

- Hellstern A, *et al.* Absolute bioavailability of metoclopramide given orally or by enema in patients with normal liver function or with cirrhosis of the liver. *Arzneimittelforschung* 1987; **37**: 733–6.
- Maguier E, *et al.* Pharmacokinetics of metoclopramide in patients with liver cirrhosis. *Br J Clin Pharmacol* 1991; **31**: 185–7.

**Blood disorders.** Responses to treatment with metoclopramide have been reported in patients with Diamond-Blackfan anaemia, probably through induction of prolactin release, although the mechanism by which prolactin affects erythropoiesis is unclear.<sup>1,2</sup> In a pilot study, 3 out of 9 evaluable patients responded after 12 to 15 weeks of therapy; high serum ferritin, pituitary dysfunction, male sex, and younger age may have contributed to the poor response to metoclopramide in other patients.<sup>1</sup> In another case, response was seen by the fourth week of treatment; at the time of the report, the patient had remained asymptomatic and transfusion independent for 8 months.<sup>2</sup>

- Akowitz JL, *et al.* Response of Diamond-Blackfan anemia to metoclopramide: evidence for a role for prolactin in erythropoiesis. *Blood* 2002; **100**: 2687–91.
- Akiyama M, *et al.* Successful treatment of Diamond-Blackfan anemia with metoclopramide. *Am J Hematol* 2005; **78**: 295–8.

**Hiccup.** Metoclopramide has been used in the management of intractable hiccup. For a discussion of hiccup and its management see p.976.

**Lactation induction.** Metoclopramide has been used<sup>1,2</sup> in doses of 10 mg three times daily for its dopamine antagonist properties to stimulate lactation in women who wish to breast feed and in whom mechanical stimulation of the nipple alone is inadequate, including mothers of adopted babies or babies born to surrogates.<sup>3,4</sup> However, pharmacological lactation induction should be viewed as adjunctive to mechanical methods and the duration of therapy should probably be limited to 7 to 14 days.<sup>1,2</sup> In addition, the efficacy of metoclopramide in stimulating lactation in women with preterm deliveries has been questioned by a controlled study.<sup>5</sup> Young women are at increased risk of extrapyramidal effects from metoclopramide—see under Adverse Effects, above. There has also been concern about the presence of the drug in breast milk. For a discussion of lactation inhibition and induction, see p.2003.

- Anderson PO, Valdés V. Increasing breast milk supply. *Clin Pharm* 1993; **12**: 479–80.
- Gabay MP. Galactagogues: medications that induce lactation. *J Hum Lact* 2002; **18**: 274–9.
- Cheales-Seibenaller NJ. Induced lactation in an adoptive mother. *J Hum Lact* 1999; **15**: 41–3.
- Bierlyet FP, *et al.* Induction of lactation in the intended mother of a surrogate pregnancy: case report. *Hum Reprod* 2001; **16**: 581–3.
- Hansen WF, *et al.* Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol* 2005; **105**: 383–9.

**Migraine.** Metoclopramide is used in the treatment of migraine (p.616) to alleviate nausea and vomiting and gastric stasis, which commonly develop as a migraine attack progresses and can lead to poor absorption of oral antimigraine preparations. It may also be given to counteract nausea and vomiting from the use of ergotamine. Metoclopramide is included in some combination analgesic preparations for the treatment of acute attacks of migraine. In a study, oral lysine aspirin with metoclopramide was as effective as oral sumatriptan in the treatment of migraine.<sup>1</sup> Metoclopramide with sumatriptan may be effective in patients unresponsive to a triptan alone.<sup>2</sup>

Parenteral metoclopramide has also been shown to be an effective treatment for acute migraine; it reduces pain, and to some extent nausea (although other antiemetics may be more effective), and a systematic review concluded that it should be considered a first-line treatment for migraine in the emergency department.<sup>3</sup> A later study found intravenous metoclopramide (with intermittent doses of diphenhydramine) to be comparable to subcutaneous sumatriptan in terms of pain relief at both 2 and 24 hours after treatment.<sup>4</sup>

- Tfelt-Hansen P, *et al.* The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet* 1995; **346**: 923–6.
- Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003; **43**: 729–33.
- Colman I, *et al.* Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. *BMJ* 2004; **329**: 1369–72.
- Friedman BW, *et al.* A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology* 2005; **64**: 463–8.

**Orthostatic hypotension.** Metoclopramide has been tried in the management of some patients with orthostatic hypotension, as mentioned on p.1530.

**Tourette's syndrome.** A small, short-term study in children and adolescents with Tourette's syndrome (see Tics, p.954) or chronic tic disorders found that treatment with oral metoclopramide (up to 40 mg daily) significantly reduced tic score and severity compared with placebo.<sup>1</sup>

- Nicolson R, *et al.* A randomized, double-blind, placebo-controlled trial of metoclopramide for the treatment of Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2005; **44**: 640–6.

