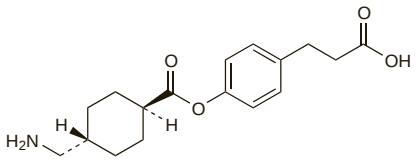
## Cetraxate Hydrochloride *(USAN, rINNM)*

Cétraxate, Chlorhydrate de; Cetraxati Hydrochloridum; DV-1006; Hidrocloruro de cetraxato. 4-(2-Carboxyethyl)phenyl tranexamate hydrochloride; 4-(2-Carboxyethyl)phenyl *trans*-4-aminomethylcyclohexanecarboxylate hydrochloride.

Цетраксата Гидрохлорид

$C_{17}H_{23}NO_4$,HCl = 341.8.

*CAS — 34675-84-8 (cetraxate); 27724-96-5 (cetraxate hydrochloride).*



*(cetraxate)*

**Pharmacopoeias.** In *Jpn*.

### Profile

Cetraxate hydrochloride is stated to be a mucosal protectant with actions on gastric microcirculation as well as prostaglandin synthesis and kallikrein. It is used in the treatment of gastritis and peptic ulcer disease (p.1702) in oral doses of 600 to 800 mg daily in divided doses.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Jpn:*** Neuer.

## Chalk

Creta; Prepared Chalk.

Мел

$CaCO_3$ = 100.1.

*CAS — 13397-25-6.*

**Pharmacopoeias.** In *Br.*

**BP 2008** (Chalk). A native form of calcium carbonate freed from most of its impurities by elutriation and dried. It consists of the calcareous shells and detritus of various foraminifera and contains not less than 97.0% and not more than 100.5% of $CaCO_3$, calculated with reference to the dried substance.

White or greyish-white, odourless or almost odourless, amorphous, earthy, small friable masses, usually conical in form, or in powder. Practically insoluble in water; slightly soluble in water containing carbon dioxide; it absorbs water readily.

### Profile

Chalk has been used as an adsorbent antidiarrhoeal. Calcium carbonate (precipitated chalk) is used as an antacid, calcium supplement, and phosphate binder, see p.1714.

Calabash chalk, also known as Calabar stone, la craie or argile, nzu, mabele, ebumba, or ulo, is ingested by some pregnant women to alleviate morning sickness. It is traditionally used by Nigerian or West African women in the form of blocks, pellets, or powders. Calabash chalk either occurs naturally or is produced from clay and mud which may be mixed with other ingredients including sand, wood ash, and sometimes, salt. However, it contains high levels of lead, as well as arsenic (see Contamination, below).

**Contamination.** Concern with regard to the safety of calabash chalk has arisen, particularly with regard to its lead and arsenic content.[1-3] Analysis of calabash chalk samples available in the UK found that the major component of calabash chalk was an aluminium silicate hydroxide from the kaolin clay group. Lead concentrations in the samples were found to be about 40 mg/kg, almost 40 times the EU recommended guidelines. Potentially toxic chromium concentrations (dependent on the oxidation state) were also found. Arsenic, cadmium, and mercury were not detectable in any of the analysed samples. Persistent organic pollutants were also identified in one sample.[1] Calabash chalk is traditionally used by pregnant women, often those from Nigerian and West African communities, as a remedy for morning sickness. Health authorities in various countries have issued warnings, and advised people, especially pregnant and breast-feeding women, not to consume calabash chalk.[2,3]


1. Dean JR, *et al.* Characterisation and analysis of persistent organic pollutants and major, minor and trace elements in calabash chalk. *Chemosphere* 2004; **57:** 21–5.
2. Health Canada. Calabash chalk may pose health risk for pregnant and breastfeeding women (issued 2nd October 2007). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_136_e.html (accessed 03/10/07)
3. Food Standards Agency. Lead contamination of calabash chalk (issued 15th October 2002). Available at: http://www.food.gov.uk/enforcement/alerts/2002/oct/94151 (accessed 03/10/07)


### Preparations

***BP 2008:*** Compound Magnesium Trisilicate Oral Powder.
**Proprietary Preparations** (details are given in Part 3)
**Multi-ingredient:** ***S.Afr.:*** Behoedmiddel vir Kinders.

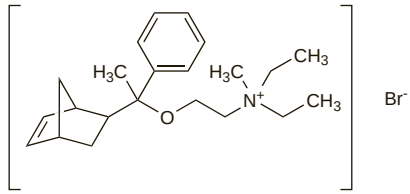
## Ciclonium Bromide *(rINN)*

Asta-3746; Bromuro de ciclonio; Ciclonii Bromidum; Ciclonium, Bromure de. Diethylmethyl{2-[(α-methyl-α-5-norbornen-2-ylbenzyl)oxy]ethyl}ammonium bromide.

Циклония Бромид

$C_{22}H_{34}BrNO$ = 408.4.

*CAS — 29546-59-6.*



NOTE. The name cyclonium or ciclonium iodide has been used to describe an unrelated antispasmodic, oxapium iodide (p.1759).

### Profile

Ciclonium bromide is an antimuscarinic that has been used in the treatment of gastrointestinal and urinary-tract disorders associated with smooth muscle spasm.

### Preparations

**Proprietary Preparations** (details are given in Part 3)
***Thai.:*** Adamon†.
**Multi-ingredient:** ***Arg.:*** Espasmo Motrax†; ***Turk.:*** Doladamon-P.

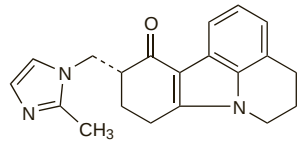
## Cilansetron *(USAN, rINN)*

Cilansétron; Cilansetrón; Cilansetronum; KC-9946. (–)-(*R*)-5,6,9,10-Tetrahydro-10-[(2-methylimidazol-1-yl)methyl]-4*H*-pyrido[3,2,1-*jk*]carbazol-11(8*H*)-one.

Цилансетрон

$C_{20}H_{21}N_3O$ = 319.4.

*CAS — 120635-74-7.*
*ATC — A03AE03.*
*ATC Vet — QA03AE03.*



### Profile

Cilansetron is a 5-$HT_3$ antagonist under investigation for the treatment of diarrhoea-predominant irritable bowel syndrome.

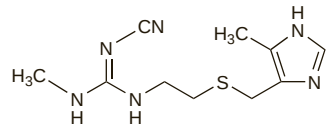
# Cimetidine *(BAN, USAN, rINN)*

Cimetidin; Cimetidina; Cimetidinas; Cimétidine; Cimetidinum; Cymetydyna; Simetidiini; Simetidin; SKF-92334. 2-Cyano-1-methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]guanidine.

Циметидин

$C_{10}H_{16}N_6S$ = 252.3.

*CAS — 51481-61-9.*
*ATC — A02BA01.*
*ATC Vet — QA02BA01.*



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

**Ph. Eur. 6.2** (Cimetidine). A white or almost white, polymorphic powder. Slightly soluble in water; soluble in alcohol; practically insoluble in dichloromethane. It dissolves in dilute mineral acids. Store in airtight containers. Protect from light.

