ataxia, confusion, disorientation, dizziness, euphoria, dysphoria, hallucinations, psychosis, depression, headache, decreased concentration, blurred vision, sleep disturbances, decreased coordination, and tremors. Adverse cardiovascular reactions including hypotension, orthostatic hypotension, and tachycardia have occurred. Gastrointestinal disturbances, decreased appetite, and abdominal pain have also been reported.

Precautions
Nabilone is extensively metabolised and largely excreted in bile, and therefore is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with a history of psychiatric disorders or depression, or those with hypertension or heart disease.

Because of the possibility of CNS depression, patients should be warned not to drive or operate machinery.

The possibility of dependence similar to that of cannabis should be borne in mind.

Interactions
Nabilone has been shown to have an additive CNS depressant effect when given with alcohol, codeine, diazepam, or other CNS depressants.

Pharmacokinetics
Nabilone is well absorbed from the gastrointestinal tract and is rapidly and extensively metabolised; one or more of the metabolites may be active. The major excretory pathway is the biliary system; about 65% of a dose is excreted in the faeces and about 20% in the urine. The elimination half-life of nabilone is about 2 hours, but the half-life of its combined metabolites is about 35 hours after an oral dose.

◊ References.

1. Rubin A, *et al.* Physiologic disposition of nabilone, a cannabinol derivative, in man. *Clin Pharmacol Ther* 1977; **22:** 85–91.

Uses and Administration
Nabilone, a synthetic cannabinoid with antiemetic properties, is used for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetics (p.1700).

The usual initial oral dose for adults is 1 mg twice daily, increased to 2 mg twice daily if necessary. The first dose should be given the evening before starting chemotherapy, and the second dose 1 to 3 hours before the first dose of antineoplastic. Nabilone may be given throughout each cycle of chemotherapy and for 48 hours after the last dose of chemotherapy, if required. The dose of nabilone should not exceed 6 mg daily, given in 3 divided doses.

◊ Reviews.

1. Tramer MR, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 2001; **323:** 16–21.
2. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Invest Drugs* 2008; **17:** 85–95.

Multiple sclerosis. There is a report of reduction in spasticity and nocturia, and improvement in mood and well-being, in a patient with multiple sclerosis (p.892) who received nabilone 1 mg every second day.[1] A subsequent small crossover study[2] in patients with chronic upper motor neurone syndrome found that oral nabilone 1 mg daily reduced spasticity-related pain in this group. There are also anecdotal reports of improvement in symptoms in patients with multiple sclerosis who took cannabis, however, a review[3] considered evidence of effectiveness to be lacking.

1. Martyn CN, *et al.* Nabilone in the treatment of multiple sclerosis. *Lancet* 1995; **345:** 579.
2. Wissel J, *et al.* Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *J Neurol* 2006; **253:** 1337–41.
3. Killestein J, *et al.* Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs* 2004; **64:** 1–11.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Cesamet; ***Canad.:*** Cesamet; ***Irl.:*** Cesamet†; ***USA:*** Cesamet.

Niperotidine Hydrochloride *(rINNM)*

Hidrocloruro de niperotidina; Nipérotidine, Chlorhydrate de; Niperotidini Hydrochloridum; Piperonyl Ranitidine Hydrochloride. *N*-[2-({5-[(Dimethylamino)methyl]furfuryl}thio)ethyl]-2-nitro-*N*′-piperonyl-1,1-ethenediamine hydrochloride.

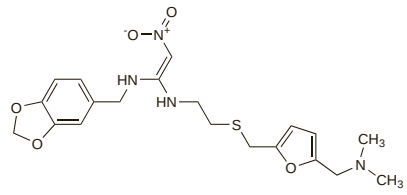
Ниперотидина Гидрохлорид

$C_{20}H_{26}N_4O_5S,HCl$ = 471.0.

CAS — 84845-75-0 (niperotidine).

ATC — A02BA05.

ATC Vet — QA02BA05.



(niperotidine)

Profile
Niperotidine hydrochloride is a histamine H_2-receptor antagonist with general properties similar to those of cimetidine (p.1716). Severe hepatic disorders have occurred in patients receiving niperotidine.

◊ References.

1. Gasbarrini G, *et al.* Acute liver injury related to the use of niperotidine. *J Hepatol* 1997; **27:** 583–6.

Nizatidine *(BAN, USAN, rINN)*

LY-139037; Nitsatidiini; Nizatidin; Nizatidina; Nizatidinas; Nizatidinum; ZL-101. 4-[2-(1-Methylamino-2-nitrovinylamino)ethylthiomethyl]thiazol-2-ylmethyl(dimethyl)amine; *N*-[2-(2-Dimethylaminomethylthiazol-4-ylmethylthio)ethyl]-*N*′-methyl-2-nitrovinylidenediamine.