**Variceal haemorrhage.** Metoclopramide 20 mg intravenously controlled bleeding from oesophageal varices within 15 minutes in 10 of 11 patients compared with 4 of 11 patients given placebo; all patients were treated by sclerotherapy.<sup>1</sup> Lower

oesophageal sphincter pressure is increased by metoclopramide, thus reducing blood flow to varices and achieving haemostasis; another study<sup>2</sup> found use of metoclopramide with intravenous glyceryl trinitrate to be more effective than glyceryl trinitrate alone in reducing intravascular pressure.

For a discussion of variceal haemorrhage and its management, see p.2346.

- Hosking SW, *et al.* Pharmacological constriction of the lower oesophageal sphincter: a simple method of arresting variceal haemorrhage. *Gut* 1988; **29**: 1098–1102.
- Sarin SK, Saraya A. Effects of intravenous nitroglycerin and nitroglycerin and metoclopramide on intravascular pressure: a double blind, randomized study. *Am J Gastroenterol* 1995; **90**: 48–53.

## Preparations

**BP 2008:** Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets;

**USP 31:** Metoclopramide Injection; Metoclopramide Oral Solution; Metoclopramide Tablets.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Celit; Fonderyl; Lizaron; Metoc; Midaten; Novomit; Proux; Primavera-N; Primmer; Reliveran; Rilaquin; Rupemet; Saften; Sintegan; **Austral.:** Maxolon; Pamin; **Austria:** Gastro-Timelets; Gastronerton; Gastrosil; Metogastrol; Paspertin; Pramidin; **Belg.:** Dibertil; Docmetoclo; Movistal; Primmeran; **Braz.:** Anistopramida; Citroplus; Clopra; Emetic; Eucl; Flucil; Metoclosan; Metoplam; Metovit; Nausil; Neolasil; No-Vomit; Plagex; Plamid; Plamidasil; Plamivon; Plasil; Pramil; Vopax; **Canad.:** Apo-Metoclo; **Chile:** Hemibe; Ita; **Cz.:** Cerucal; Degam; MCP; Pramidin; **Denm.:** Emperal; Gastro-Timelets; Primmeran; **Fin.:** Metopram; Primmeran; **Fr.:** Anausin; Primmeran; **Ger.:** Cerucal; Gastronerton; Gastrosil; Gastrotranquil; Hyrin; MCP; MCPHam; Paspertin; **Gr.:** Primmeran; Primmeran; **Hong Kong:** Maril; Martomide; Maxolon; Metocyl; Metram; Primmeran; **Hung.:** Cerucal; Paspertin; **India:** Maxeron; Metocotint; Perinorm; Reglan; Tomid; Vominorm; **Indon.:** Clopramel; Damaben; Emeran; Ethiferan; Gavistal; Lexapram; Mepramide; Metolon; Nilatik; Nofoklam; Norfastin; Obteran; Opram; Piralen; Plasil; Praminal; Primmeran; Radlonid; Reguloop; Sotatic; Tivomit; Tomit; Vertivom; Vilapon; Vomidex; Vomipram; Vomitol; Zumatrol; **Irl.:** Antimet; Gastrobid Continus; Maxolon; Metocyl; **Israel:** Pram; **Ital.:** Citropulst; Clopan; Delipramil; Isaprandil; Plasil; Pramidin; Randum; **Jpn.:** Primmeran; **Malaysia:** Maril; Maxolon; Metocyl; Primmeran; Pulin; **Mex.:** Biopram; Carnotprim; Cirulan; Clorimet-Z; Dolmisin; Eudiges; Gigemec; Hopram; Meclomid; Midetol; Mipramid; Plasil; Polotec; Pradex; Pramilem; Pramotil; Primmeran; Propace; Synespramid; **Neth.:** Primmeran; **Norw.:** Alipram; Primmeran; **NZ:** Maxolon; Metamid; **Philipp.:** Bidomet; Novom; Plasil; **Pol.:** Pramidin; **Port.:** Metoclan; Primmeran; Reglan; **Rus.:** Apo-Metoclo (Апо-метоклол); Cerucal (Церукал); Perinorm (Перинорм); **S.Afr.:** Acumet; Ametic; Betaclopramide; Clopanom; Contromet; Maxolon; Metalon; Perinorm; Pramalon; **Setin; Singapore:** Maril; Maxolon; Metocyl; Metolon; Primmeran; Pulin; **Spain:** Metagliz; Primmeran; **Swed.:** Primmeran; **Switz.:** Gastrosil; Paspertin; Primmeran; **Thai:** Emetal; Gensil; H-Peran; Hawkpram; Maril; Meramide; Met-Sil; Metoclor; Nausil; Plasil; **Turk.:** Metoklamid; Metpamid; Primmeran; **UAE:** Premosan; **UK:** Gastrobid Continus; Gastroflux; Maxolon; Primmeran; **USA:** Clopra; Maxolon; Octamide; Redclomid; Reglan; **Venez.:** Clodoxin; Clopt; Irtpan; Mepramide; Peremid; Pradamint; Pramide; Primmeran; Vibrant.