**USP 31** (Cimetidine). A white to off-white crystalline powder, odourless or with a slight mercaptan odour. Slightly soluble in water and in chloroform; soluble in alcohol and in macrogol 400; practically insoluble in ether; sparingly soluble in isopropyl alcohol; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

## Cimetidine Hydrochloride *(BANM, USAN, rINNM)*

Cimétidine, chlorhydrate de; Cimetidin-hidroklorid; Cimetidinhydroklorid; Cimetidini hydrochloridum; Cimetidino hidrochloridas; Hidrocloruro de cimetidina; Simetidiinihydrokloridi.

Циметидина Гидрохлорид

$C_{10}H_{16}N_6S$,HCl = 288.8.

*CAS — 70059-30-2.*
*ATC — A02BA01.*
*ATC Vet — QA02BA01.*

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

**Ph. Eur. 6.2** (Cimetidine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; sparingly soluble in dehydrated alcohol. A 1% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

**USP 31** (Cimetidine Hydrochloride). Store in airtight containers. Protect from light.

### Adverse Effects

Adverse reactions to cimetidine and other histamine $H_2$-antagonists are generally infrequent. The commonest adverse effects reported have been diarrhoea and other gastrointestinal disturbances, dizziness, tiredness, headache, and rashes.

Altered liver function tests have occurred and there have been rare reports of hepatotoxicity. Reversible confusional states, especially in the elderly or in seriously ill patients such as those with renal failure, have occasionally occurred. Other adverse effects that have been reported rarely are hypersensitivity reactions and fever, arthralgia and myalgia, blood disorders including agranulocytosis, leucopenia, and thrombocytopenia, acute pancreatitis, interstitial nephritis, hallucinations and depression, and cardiovascular disorders including bradycardia, tachycardia, and heart block. Rapid intravenous injection should be avoided as there have been rare associations with cardiac arrest and arrhythmias; transient hypotension has also been seen.

In patients such as the elderly, those with chronic lung disease, diabetes mellitus, or the immunocompromised, treatment with $H_2$-antagonists may be associated with an increased risk of developing community-acquired pneumonia.

Cimetidine has a weak anti-androgenic effect and gynaecomastia and impotence have also occasionally occurred in men; these are usually reversible.

**Incidence of adverse effects.** In a meta-analysis of 24 double-blind placebo-controlled studies,[1] the incidence of adverse effects with cimetidine was not significantly different from placebo. The most common adverse effects reported by patients taking cimetidine who were followed up for at least one year[2,3] were diarrhoea, headache, fatigue, skin rash or pruritus, and gynaecomastia. The incidence of adverse effects was dose-related and decreased with length of treatment.[3] No fatal adverse effect of cimetidine could be found in a mortality survey involving 9928 patients taking cimetidine and 9351 controls;[4] although the mortality rate was higher in the cimetidine patients, this was explained by the presence of underlying disease (known or unknown) before starting cimetidine treatment and the use of cimetidine to counter adverse gastric effects of other drugs. Follow-up of 9377 of these cimetidine-treated patients for a further 3 years[5] still revealed no fatal disorder attributable to cimetidine treatment and a steady fall in the excess death rate in cimetidine users was seen with increasing length of follow-up; by the fourth year there was little difference between the observed and expected death rate. Cimetidine still appeared to be safe after 10 years of follow-up.[6]


1. Richter JM, *et al.* Cimetidine and adverse reactions: a meta-analysis of randomized clinical trials of short-term therapy. *Am J Med* 1989; **87:** 278–84.
2. Colin Jones DG, *et al.* Post-marketing surveillance of the safety of cimetidine: twelve-month morbidity report. *Q J Med* 1985; **54:** 253–68.
3. Bardhan KD, *et al.* Safety of longterm cimetidine (CIM) treatment: the view from one centre. *Gut* 1990; **31:** A599.
4. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; **286:** 1713–16.
5. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; **291:** 1084–8.
6. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 10 year mortality report. *Gut* 1992; **33:** 1280–4.

**Carcinogenicity.** An association between $H_2$-antagonists and gastric cancer was proposed after individual case reports, the finding of tumours in long-term high-dose *animal* studies, and the possibility that nitrites and nitroso compounds may be produced, but seemed of little clinical relevance.[1,2] The excess risk of gastric cancer reported in patients taking cimetidine[3-6] or ranitidine[6] decreases with time and there is no evidence for any long-term persistence of the effect.[6] The increased risk may be explained by misdiagnosis and inappropriate cimetidine treatment of existing malignancy.[3-5] An apparently protective effect has been seen for $H_2$-antagonist use starting 10 or more years before diagnosis of gastric cancer.[6]

The observed excess risk for cancers of the respiratory system is probably related to smoking, since this is causally related to both peptic ulcer and lung cancer and the excess risk does not decline with time.[3-5]


1. Penston J, Wormsley KG. H -receptor antagonists and gastric cancer. *Med Toxicol* 1986; **1:** 163–8.
2. Møller H, *et al.* Use of cimetidine and other peptic ulcer drugs in Denmark 1977–1990 with analysis of the risk of gastric cancer among cimetidine users. *Gut* 1992; **33:** 1166–9.
3. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: 12 month mortality report. *BMJ* 1983; **286:** 1713–16.
4. Colin-Jones DG, *et al.* Postmarketing surveillance of the safety of cimetidine: mortality during second, third, and fourth years of follow up. *BMJ* 1985; **291:** 1084–8.
5. Møller H, *et al.* Cancer occurrence in a cohort of patients treated with cimetidine. *Gut* 1989; **30:** 1558–62.
6. La Vecchia C, *et al.* Histamine-2-receptor antagonists and gastric cancer risk. *Lancet* 1990; **336:** 355–7.


**Effects on the blood.** A review[1] in 1988 noted that leucopenia, thrombocytopenia, and pancytopenia have all been reported with cimetidine and ranitidine, with neutropenia and agranulocytosis occurring most often. There were also isolated reports of haemolytic anaemia and leucocytosis associated with cimetidine therapy. The overall incidence of cimetidine-associated blood cytopenia was estimated as 2.3 per 100 000 treated patients; the incidence for ranitidine was less and although there were reports with famotidine the incidence had not been determined. A subsequent case-control study,[2] concluded that the risk of hospitalisation due to neutropenia in patients receiving a 6-week course of cimetidine was no more than 1 in 116 000, while agranulocytosis did not occur in more than 1 in 573 000 patients.

A review[3] of the safety profile of famotidine noted that as of May 1992 there had been 60 reports of serious blood dyscrasias in patients receiving famotidine, of which 22 were considered possibly related to drug therapy (6 cases of pancytopenia or bone marrow depression, 5 of thrombocytopenia, 4 of leucopenia, 3 of combined leucopenia and thrombocytopenia, and 3 of agranulocytosis).


1. Aymard J-P, *et al.* Haematological adverse effects of histamine H -receptor antagonists. *Med Toxicol* 1988; **3:** 430–48.
2. Strom BL, *et al.* Is cimetidine associated with neutropenia? *Am J Med* 1995; **99:** 282–90.
3. Howden CW, Tytgat GNJ. The tolerability and safety profile of famotidine. *Clin Ther* 1996; **18:** 36–54.