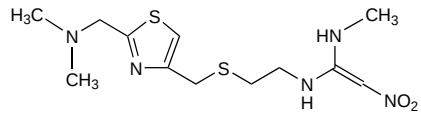
Низатидин

$C_{12}H_{21}N_5O_2S_2$ = 331.5.

CAS — 76963-41-2.

ATC — A02BA04.

ATC Vet — QA02BA04.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Nizatidine). An almost white or slightly brownish, crystalline powder. Sparingly soluble in water; soluble in methyl alcohol. A 1% solution in water has a pH of 8.5 to 10.0.
USP 31 (Nizatidine). An off-white to buff crystalline solid. Sparingly soluble in water; freely soluble in chloroform; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Adverse Effects
As for Cimetidine, p.1716. Some patients taking nizatidine may experience excessive sweating and urticaria; anaemia may also occur.

Nizatidine is considered to have little or no anti-androgenic activity although there are isolated reports of gynaecomastia and impotence.

Effects on the cardiovascular system. Nizatidine has been reported to reduce heart rate in healthy subjects,[1,2] an effect that was not seen when they were pretreated with ranitidine[1] or also given the antimuscarinic pirenzepine.[2] As with other H_2-antagonists (see Cimetidine, p.1717), tachycardia, bradycardia, orthostatic hypotension and syncope have been reported rarely with rapid intravenous injection of nizatidine.

1. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
2. Hinrichsen H, *et al.* Dose-dependent heart rate reducing effect of nizatidine, a histamine H -receptor antagonist. *Br J Clin Pharmacol* 1993; **35:** 461–6.

Effects on the endocrine system. A report of reversible impotence in a patient taking nizatidine 300 mg at night.[1]

1. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **i:** 963.

Effects on the skin. Similarly to cimetidine (p.1717), vasculitis has been reported with nizatidine.[1] Exfoliative dermatitis has also occurred.

1. Suh J-G, *et al.* Leukocytoclastic vasculitis associated with nizatidine therapy. *Am J Med* 1997; **102:** 216–17.

Precautions
As for Cimetidine, p.1718.

Interactions
Unlike cimetidine (p.1718) nizatidine does not inhibit cytochrome P450, and therefore is considered to have little effect on the metabolism of other drugs. However, like other H_2-antagonists its effects on gastric pH may affect the absorption of some other drugs.

Pharmacokinetics
Nizatidine is readily and almost completely absorbed from the gastrointestinal tract. The bioavailability of nizatidine after oral doses exceeds 70% and may be slightly increased by the presence of food. It is widely distributed and is about 35% bound to plasma proteins.

The elimination half-life of nizatidine is 1 to 2 hours and is prolonged in renal impairment. Nizatidine is partly metabolised in the liver: nizatidine *N*-2-oxide, nizatidine *S*-oxide, and *N*-2-monodesmethylnizatidine have been identified, the latter having about 60% of the activity of nizatidine.

More than 90% of a dose of nizatidine is excreted in the urine, in part by active tubular secretion, within 12 hours, about 60% as unchanged drug. Less than 6% is excreted in the faeces. Nizatidine is distributed into breast milk.

◊ References.

1. Callaghan JT, *et al.* A pharmacokinetic profile of nizatidine in man. *Scand J Gastroenterol* 1987; **22** (suppl 136): 9–17.
2. Abdel-Rahman SM, *et al.* Single-dose pharmacokinetics of nizatidine (Axid) in children. *J Clin Pharmacol* 2002; **42:** 1089–96.
3. Blum RA, *et al.* Pharmacokinetics and pharmacodynamics of a novel nizatidine controlled-release formulation in healthy subjects. *J Clin Pharmacol* 2003; **43:** 74–83.

Bioavailability. The bioequivalence of 3 oral liquid formulations of nizatidine was investigated relative to a commercially available nizatidine capsule. Of the 3 liquid formulations, one was a commercially available oral syrup (15 mg/mL), and 2 others were extemporaneously prepared, one as a solution in apple juice (1.2 mg/mL) and another as a suspension in an infant formula (*Enfamil; Ross, USA*; 15 mg/mL). Nizatidine in apple juice showed markedly less bioavailability, whereas the other 2 formulations were considered to be bioequivalent to the reference capsule.[1]

1. Abdel-Rahman SM, *et al.* The bioequivalence of nizatidine (Axid) in two extemporaneously and one commercially prepared oral liquid formulations compared with capsule. *J Clin Pharmacol* 2003; **43:** 148–53.

