmiror; ***Ger.:*** Inimur; ***Hong Kong:*** Macmiror; ***Ital.:*** Macmiror; ***Mex.:*** Macmiror; ***Pol.:*** Macmiror; ***Rus.:*** Macmiror (Макмирор).

Multi-ingredient: ***Cz.:*** Macmiror Complex; ***Hong Kong:*** Macmiror Complex; ***Ital.:*** Macmiror Complex; ***Mex.:*** Macmiror Complex V; ***Pol.:*** Macmiror Complex; ***Port.:*** Dafnegil; ***Rus.:*** Macmiror Complex (Макмирор Комплекс).