**Effects on the cardiovascular system.** Bradycardia,[1-4] AV block,[5,6] tachycardia,[7] and hypotension[4,8] have been reported during cimetidine treatment given by mouth and by intravenous injection or infusion. Although there are studies in patients[9] and healthy subjects[10,11] that have found no significant cardiovascular effects associated with cimetidine treatment, it is likely that a small proportion of patients are more susceptible to the cardiovascular effects of cimetidine. Caution is recommended if the drug is given intravenously to patients with cardiovascular disease (see Precautions, below).

See also under Overdosage, below.


1. Jefferys DB, Vale JA. Cimetidine and bradycardia. *Lancet* 1978; **i:** 828.
2. Ligumsky M, *et al.* Cimetidine and arrhythmia suppression. *Ann Intern Med* 1978; **89:** 1008–9.
3. Tanner LA, Arrowsmith JB. Bradycardia and H antagonists. *Ann Intern Med* 1988; **109:** 434–5.
4. Drea EJ, *et al.* Cimetidine-associated adverse reaction. *DICP Ann Pharmacother* 1990; **24:** 581–3.
5. Tordjman T, *et al.* Complete atrioventricular block and long-term cimetidine therapy. *Arch Intern Med* 1984; **144:** 861.
6. Ishizaki M, *et al.* First-degree atrioventricular block induced by oral cimetidine. *Lancet* 1987; **i:** 225–6.
7. Dickey W, Symington M. Broad-complex tachycardia after intravenous cimetidine. *Lancet* 1987; **i:** 99–100.
8. Mahon WA, Kolton M. Hypotension after intravenous cimetidine. *Lancet* 1978; **i:** 828.
9. Jackson G, Upward JW. Cimetidine, ranitidine, and heart rate. *Lancet* 1982; **ii:** 265.
10. Hughes DG, *et al.* Cardiovascular effects of H -receptor antagonists. *J Clin Pharmacol* 1989; **29:** 472–7.
11. Hilleman DE, *et al.* Impact of chronic oral H -antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.


**Effects on the endocrine system.** Cimetidine has dose-related mild anti-androgenic properties and reduced sperm counts and raised serum-prolactin concentrations have been reported in men during cimetidine treatment[1] as have gynaecomastia, breast tenderness, and impotence.[2] Those symptoms resolved after withdrawal of cimetidine,[1,2] reduction of the dose,[2] or transfer to ranitidine.[2]

A study by the Boston Collaborative Drug Surveillance Program, using data from 81 535 men in the UK, found that cimetidine was associated with an incidence of 3.29 cases of gynaecomastia per 1000 person years, representing a relative risk 7.2 times greater than that of non-users.[3] The period at highest risk seemed to be between the seventh and twelfth month after starting treatment, and the occurrence was related to dose, with most of the risk associated with doses over 1 g daily. This large study found no significant risk of gynaecomastia with ranitidine or omeprazole. However, there have been isolated reports of gynaecomastia or impotence with ranitidine (p.1766), nizatidine (p.1751), and famotidine (p.1730).


1. Wang C, *et al.* Effect of cimetidine on gonadal function in man. *Br J Clin Pharmacol* 1982; **13:** 791–4.
2. Jensen RT, *et al.* Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308:** 883–7.
3. García Rodríguez LA, Jick H. Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs. *BMJ* 1994; **308:** 503–6. Correction. *ibid.*; 819.


**Effects on the eyes.** Ocular pain, blurred vision, and a rise in intra-ocular pressure occurred in a patient with chronic glaucoma during treatment with cimetidine; ocular symptoms associated with raised intra-ocular pressure subsequently developed during ranitidine treatment.[1] However, a study suggested that cimetidine had no effect on intra-ocular pressure.[2] A cohort study involving 140 128 patients receiving anti-ulcer therapy, 68 504 of whom received cimetidine, found no evidence that any of the drugs were associated with a major increased risk of vascular or inflammatory disorders of the eye.[3]


1. Dobrilla G, *et al.* Exacerbation of glaucoma associated with both cimetidine and ranitidine. *Lancet* 1982; **i:** 1078.
2. Feldman F, Cohen MM. Intraocular pressure and H receptor antagonists. *Lancet* 1982; **i:** 1359.
3. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.


**Effects on the kidneys.** A review[1] of the nephrotoxicity and hepatotoxicity of $H_2$-antagonists noted that mild elevation of serum-creatinine was relatively common after use of cimetidine but appeared to have no clinical significance. However, the authors found 25 published reports of acute interstitial nephritis associated with this class of drug (20 with cimetidine, 4 with ranitidine, and 1 with famotidine) and 16 cases reported to the Australian Drug Reaction Advisory Committee (ADRAC) between 1972 and 1999 (11 with cimetidine, 4 with ranitidine, and 1 with famotidine). Symptoms were mostly non-specific, and did not seem to be associated with the rash, arthralgia, and flank pain that may be seen in nephritis induced by other drugs. Nephritis invariably resolved when the drug was withdrawn; in 6 cases, rechallenge resulted in prompt return of clinical features, although there was some evidence that patients who developed nephrotoxicity with one $H_2$-antagonist might be able to tolerate substitution with another. The effect was rare (an earlier analysis estimated an incidence of around 1 in 100 000 treated patients[2]) but with the increasing availability of over-the-counter $H_2$-antagonist formulations it was important to be aware of the risk.


1. Fisher AA, Le Couteur DG. Nephrotoxicity and hepatotoxicity of histamine H receptor antagonists. *Drug Safety* 2001; **24:** 39–57.
2. Rowley-Jones D, Flind AC. Cimetidine-induced renal failure. *BMJ* 1982; **285:** 1422–3.


**Effects on the liver.** A cohort study[1] involving 108 891 patients given cimetidine, ranitidine, famotidine, or omeprazole between 1990 and 1993, found 33 cases meeting the authors' definition of clinically serious liver injury (cholestatic in 8 cases, hepatocellular in 15 and mixed in 10), most of whom presented with jaundice. Of these cases of liver injury, 12 were among current users of cimetidine, compared with 5 among users of ranitidine and 1 omeprazole user. It was estimated that the incidence of hepatotoxicity among patients using cimetidine was 2.3 cases per 10 000 users, and the adjusted relative risk was 5.5 times that of non-users. The relative risk for use of ranitidine or omeprazole was calculated at 1.7 and 2.1 respectively. The risk with cimetidine was greatest at high doses (800 mg daily or above) and at the beginning of therapy. For reports of liver damage with famotidine and cimetidine, see p.1730.


1. García Rodríguez LA, *et al.* The risk of acute liver injury associated with cimetidine and other acid-suppressing anti-ulcer drugs. *Br J Clin Pharmacol* 1997; **43:** 183–8.