Distribution into breast milk. About 0.1% of an oral dose of nizatidine was secreted in breast milk in a study in lactating women.[1] The milk to serum ratio varied (from 1:1 to 4.9:1) with the time of samples.

1. Obermeyer BD, *et al.* Secretion of nizatidine into human breast milk after single and multiple doses. *Clin Pharmacol Ther* 1990; **47:** 724–30.

Uses and Administration
Nizatidine is a histamine H_2-antagonist with actions and uses similar to those of cimetidine (see p.1719). It is given orally and by intravenous infusion.

In the management of benign **gastric** and **duodenal ulceration** (p.1702) a single daily oral dose of nizatidine 300 mg at night is recommended, which should be given initially for 4 weeks and may be extended to 8 weeks if necessary; alternatively 150 mg may be given twice daily in the morning and evening. Where appropriate a maintenance dose of 150 mg daily may be given at night. In patients who are unsuited to receive oral therapy nizatidine may be given on a short-term basis by continuous intravenous infusion of 10 mg/hour; alternatively 100 mg may be diluted in 50 mL of infusion fluid and be given over 15 minutes, three times daily. The total intravenous dose should not exceed 480 mg daily.

In **gastro-oesophageal reflux disease** (p.1696) an oral dose of 150 to 300 mg twice daily is recommended for up to 12 weeks. In children aged 12 years and older, a dose of 150 mg twice daily may be given for up to 8 weeks.

For the short-term symptomatic relief of **dyspepsia** a dose of 75 mg, repeated if necessary, up to a maximum of 150 mg daily may be taken by mouth for up to 14 days.

Doses of nizatidine should be reduced in patients with renal impairment (see below).

Administration in renal impairment. The dosage of nizatidine should be reduced in patients with renal impairment accord-

ing to creatinine clearance (CC). Licensed product information recommends the following oral doses in renal impairment:

- CC 20 to 50 mL/minute: doses should be reduced by 50%, *or* where the standard dose would be 150 mg daily, 150 mg may be given on alternate days
- CC less than 20 mL/minute: doses should be reduced by 75%, *or* where the standard dose would be 300 mg daily, 150 mg may be given on alternate days, and where the standard dose would be 150 mg daily, 150 mg may be given every third day

Preparations

BP 2008: Nizatidine Intravenous Infusion;
USP 31: Nizatidine Capsules.

Proprietary Preparations (details are given in Part 3)

Austral.: Nizac; Tacidine; Tazac; ***Austria:*** Ulxit; ***Belg.:*** Panaxid†; ***Braz.:*** Axid; ***Canad.:*** Axid; ***Chile:*** Nizaxid; ***Denm.:*** Izatax; Nizax; ***Fin.:*** Nizax; ***Fr.:*** Nizaxid; ***Ger.:*** Gastrax†; Nizax; ***Gr.:*** Axid†; Flectar†; Flexidon†; Ozeltan†; Ulcogastrin†; ***Hong Kong:*** Axid; ***Hung.:*** Naxidin; ***Indon.:*** Axid; ***Irl.:*** Axid; ***Ital.:*** Cronizat; Nizax; Zaniza†; ***Malaysia:*** Axid†; ***Mex.:*** Axid; Uldadin†; ***Neth.:*** Axid; ***Philipp.:*** Axid; ***Port.:*** Nizaxid; Prospaxid; ***S.Afr.:*** Antizid; ***Spain:*** Distaxid; ***Swed.:*** Nizax†; ***Switz.:*** Calmaxid†; ***Thai.:*** Axid†; ***Turk.:*** Axid; ***UK:*** Axid; ***USA:*** Axid; ***Venez.:*** Axid†.

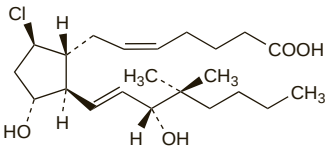
Nocloprost *(rINN)*

Nocloprostum. (*Z*)-7-[(1*R*,2*R*,3*R*,5*R*)-5-Chloro-3-hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4,4-dimethyl-1-octenyl]cyclopentyl]-5-heptenoic acid.

Ноклопрост

$C_{22}H_{37}ClO_4$ = 401.0.

CAS — 79360-43-3.



