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.

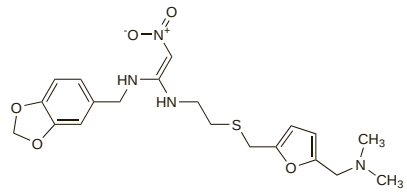
Ниперотидина Гидрохлорид

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

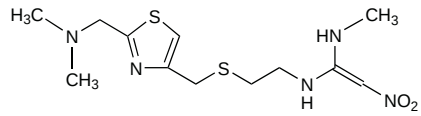
Низатидин

$C_{12}H_{21}N_5O_2S_2$ = 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-