**Effects on the nervous system.** Cimetidine has been associated with a number of adverse neurological effects including confusion,[1-8] bizarre behaviour,[9] reversible brain stem syndrome (with ataxia, dysarthria, visual impairment, deafness, and paraesthesia),[10] coma,[8,11] convulsions,[7] encephalopathy,[12] visual hallucinations,[9,13,14] paranoia,[5] chorea,[15,16] myopathy,[17] and neuropathy.[18,19] These reactions occur mainly in patients who are elderly, critically ill, or with impaired renal or hepatic function, in whom there may be increased penetration of the blood-brain barrier by cimetidine. Single-dose studies in young healthy subjects[20] have found no adverse changes in performance, central nervous function, or subjective assessment of mood after oral cimetidine 200 or 400 mg.

There is no clear evidence that cimetidine is a more frequent cause of CNS reactions than ranitidine, famotidine, or nizatidine.[21]


1. Robinson TJ, Mulligan TO. Cimetidine and mental confusion. *Lancet* 1977; **ii:** 719.
2. Spears JB. Cimetidine and mental confusion. *Am J Hosp Pharm* 1978; **35:** 1035.
3. Wood CA, *et al.* Cimetidine and mental confusion. *JAMA* 1978; **239:** 2550–1.
4. McMillen MA, *et al.* Cimetidine and mental confusion. *N Engl J Med* 1978; **298:** 284–5.
5. Kinnell HG, Webb A. Confusion associated with cimetidine. *BMJ* 1979; **ii:** 1438.
6. Mogelnicki SR, *et al.* Physostigmine reversal of cimetidine-induced mental confusion. *JAMA* 1979; **241:** 826–7.
7. Edmonds ME, *et al.* Cimetidine: does neurotoxicity occur? Report of three cases. *J R Soc Med* 1979; **72:** 172–5.
8. Sonnenblick M, *et al.* Neurological and psychiatric side effects of cimetidine—report of 3 cases with review of the literature. *Postgrad Med J* 1982; **58:** 415–18.
9. Papp KA, Curtis RM. Cimetidine-induced psychosis in a 14-year-old girl. *Can Med Assoc J* 1984; **131:** 1081–4.
10. Cumming WJK, Foster JB. Cimetidine-induced brainstem dysfunction. *Lancet* 1978; **i:** 1096.
11. Levine ML. Cimetidine-induced coma in cirrhosis of the liver. *JAMA* 1978; **240:** 1238.
12. Niv Y, *et al.* Cimetidine and encephalopathy. *Ann Intern Med* 1986; **105:** 977.
13. Agarwal SK. Cimetidine and visual hallucinations. *JAMA* 1978; **240:** 214.
14. Rushton AR. Pseudohypoparathyroidism, cimetidine, and neurologic toxicity. *Ann Intern Med* 1983; **98:** 677.
15. Kushner MJ. Chorea and cimetidine. *Ann Intern Med* 1982; **96:** 126.
16. Lehmann AB. Reversible chorea due to ranitidine and cimetidine. *Lancet* 1988; **ii:** 158.
17. Feest TG, Read DJ. Myopathy associated with cimetidine? *BMJ* 1980; **281:** 1284–5.
18. Walls TJ, *et al.* Motor neuropathy associated with cimetidine. *BMJ* 1980; **281:** 974–5.
19. Atkinson AB, *et al.* Neurological dysfunction in two patients receiving captopril and cimetidine. *Lancet* 1980; **ii:** 36–7.
20. Nicholson AN, Stone BM. The H -antagonists, cimetidine and ranitidine: studies on performance. *Eur J Clin Pharmacol* 1984; **26:** 579–82.
21. Cantú TG, Korek JS. Central nervous system reactions to histamine-2 receptor blockers. *Ann Intern Med* 1991; **114:** 1027–34.


**Effects on the skin.** Widespread erythrosis-like lesions in a 36-year-old man were probably induced by cimetidine.[1] There has been a report[2] of a skin eruption clinically consistent with erythema annulare centrifugum developing in a patient after 6 months of treatment with cimetidine; the eruption resolved after withdrawal of cimetidine and reappeared on rechallenge. The condition had not recurred during therapy with ranitidine. Erythema multiforme eruptions occurred after both cimetidine and famotidine in one patient (see p.1730). There have been reports of the Stevens-Johnson syndrome during cimetidine treatment in patients with a history of hypersensitivity to penicillin[3] or sulfonamides,[4] and a report of toxic epidermal necrolysis.[5]

Urticarial vasculitis[6] and alopecia[7] have also been associated with cimetidine treatment.


1. Angelini G, *et al.* Cimetidine and erythrosis-like lesions. *BMJ* 1979; **i:** 1147–8.
2. Merrett AC, *et al.* Cimetidine-induced erythema annulare centrifugum: no cross-sensitivity with ranitidine. *BMJ* 1981; **283:** 698.
3. Ahmed AH, *et al.* Stevens-Johnson syndrome during treatment with cimetidine. *Lancet* 1978; **ii:** 433.
4. Guan R, Yeo PPB. Stevens-Johnson syndrome: was it cimetidine? *Aust N Z J Med* 1983; **13:** 182.
5. Tidwell BH, *et al.* Cimetidine-induced toxic epidermal necrolysis. *Am J Health-Syst Pharm* 1998; **55:** 163–4.
6. Mitchell GG, *et al.* Cimetidine-induced cutaneous vasculitis. *Am J Med* 1983; **75:** 875–6.
7. Khalsa JH, *et al.* Cimetidine-associated alopecia. *Int J Dermatol* 1983; **22:** 202–4.


**Fever.** There are reports of febrile reactions associated with cimetidine.[1-4] Fever has also been reported with famotidine (p.1730) and ranitidine (p.1766).


1. Ramboer C. Drug fever with cimetidine. *Lancet* 1978; **i:** 330–1.
2. McLoughlin JC, *et al.* Cimetidine fever. *Lancet* 1978; **ii:** 499–500.
3. Corbett CL, Holdsworth CD. Fever, abdominal pain, and leucopenia during treatment with cimetidine. *BMJ* 1978; **i:** 753–4.
4. Landolfo K, *et al.* Cimetidine-induced fever. *Can Med Assoc J* 1984; **130:** 1580.


**Hypersensitivity.** Facial oedema,[1] laryngospasm,[1] pruritus,[2,3] rash,[2,3] angioedema[3] and anaphylaxis[4] have been reported in patients receiving cimetidine by mouth or intravenously.

See also under Effects on the Skin, above.


1. Delaunois L. Hypersensitivity to cimetidine. *N Engl J Med* 1979; **300:** 1216.
2. Hadfield WA. Cimetidine and giant urticaria. *Ann Intern Med* 1979; **91:** 128–9.
3. Sandhu BS, Requena R. Hypersensitivity to cimetidine. *Ann Intern Med* 1982; **97:** 138.
4. Knapp AB, *et al.* Cimetidine-induced anaphylaxis. *Ann Intern Med* 1982; **97:** 374–5.


**Infection.** Treatment with $H_2$-antagonists may predispose patients to salmonella infection, probably because the decrease in gastric acidity reduces the gastric killing of ingested organisms.[1] The greatest increase in risk was seen in patients over 65 years of age.