Profile

Nocloprost is a synthetic analogue of dinoprostone (prostaglandin E_2) that has been investigated in the treatment of peptic ulcer disease.

◊ References.

1. Täuber U, *et al.* Pharmacokinetics of nocloprost in human volunteers and its relation to dose. *Eur J Clin Pharmacol* 1993; **44:** 497–500.
2. Konturek JW, *et al.* Epidermal growth factor in gastric ulcer healing by nocloprost, a stable prostaglandin E2 derivative. *Scand J Gastroenterol* 1997; **32:** 980–4.

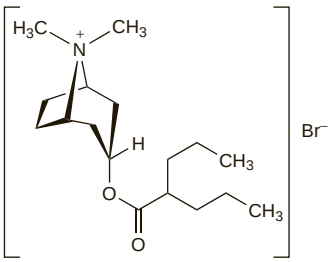
Octatropine Methylbromide *(BAN, rINN)*

Anisotropine Methobromide; Anisotropine Methylbromide *(USAN)*; Metilbromuro de octatropina; Octatropine, Méthylbromure d'; Octatropini Methylbromidum. (1*R*,3*r*,5*S*)-8-Methyl-3-(2-propylvaleryloxy)tropanium bromide.

Октатропина Метилбромид

$C_{17}H_{32}BrNO_2$ = 362.3.

CAS — 80-50-2.



Pharmacopoeias. In *It.*

Profile

Octatropine methylbromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease and to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Espasmo Dioxadol; ***Chile:*** Bufacyl; Valpin; ***Ital.:*** Valpinax.

Olsalazine Sodium *(BANM, USAN, rINNM)*

Azodisal Sodium; CI Mordant Yellow 5; CJ-91B; Colour Index No. 11130; Natrii Olsalazinum; Olsalatsiininatrium; Olsalazin disodná sůl; Olsalazin Sodyum; Olsalazina sódica; Olsalazine sodique; Olsalazinnatrium; Olsalazino natrio druska; Olsalazinum Dinatricum; Olsalazinum natricum; Olszalazin-nátrium; Sodium Azodisalicylate. Disodium 5,5′-azodisalicylate.

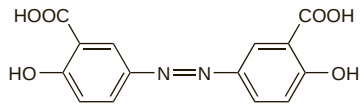
Натрий Ольсалазин

$C_{14}H_8N_2Na_2O_6$ = 346.2.

CAS — 6054-98-4.

ATC — A07EC03.

ATC Vet — QA07EC03.



(olsalazine)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Olsalazine Sodium). A yellow, fine, crystalline powder; it exhibits polymorphism. Sparingly soluble in water; soluble in dimethyl sulfoxide; very slightly soluble in methyl alcohol.

Adverse Effects and Precautions

As for Mesalazine, p.1745. The most common adverse effects associated with olsalazine sodium are diarrhoea, arthralgia, and skin rashes. Diarrhoea may be watery in some patients; it may resolve with dosage reduction but can be severe enough to require withdrawal of treatment. Diarrhoea is less likely if the drug is taken after meals. There have been a few reports of blood dyscrasias. 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 haematotoxicity and should be advised to seek immediate medical attention if symptoms such as fever, sore throat, mouth ulcers, bruising, or bleeding develop.

Incidence of adverse effects. In an open study[1] of olsalazine 1 g daily by mouth involving 160 patients with active ulcerative colitis and a history of sulfasalazine intolerance, 103 (64.4%) patients had no adverse effects; 29 patients reported only minor adverse effects: gastrointestinal disturbances in 22 patients, transient skin rash in 3, and headache, increased salivation, cough, and irritability each in one patient. The most common adverse effect was frequent loose stools which affected 25 patients, 20 of whom had to stop treatment. This adverse effect occurred early in treatment, within 10 hours of the first dose in 13 patients. Severe diarrhoea was more frequent in patients with widespread disease, but the incidence of diarrhoea did not correlate with disease severity.

A subsequent study[2] in healthy subjects has shown that olsalazine has a significant inhibitory effect on water and electrolyte absorption in the small intestine, which may account, at least in part, for the induction of diarrhoea. Patients with extensive colitis have reduced colonic absorptive function and may be less able to assimilate the increased colonic inflow volumes.

1. Sandberg-Gertzén H, *et al.* Azodisal sodium in the treatment of ulcerative colitis: a study of tolerance and relapse-prevention properties. *Gastroenterology* 1986; **90:** 1024–30.
2. Raimundo AH, *et al.* Effects of olsalazine and sulphasalazine on jejunal and ileal water and electrolyte absorption in normal human subjects. *Gut* 1991; **32:** 270–4.