**Multi-ingredient:** **Arg.:** Bil 13 Enzimatico; Btecan AA; Digesplen; Facigest; Factorin; Faradil; Faradil Enzimatico; Migral Compositum; Pakinase; Pankron Total; Tetralgin; Vacubil Plus; **Austral.:** Anagrain; Metomax; **Austria:** Ceolat Compositum; Paspertase; **Belg.:** Migry; **Braz.:** Cefalium; Diagrin; Digeplus; Emetrol; Enjol; Essen; Estac; Plagon; Plasil Enzimatico; Sintozina; Vominil; **Chile:** Aero Itan; Aeroflat; Aerogastrol; Digeplus; Gaceptol; Gaseofin; No-Ref; Pangastren; **Cz.:** Cephalgan; Migpr; Migranerton; **Denm.:** Migpr; **Fin.:** Migpr; **Fr.:** Cephalgan; Migpr; **Ger.:** Migraeflux MCP; Migralave + MCP; Migra-Neural; Migranerton; Paspertase; **Gr.:** Premig; **Hung.:** Migpr; **India:** Olanorm Plus; Pacimol M; Paramet; **Indon.:** Primadol; Primmeran Compositum; **Irl.:** Paramax; **Ital.:** Gelfer; Migpr; Migpram; **Mex.:** Antigam; Digenor; Digenor Plus; Espaven MD; Espraden; Plasil Enzimatico; Pramgel; Primesasy; **Neth.:** Migrafin; **Norw.:** Migpr; **NZ:** Paramax; **Pol.:** Migpr; **Spain:** Aero Plus; Aeroflat; Anti Anorex Triple; Novo Aerofl Sedante; Paidox; Salmecet; Suxidina; **Swed.:** Migpr; **Switz.:** Migpr; **UK:** Migramax; Paramax.

## Metopimazine (BAN, USAN, INN)

EXP-999; Metopimazine; Métopimazine; Metopimazinum; RP-9965. 1-[3-(2-Methylsulphonylphenothiazin-10-yl)propyl]piperidine-4-carboxamide.

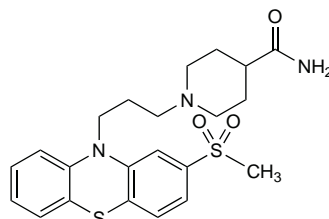
Метопимазин

$C_{22}H_{27}N_3O_3S_2 = 445.6$ .

CAS — 14008-44-7.

ATC — A04AD05.

ATC Vet — QA04AD05.



## Pharmacopoeias. In Fr:

### Profile

Metopimazine, a phenothiazine dopamine antagonist, is an antiemetic with general properties similar to those of chlorpromazine (p.969). It is used in the management of nausea and vomiting, including that associated with cancer chemotherapy (p.1700). It is given in usual oral doses of 15 to 30 mg daily, in 2 to 4 divided doses; similar daily doses have been given by rectum in 3 divided

doses. It has also been given by injection in a dose of 10 to 20 mg daily, usually intramuscularly but occasionally by the intravenous route. Higher doses of 30 to 50 mg daily by intramuscular injection or intravenous infusion have been given for chemotherapy-induced nausea and vomiting.

## Preparations

**Proprietary Preparations** (details are given in Part 3)

**Denm.:** Vogalene; **Fr.:** Vogalene; Vogalib.

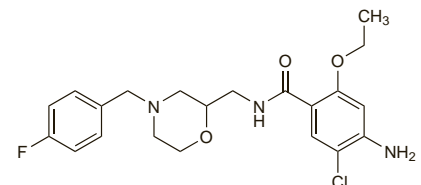
## Mosapride Citrate (rINN)

AS-4370; Citrato de mosaprida; Mosapride, Citrate de; Mosapridi Citras; Rimpopride Citrate. (±)-4-Amino-5-chloro-2-ethoxy-N-[(4-(p-fluorobenzyl)-2-morpholinyl)methyl]benzamide citrate dihydrate.

Мозаприда Цитрат

$C_{21}H_{25}ClFN_3O_3 \cdot C_6H_8O_7 \cdot 2H_2O = 650.0$ .

CAS — 112885-41-3 (mosapride); 112885-42-4 (mosapride citrate).