There are conflicting data on whether the use of $H_2$-antagonists for prophylaxis of stress ulcers in critically ill patients increases the risk for pneumonia (see under Peptic Ulcer Disease, p.1702). However, a case-control study in a large cohort of patients in primary care suggested that the risk of developing pneumonia in these less-severely ill patients was increased by antisecretory drugs: the relative risk was 1.63 in patients receiving $H_2$-antagonists, and 1.89 in those prescribed a proton pump inhibitor; there was also some evidence of a dose-response relationship in the latter group.[2]

Data from case-control studies[3] suggest that gastric acid suppression by $H_2$-antagonists may also be a risk factor for *Clostridium difficile*-associated disease. A case-control study in very low birth-weight infants found that use of $H_2$-antagonists was associated with an increased incidence of necrotising enterocolitis.[4] The authors postulate that this could be due to bacterial overgrowth in a less acidic gastric environment.


1. Neal KR, *et al.* Recent treatment with H antagonists and antibiotics and gastric surgery as risk factors for salmonella infection. *BMJ* 1994; **308**: 176.
2. Laheij RJF, *et al.* Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; **292:** 1955–60.
3. Dial S, *et al.* Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294:** 2989–95.
4. Guillet R, *et al.* National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2006; **117:** e137–42. Also available at: http://pediatrics.aappublications.org/cgi/reprint/117/2/e137 (accessed 09/04/08)


**Malabsorption.** Vitamin $B_{12}$ deficiency has been reported in association with acid-suppressive therapy, including $H_2$-antagonists. The deficiency was thought to result from impaired release of vitamin $B_{12}$ from food protein, which requires gastric acid and pepsin.[1]


1. Ruscin JM, *et al.* Vitamin B deficiency associated with histamine -receptor antagonists and a proton-pump inhibitor. *Ann Pharmacother* 2002; **36:** 812–16.


**Overdosage.** No serious toxic effects were noted in reports[1-3] of overdosage in patients who took cimetidine 5.2 to 20 g (including one patient who took about 12 g daily for 5 days[1]). Resultant plasma concentrations had been up to 57 micrograms/mL compared with a usual peak plasma concentration of 1 microgram/mL after a 200-mg dose. However, an overdose of about 12 g produced high pulse rate, dilated pupils, speech disturbances, agitation and disorientation in one patient[4] and respiratory depression in another patient who had chronic schizophrenia and was also taking trifluoperazine and hydroxyzine.[5] Also, fatal bradycardia has been reported after overdosage with an unknown amount of cimetidine and diazepam.[6] In a review of 881 cases of cimetidine overdose, excluding cases where several drugs were taken, it was concluded that the toxicity of cimetidine after acute overdose was very low.[7] No symptoms were observed in 79% of cases, which included ingestions of up to 15 g of cimetidine, and only 3 patients had moderate clinical manifestations (dizziness and bradycardia; CNS depression; vomiting). No patients had major medical outcomes and there were no fatalities. Gastric emptying was performed in 34% of cases but supportive measures and symptomatic treatment alone may be adequate. Forced diuresis does not appear to enhance the excretion of cimetidine from the body, and is not recommended.[3]


1. Gill GV. Cimetidine overdose. *Lancet* 1978; **i:** 99.
2. Illingworth RN, Jarvie DR. Absence of toxicity in cimetidine overdosage. *BMJ* 1979; **i:** 453–4.
3. Meredith TJ, Volans GN. Management of cimetidine overdose. *Lancet* 1979; **ii:** 1367.
4. Nelson PG. Cimetidine and mental confusion. *Lancet* 1977; **ii:** 928.
5. Wilson JB. Cimetidine overdosage. *BMJ* 1979; **i:** 955.
6. Hiss J, *et al.* Fatal bradycardia after intentional overdose of cimetidine and diazepam. *Lancet* 1982; **ii:** 982.
7. Krenzelok EP, *et al.* Cimetidine toxicity: an assessment of 881 cases. *Ann Emerg Med* 1987; **1:** 1217–21.


## Precautions

Before giving cimetidine or other histamine $H_2$-antagonists to patients with gastric ulcers the possibility of malignancy should be considered since these drugs may mask symptoms and delay diagnosis. They should be given in reduced dosage to patients with renal impairment.

Intravenous injections of cimetidine should be given slowly and intravenous infusion is preferred, particularly for high doses and in patients with cardiovascular impairment.

**Breast feeding.** In the UK, manufacturers advise that mothers receiving cimetidine avoid breast feeding. Cimetidine is reported to be actively transported into breast milk, resulting in a milk:serum ratio 5.5 times higher than that expected with passive diffusion.[1] In one case, where cimetidine was detected in the milk of a nursing mother in concentrations higher than in her plasma, it was calculated[2] that the maximum amount of cimetidine that an infant could ingest assuming an intake of about 1 litre of milk daily and fed at the time of peak concentrations would be about 6 mg. However, the Committee on Drugs of the American Academy of Pediatrics has pointed out that there was no evidence of signs or symptoms attributable to the drug in the infant in this case,[3] despite 6 months of breast feeding, and cimetidine has been classified by that body as usually compatible with breast feeding.[4]


1. Oo CY, *et al.* Active transport of cimetidine into human milk. *Clin Pharmacol Ther* 1995; **58:** 548–55.
2. Somogyi A, Gugler R. Cimetidine excretion into breast milk. *Br J Clin Pharmacol* 1979; **7:** 627–9.
3. Berlin CM. Cimetidine and breast-feeding. *Pediatrics* 1991; **88:** 1294.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 07/05/04)


**Burns.** The clearance of cimetidine has been reported to be increased in burn patients, with the increase correlating to the size of the burn.[1] Despite another study that reported a decreased renal clearance (but an increased non-renal clearance) early in the evolution of burn injury,[2] it has been recommended that the dosage of cimetidine be increased in patients with burns, depending on the extent of injury. A requirement for increased dosage has also been noted in paediatric burns patients.[3]


1. Martyn JAJ, *et al.* Increased cimetidine clearance in burn patients. *JAMA* 1985; **253:** 1288–91.
2. Ziemniak JA, *et al.* Cimetidine kinetics during resuscitation from burn shock. *Clin Pharmacol Ther* 1984; **36:** 228–33.
3. Martyn JAJ, *et al.* Alteration by burn injury of the pharmacokinetics and pharmacodynamics of cimetidine in children. *Eur J Clin Pharmacol* 1989; **36:** 361–7.


**Helicobacter pylori testing.** In one study,[1] 2 of 11 patients with *Helicobacter pylori* infection had false-negative urea breath tests while receiving high dose ranitidine (600 mg daily). The breath test became positive again within 5 days of stopping therapy. The manufacturers of the breath test recommend it should not be performed for at least 2 weeks after stopping antisecretory drug therapy.


1. Chey WD, *et al.* Lansoprazole and ranitidine affect the accuracy of the C-urea breath test by a pH-dependent mechanism. *Am J Gastroenterol* 1997; **92:** 446–50.


**Hepatic impairment.** An increased resistance to $H_2$-receptor antagonists has been reported in patients with cirrhosis, see Ranitidine, p.1766. For a suggestion that dosage reduction of cimetidine may be required in patients with portal systemic encephalopathy, see Administration in Hepatic Impairment, below.