Breast feeding. A study[1] involving a 39-year-old woman with Crohn's disease found that olsalazine did not appear to present a clinically significant risk to the breast-fed infant. Olsalazine was undetectable in the breast milk for 48 hours after a single oral 500-mg dose, and although small amounts of the metabolite acetylated 5-aminosalicylic acid were detected in breast milk the infant showed no adverse effects during the 3 weeks afterwards in which the mother continued taking olsalazine.

1. Miller LG, *et al.* Disposition of olsalazine and metabolites in breast milk. *J Clin Pharmacol* 1993; **33:** 703–6.

Effects on the blood. As of July 1995, the UK CSM had received 4 reports of blood dyscrasias associated with olsalazine, none of them fatal.[1] It was recommended that a blood count be performed and the drug stopped immediately if there was suspicion of a dyscrasia. See also under Mesalazine, p.1745.

1. 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)

Effects on the kidneys. A report of nephrotoxicity, characterised by interstitial nephritis, was associated with the use of olsalazine.[1] Symptoms resolved on stopping of the drug. See also under Mesalazine, p.1745.

1. Wilcox GM, *et al.* Nephrotoxicity associated with olsalazine. *Am J Med* 1996; **100:** 238–40.

Interactions

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

Pharmacokinetics

Very little of an oral dose of olsalazine is absorbed via the upper gastrointestinal tract, and almost the entire dose reaches its site of action in the colon intact. It is broken down by the colonic bacterial flora into 2 molecules of 5-aminosalicylic acid (mesalazine). Some mesalazine is absorbed and acetylated (see p.1746) but systemic concentrations of mesalazine and its metabolite are lower than after comparable oral doses of mesalazine, perhaps because there is less release of mesalazine in the small intestine, where absorption is better. Mesalazine concentrations in the colon after a dose of olsalazine are stated to be about 1000 times greater than systemic concentrations.

The small amounts (1 to 2% of the dose or less) of intact olsalazine that are absorbed are excreted mainly in urine; the elimination half-life after an intravenous dose has been calculated at about 1 hour. Some olsalazine is metabolised by sulfate conjugation in the liver: the elimination half-life of the metabolite is reported to be about 7 days.

◊ References.

1. Ryde EM. Pharmacokinetic aspects of drugs targeted for the colon, with special reference to olsalazine. *Acta Pharm Suec* 1988; **25:** 327–8.
2. Laursen LS, *et al.* Disposition of 5-aminosalicylic acid by olsalazine and three mesalazine preparations in patients with ulcerative colitis: comparison of intraluminal colonic concentrations, serum values, and urinary excretion. *Gut* 1990; **31:** 1271–6.

Uses and Administration

Olsalazine consists of two molecules of mesalazine (p.1745) linked with an azo bond. It is activated in the colon where the active mesalazine is released. It is used as the sodium salt in the management of acute mild ulcerative colitis and for the maintenance of remission (see Inflammatory Bowel Disease, p.1697). The usual initial dose of olsalazine sodium is 1 g by mouth daily in divided doses and this is gradually increased, if necessary, over one week, to a maximum dose of 3 g daily. The usual dose for the maintenance of remission is 500 mg twice daily. Doses should be taken after meals and a single dose should not exceed 1 g. Although not licensed for use in children, the *BNFC* includes a dose for children aged 2 years and over; the adult dose may be given for management of an acute attack of mild ulcerative colitis, and a dose of 250 to 500 mg twice daily may be used for maintenance.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dipentum†; ***Austral.:*** Dipentum; ***Austria:*** Dipentum; ***Canad.:*** Dipentum; ***Chile:*** Dipentum; ***Denm.:*** Dipentum; ***Fin.:*** Dipentum; ***Fr.:*** Dipentum; ***Ger.:*** Dipentum; ***Gr.:*** Dipentum†; ***Hong Kong:*** Dipentum; ***Hung.:*** Dipentum†; ***Irl.:*** Dipentum; ***Israel:*** Dipentum†; ***Ital.:*** Dipentum†; ***Neth.:*** Dipentum; ***Norw.:*** Dipentum; ***NZ:*** Dipentum; ***S.Afr.:*** Dipentum; ***Spain:*** Rasal†; ***Swed.:*** Dipentum; ***Switz.:*** Dipentum; ***Turk.:*** Dipentum; ***UK:*** Dipentum; ***USA:*** Dipentum.