(mosapride)

## Profile

Mosapride is a substituted benzamide used for its prokinetic properties. It is reported to be an agonist at 5-HT<sub>4</sub> receptors, increasing acetylcholine release and stimulating gastrointestinal motility (see also Cisapride, p.1721), as well as having 5-HT<sub>3</sub> antagonist properties. It is given orally as the citrate dihydrate, but doses are expressed as the anhydrous citrate, and are 5 mg three times daily before or after meals.

## References

- Sakashita M, *et al.* Pharmacokinetics of the gastrokinetic agent mosapride citrate after single and multiple oral administrations in healthy subjects. *Arzneimittelforschung* 1993; **43**: 867–72.
- Ruth M, *et al.* The effect of mosapride, a novel prokinetic, on acid reflux variables in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1998; **12**: 35–40.
- Ruth M, *et al.* The effect of mosapride on oesophageal motor function and acid reflux in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2003; **15**: 1115–21.
- Asakawa H, *et al.* Effect of mosapride on glycemic control and gastric emptying in type 2 diabetes mellitus patients with gastropathy. *Diabetes Res Clin Pract* 2003; **61**: 175–82.
- Liu Z, *et al.* Mosapride citrate, a novel 5-HT<sub>4</sub> agonist and partial 5-HT<sub>3</sub> antagonist, ameliorates constipation in parkinsonian patients. *Mov Disord* 2005; **20**: 680–6.
- He M, *et al.* Mosapride citrate prolongs survival in stroke patients with gastrostomy. *J Am Geriatr Soc* 2007; **55**: 142–4.
- Curran MP, Robinson DM. Mosapride: in gastrointestinal disorders. *Drugs* 2008; **68**: 981–91.

## Preparations

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Galopran; Intesul; Levusid; Lostapride; Mosar; Vagantyl; **India:** Mosafe; Mosapid; Mosart; Penipride; **Jpn.:** Gasmotin.

**Multi-ingredient:** **Arg.:** Gastrimet; Mosar Enzimatico; Mosar Plus.

## Nabilone (BAN, USAN, INN) ⊗

Compound 109514; Lilly-109514; Nabilon; Nabilona; Nabiloni; Nabilonum. (±)-(6aR,10aR)-3-(1,1-Dimethylheptyl)-6a,7,8,9,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-6H-benzo[c]chromen-9-one.

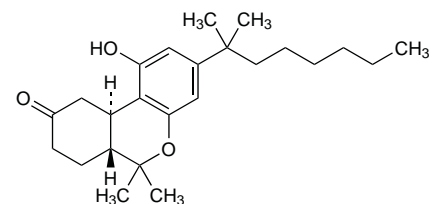
Набилон

$C_{24}H_{36}O = 372.5$ .

CAS — 51022-71-0.

ATC — A04AD11.

ATC Vet — QA04AD11.



## Adverse Effects

Nabilone may produce adverse effects similar to those of cannabis (see p.2275). The most common adverse effects are drowsiness, vertigo, and dry mouth. Neurological effects have included

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.<sup>1</sup> A subsequent small crossover study<sup>2</sup> 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<sup>3</sup> 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*)

Hydrocloruro 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

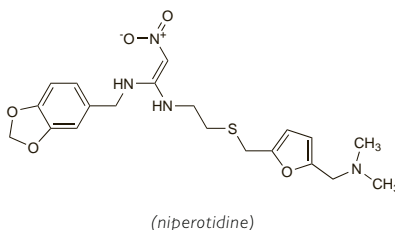
$C_{20}H_{26}N_4O_5S \cdot HCl = 471.0$ .

**CAS** — 84845-75-0 (*niperotidine*).

**ATC** — A02BA05.

**ATC Vet** — QA02BA05.

The symbol † denotes a preparation no longer actively marketed



### 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)ethylthio]methyl]thiazol-4-ylmethyl(dimethyl)amine; *N*-[2-[(2-Dimethylaminomethyl)thiazol-4-ylmethylthio]ethyl]-*N'*-methyl-2-nitrovinylbenzimidazole.

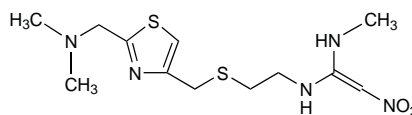
Низатидин

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

**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,<sup>1,2</sup> an effect that was not seen when they were pretreated with ranitidine<sup>1</sup> or also given the antimuscarinic pirenzepine.<sup>2</sup> 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  $H_2$ -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.<sup>1</sup>

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.<sup>1</sup> 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 (Axiid) 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.<sup>1</sup>

1. Abdel-Rahman SM, *et al.* The bioequivalence of nizatidine (Axiid) 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.<sup>1</sup> 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-

The symbol ⊗ denotes a substance whose use may be restricted in certain sports (see p.vii)