**Porphyria.** Cimetidine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

For reference to clinical and biochemical improvement in porphyric patients receiving cimetidine, see below.

**Renal impairment.** The clearance of cimetidine is reduced in renal impairment and dosage reduction is recommended (see under Administration in Renal Impairment, below).

## Interactions

Cimetidine and other $H_2$-antagonists can reduce the absorption of drugs such as dasatinib, ketoconazole, and possibly itraconazole, whose absorption is dependent on an acid gastric pH. For the effect of itraconazole on cimetidine see Antifungals, below.

Cimetidine may inhibit the hepatic metabolism of many drugs by binding to cytochrome P450 isoenzymes, notably CYP1A2, CYP2C9, CYP2D6, and CYP3A4. Although many such interactions may occur, only a few are considered clinically significant, notably those with phenytoin, theophylline, lidocaine, and oral anticoagulants. Avoidance of the combination, or a reduction in the dosage of these drugs may be required.

◊ Cimetidine can affect a wide range of drugs[1-4] but these interactions are of clinical significance for only a few, particularly those that have a narrow therapeutic index where the risk of toxicity may necessitate adjustment of dosage. The majority of interactions are due to binding of cimetidine to cytochrome P450 isoenzymes in the liver with subsequent inhibition of microsomal oxidative metabolism and increased bioavailability or plasma concentrations of drugs metabolised by these enzymes. A few interactions are due to competition for renal tubular secretion. Other mechanisms of interaction such as changes in hepatic blood flow play only a minor role.

Significant or potentially significant interactions have occurred with

- antiepileptics such as phenytoin (p.500) and carbamazepine (p.475)
- biguanide antidiabetics (p.438)
- lidocaine (p.1864)
- nifedipine (p.1353)
- opioid analgesics (p.103)
- procainamide (p.1378)
- theophylline (p.1145)
- tricyclic antidepressants such as amitriptyline (p.380)
- warfarin and other oral anticoagulants (p.1430)
- zalcitabine (p.913)
- zolmitriptan (p.628)

Combinations of these drugs and cimetidine should be avoided or used with caution, with monitoring of effects or plasma-drug concentrations and reductions in dosage as appropriate.

Famotidine, nizatidine, and ranitidine do not inhibit cytochrome P450, and the potential for drug interactions is therefore reduced.


1. Penston J, Wormsley KG. Adverse reactions and interactions with H -receptor antagonists. *Med Toxicol* 1986; **i:** 192–216.
2. Somogyi A, Muirhead M. Pharmacokinetic interactions of cimetidine 1987. *Clin Pharmacokinet* 1987; **12:** 321–66.
3. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.
4. Shinn AF. Clinical relevance of cimetidine drug interactions. *Drug Safety* 1992; **7:** 245–67.


**Alcohol.** Any interaction between $H_2$-antagonists and alcohol is generally thought unlikely to be clinically significant (see p.1627).

**Antacids.** Single-dose studies of the interaction between cimetidine and antacids[1] have shown reduced bioavailability of cimetidine as well as no interaction. The neutralising capacity of the antacid appears to be a factor in determining whether an interaction occurs and a dose with less than 50 mmol neutralising capacity will have little, if any, effect on cimetidine absorption. There is no evidence that the therapeutic efficacy of cimetidine is reduced and with long-term use of the combination the bioavailability of cimetidine is unlikely to be reduced.


1. Gugler R, Allgayer H. Effects of antacids on the clinical pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1990; **18:** 210–19.


**Antifungals.** *Itraconazole* increased the area under the concentration-time curve of cimetidine, and reduced the total plasma clearance and renal tubular secretory clearance of cimetidine in a pharmacokinetic study in 8 healthy subjects.[1] The authors proposed that this was due to inhibition of P-glycoprotein-mediated renal tubular secretion.


1. Karyekar CS, *et al.* Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol* 2004; **44:** 919–27.


**Antimuscarinics.** The antimuscarinic *propantheline* delays gastric emptying and reduces intestinal motility and has been reported to reduce the bioavailability of cimetidine.[1]


1. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11:** 629–31.


**Prokinetic drugs.** *Metoclopramide* may reduce the bioavailability of cimetidine possibly due to reduction of gastrointestinal transit time.[1-3] A similar interaction has been reported between cimetidine and the prokinetic drug *cisapride*.[4] The clinical significance of this interaction is questionable since such combinations may be clinically effective, although the use of cisapride is now restricted in many countries.


1. Gugler R, *et al.* Impaired cimetidine absorption due to antacids and metoclopramide. *Eur J Clin Pharmacol* 1981; **20:** 225–8.
2. Kanto J, *et al.* The effect of metoclopramide and propantheline on the gastrointestinal absorption of cimetidine. *Br J Clin Pharmacol* 1981; **11:** 629–31.
3. Barzaghi N, *et al.* Effects on cimetidine bioavailability of metoclopramide and antacids given two hours apart. *Eur J Clin Pharmacol* 1989; **37:** 409–10.
4. Kirch W, *et al.* Cisapride-cimetidine interactions; enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11:** 411–14.


**Sucralfate.** Licensed product information for the mucosal protectant sucralfate states that it has been shown to reduce the bioavailability of cimetidine and other $H_2$ antagonists, presumably due to binding in the gastrointestinal tract. The effect can be avoided by separating doses of the two drugs by 2 hours, but it is not clear whether the interaction has a clinical significance.

## Pharmacokinetics

Cimetidine is readily absorbed from the gastrointestinal tract and peak plasma concentrations are obtained after about an hour when given on an empty stomach; a second peak may be seen after about 3 hours. Food delays the rate and may slightly decrease the extent of absorption, with the peak plasma concentration occurring after about 2 hours.

The bioavailability of cimetidine after oral doses is about 60 to 70%. Cimetidine is widely distributed and has a volume of distribution of about 1 litre/kg and is weakly bound, about 20%, to plasma proteins. The elimination half-life from plasma is about 2 hours and is increased in renal impairment. Cimetidine is partially metabolised in the liver to the sulfoxide and to hydroxymethylcimetidine. About 50% of an oral dose, and 75% of an intravenous dose, is excreted unchanged in the urine in 24 hours. Cimetidine crosses the placental barrier and is distributed into breast milk.

◊ Reviews.


1. Somogyi A, Gugler R. Clinical pharmacokinetics of cimetidine. *Clin Pharmacokinet* 1983; **8:** 463–95.

2. Lin JH. Pharmacokinetic and pharmacodynamic properties of histamine H -receptor antagonists: relationship between intrinsic potency and effective plasma concentrations. *Clin Pharmacokinet* 1991; **20:** 218–36.
3. Gladziwa U, Klotz U. Pharmacokinetics and pharmacodynamics of H -receptor antagonists in patients with renal insufficiency. *Clin Pharmacokinet* 1993; **24:** 319–32.

**Children.** Renal function is limited in the first few months of life and half-lives of 1.1 to 3.7 hours have been reported for cimetidine in neonates.[1-3] A dosage regimen for neonates based on renal function has been suggested[1] with 15 to 20 mg/kg daily for full-term neonates, but with lower doses for premature neonates and those with renal dysfunction. However, single doses of 5 to 7 mg/kg may be sufficient to suppress gastric acid secretion in neonates.[3]

In older infants and children maturation of renal function is complete and the clearance of cimetidine is increased compared with that in adults while younger children show higher clearance values than older children. A typical dosage regimen for children is 30 mg/kg daily, in 3 or 4 divided doses.[4] However, even this dose might not produce optimal control of gastric acid.[5]

1. Ziemniak JA, *et al.* The pharmacokinetics and metabolism of cimetidine in neonates. *Dev Pharmacol Ther* 1984; **7:** 30–8.
2. Lloyd CW, *et al.* The pharmacokinetics of cimetidine and metabolites in a neonate. *Drug Intell Clin Pharm* 1985; **19:** 203–5.
3. Stile IL, *et al.* Pharmacokinetic evaluation of cimetidine in newborn infants. *Clin Ther* 1985; **7:** 361–4.
4. Somogyi A, *et al.* Cimetidine pharmacokinetics and dosage requirements in children. *Eur J Pediatr* 1985; **144:** 72–6.
5. Lambert J, *et al.* Efficacy of cimetidine for gastric acid suppression in pediatric patients. *J Pediatr* 1992; **120:** 474–8.

## Uses and Administration

Cimetidine is a histamine $H_2$-antagonist and inhibits actions of histamine mediated by $H_2$-receptors such as gastric acid secretion and pepsin output. It is used where inhibition of gastric acid secretion may be beneficial, as in peptic ulcer disease, including stress ulceration (p.1702), gastro-oesophageal reflux disease (p.1696), selected cases of persistent dyspepsia (p.1695), pathological hypersecretory states such as the Zollinger-Ellison syndrome (p.1704), and in patients at risk of acid aspiration (p.1693) during general anaesthesia or child birth. Cimetidine may also be used to reduce malabsorption and fluid loss in patients with the short bowel syndrome and to reduce the degradation of enzyme supplements given to patients with pancreatic insufficiency.

Cimetidine may be given orally, by the nasogastric route, or parenterally by the intravenous or intramuscular routes; the total daily dose by any route should not normally exceed 2.4 g. Although some formulations are prepared as the hydrochloride, strengths and doses are expressed in terms of the base. Cimetidine 100 mg is equivalent to about 114.4 mg of cimetidine hydrochloride. Doses should be reduced in renal impairment and may also need to be reduced in hepatic impairment (see below).

SPECIFIC DISEASE DOSES.

In the management of benign **gastric** and **duodenal ulceration** a single daily oral dose of 800 mg at bedtime is recommended, which should be given for at least 4 weeks in the case of duodenal, and for at least 6 weeks in the case of gastric, ulcers. Where appropriate a maintenance dose of 400 mg may then be given once daily at bedtime, or twice daily in the morning and at bedtime. Other regimens have also been used for treatment and maintenance.

In **gastro-oesophageal reflux disease** the recommended oral dose is 400 mg four times daily (with meals and at bedtime), or 800 mg twice daily, for 4 to 8 weeks. In pathological hypersecretory conditions, such as the **Zollinger-Ellison syndrome**, an oral dose of 300 or 400 mg four times daily is normally used, although sometimes higher doses may be necessary.

Doses of 200 to 400 mg orally, by nasogastric tube, or parenterally (200 mg only for direct intravenous injection) every 4 to 6 hours are recommended for the management of patients at risk from **stress ulceration** of the upper gastrointestinal tract. In patients at risk of developing the **acid aspiration syndrome**, an oral dose of 400 mg may be given 90 to 120 minutes before the induction of anaesthesia, or at the start of labour (in obstetric practice), and doses of up to 400 mg (by the parenteral route if appropriate, see below) may be repeated at intervals of 4 hours if required.

Doses of up to 200 mg four times daily have been taken for non-ulcer **dyspepsia**; 100 mg at night has been used in the prophylaxis of nocturnal heartburn.

To reduce the degradation of pancreatic enzyme supplements, patients with **pancreatic insufficiency**, as in cystic fibrosis (p.166), may be given oral cimetidine 800 to 1600 mg daily in 4 divided doses, 60 to 90 minutes before meals.

PARENTERAL ADMINISTRATION.

In the UK, the usual dose of cimetidine by intravenous injection is 200 mg, which should be given slowly over at least 5 minutes and may be repeated every 4 to 6 hours. If a larger dose is required, or if the patient has cardiovascular impairment, intravenous infusion is recommended. For an intermittent intravenous infusion the recommended dose is 200 to 400 mg every 4 to 6 hours if necessary. For a continuous intravenous infusion the recommended rate is 50 to 100 mg/hour. The usual intramuscular dose is 200 mg which may be repeated at intervals of 4 to 6 hours. In the USA, parenteral dosage recommendations are 300 mg every 6 to 8 hours by intramuscular injection or by slow intravenous injection over at least 5 minutes. The same dosage may be given by intermittent intravenous infusion over 15 to 20 minutes; for continuous intravenous infusion the recommended rate is 37.5 mg/hour, which may be preceded by 150 mg as an intravenous loading dose. However, a rate of 50 mg/hour is recommended for prevention of stress ulceration.

CHILDREN'S DOSES.

For **children** over one year of age 25 to 30 mg/kg daily may be given in divided doses, by mouth or parenterally. Under 1 year of age, 20 mg/kg daily in divided doses has been used (see also Children, under Pharmacokinetics, above).

**Administration in hepatic impairment.** The bioavailability of cimetidine may be increased in patients with cirrhosis[1,2] and a dosage reduction of up to 40% has been suggested in patients with portal systemic encephalopathy.[3] However, UK and US licensed drug information does not include recommendations for dosage adjustment in hepatic impairment.

1. Gugler R, *et al.* Altered disposition and availability of cimetidine in liver cirrhotic patients. *Br J Clin Pharmacol* 1982; **14:** 421–30.
2. Cello JP, Øie S. Cimetidine disposition in patients with Laennec's cirrhosis during multiple dosing therapy. *Eur J Clin Pharmacol* 1983; **25:** 223–9.
3. Ziemniak JA, *et al.* Hepatic encephalopathy and altered cimetidine kinetics. *Clin Pharmacol Ther* 1983; **34:** 375–82.

**Administration in renal impairment.** The dosage of cimetidine should be reduced in patients with renal impairment; suggested doses according to creatinine clearance (CC) are:

- CC over 50 mL/minute: normal dosage
- CC 30 to 50 mL/minute: 200 mg four times daily
- CC 15 to 30 mL/minute: 200 mg three times daily
- CC 0 to 15 mL/minute: 200 mg twice daily

Cimetidine is removed by haemodialysis, but not significantly removed by peritoneal dialysis.

**Bladder disorders.** Cimetidine effectively relieved symptoms in patients with painful bladder disease (encompassing conditions including cystitis, painful bladder syndrome, and urethral syndrome), especially suprapubic pain and nocturia, despite no apparent histological change in the bladder mucosa after treatment.[1]

1. Thilagarajah R, *et al.* Oral cimetidine gives effective symptom relief in painful bladder disease: a prospective, randomized, double-blind placebo-controlled trial. *BJU Int* 2001; **87:** 207–12.

**Dapsone toxicity.** Cimetidine might reduce the haemolysis and methaemoglobinaemia associated with dapsone. For references supporting this suggestion, see Effects on the Blood, under Dapsone, p.261.

**Diagnostic use.** Cimetidine blocks renal tubular secretion of creatinine and has been used experimentally to improve the accuracy of estimations of glomerular filtration rate from creatinine clearance in patients with renal disease.[1] Best results were achieved with a bolus dose of 1.2 g and the use of such a high dose was questioned.[2]

1. van Acker BAC, *et al.* Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 1992; **340:** 1326–9.
2. Agarwal R. Creatinine clearance with cimetidine for measurement of GFR. *Lancet* 1993; **341:** 188.

**Echinococcosis.** Cimetidine has been given with albendazole to increase its effect (by inhibiting its metabolism) in the treatment of echinococcosis (p.136).

**Immunomodulation.** Studies in *mice* and humans have shown that $H_2$-antagonists have an immunoregulatory effect.[1] T-lymphocyte suppressor cells have histamine $H_2$ receptors and cimetidine has been reported to reduce activity of these cells, thus enhancing immune response.[1,2] There is also some evidence that it enhances cellular immunity, notably natural killer cell activity.[3] This discovery has led to the investigation of cimetidine in a number of disorders associated with alteration of the immune response including eosinophilic fasciitis, herpesvirus infections, mucocutaneous candidiasis,[4] hypogammaglobulinaemia,[5] and various malignancies.[1]

1. Kumar A. Cimetidine: an immunomodulator. *DICP Ann Pharmacother* 1990; **24:** 289–95.
2. Snyman JR, *et al.* Cimetidine as modulator of the cell-mediated immune response in vivo using the tuberculin skin test as parameter. *Br J Clin Pharmacol* 1990; **29:** 257–60.
3. Katoh J, *et al.* Cimetidine and immunoreactivity. *Lancet* 1996; **348:** 404–5.
4. Polizzi B, *et al.* Successful treatment with cimetidine and zinc sulphate in chronic mucocutaneous candidiasis. *Am J Med Sci* 1996; **311:** 189–90.
5. White WB, Ballow M. Modulation of suppressor-cell activity by cimetidine in patients with common variable hypogammaglobulinemia. *N Engl J Med* 1985; **312:** 198–202.

***EOSINOPHILIC FASCIITIS.*** Eosinophilic fasciitis is a scleroderma-like syndrome of inflammation of the muscle fascia and associated eosinophilia and hypergammaglobulinaemia. Although it responds well to corticosteroid therapy in most cases, cimetidine has also been tried. The effect of cimetidine on eosinophilic fasciitis is unpredictable with both remission[1-4] and lack of response[5,6] having been reported in a few patients.

1. Solomon G, *et al.* Eosinophilic fasciitis responsive to cimetidine. *Ann Intern Med* 1982; **97:** 547–9.
2. Laso FJ, *et al.* Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; **98:** 1026.
3. Garcia-Morteo O, *et al.* Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1984; **100:** 318–19.
4. Farrell AM, *et al.* Eosinophilic fasciitis associated with autoimmune thyroid disease and myelodysplasia treated with pulsed methylprednisolone and antihistamines. *Br J Dermatol* 1999; **140:** 1185–7.
5. Loftin EB. Cimetidine and eosinophilic fasciitis. *Ann Intern Med* 1983; **98:** 111–12.
6. Herson S, *et al.* Cimetidine in eosinophilic fasciitis. *Ann Intern Med* 1990; **113:** 412–13.

***HERPESVIRUS AND PAPILLOMAVIRUS INFECTIONS.*** Although there have been numerous isolated and anecdotal reports of a beneficial response to cimetidine in patients with infections due to various *herpesviruses* (p.853), including genital herpes simplex,[1] infectious mononucleosis,[2,3] and herpes zoster[4-7] some of these reports have been criticised[8,9] mainly on the grounds that the majority of cases of herpes zoster will resolve within 2 to 3 weeks whether any treatment is given or not. Also, a double-blind placebo-controlled study involving 63 patients with herpes zoster[10] found no evidence that cimetidine relieved the pain or accelerated the rate of healing of lesions.

There are reports[11] of benefit from the use of cimetidine in patients with *viral warts* (p.1584), but controlled studies have failed to show significant benefit.[12,13]

1. Wakefield D. Cimetidine in recurrent genital herpes simplex infection. *Ann Intern Med* 1984; **101:** 882.
2. Goldstein JA. Cimetidine and mononucleosis. *Ann Intern Med* 1983; **99:** 410–11.
3. Goldstein JA. Cimetidine, ranitidine, and Epstein-Barr virus infection. *Ann Intern Med* 1986; **105:** 139.
4. Hayne ST, Mercer JB. Herpes zoster: treatment with cimetidine. *Can Med Assoc J* 1983; **129:** 1284–5.
5. Shandera R. Treatment of herpes zoster with cimetidine. *Can Med Assoc J* 1984; **131:** 279.
6. Mavligit GM, Talpaz M. Cimetidine for herpes zoster. *N Engl J Med* 1984; **310:** 318–19.
7. Arnot RS. Herpes zoster and cimetidine. *Med J Aust* 1984; **141:** 903.
8. Tyrrell DL. Course of herpes zoster. *Can Med Assoc J* 1984; **130:** 1109.
9. Giles KE. Herpes zoster and cimetidine. *Med J Aust* 1985; **142:** 283.
10. Levy DW, *et al.* Cimetidine in the treatment of herpes zoster. *J R Coll Physicians Lond* 1985; **19:** 96–8.
11. Glass AT, *et al.* Cimetidine therapy for recalcitrant warts in adults. *Arch Dermatol* 1996; **132:** 680–2.
12. Karabulut AA, *et al.* Is cimetidine effective for nongenital warts: a double-blind, placebo-controlled study. *Arch Dermatol* 1997; **133:** 533–4.
13. Rogers CJ, *et al.* Cimetidine therapy for recalcitrant warts in adults: is it any better than placebo? *J Am Acad Dermatol* 1999; **41:** 123–7.

***MALIGNANT NEOPLASMS.*** Because of its immunomodulatory effects cimetidine has been tried, with some reported benefit,[1-3] as an adjuvant in the management of a variety of malignant neoplasms such as those of the gastrointestinal tract (see p.664). However, a large randomised study[4] failed to show any benefit for cimetidine compared with placebo in gastric cancer. A similar study with ranitidine also failed to show any significant benefit.[5]

1. Tønnesen H, *et al.* Effect of cimetidine on survival after gastric cancer. *Lancet* 1988; **ii:** 990–2.
2. Adams WJ, Morris DL. Short-course cimetidine and survival with colorectal cancer. *Lancet* 1994; **344:** 1768–9.

3. Matsumoto S. Cimetidine and survival with colorectal cancer. *Lancet* 1995; **346:** 115.
4. Langman MJS, *et al.* Prospective, double-blind, placebo-controlled randomized trial of cimetidine in gastric cancer. *Br J Cancer* 1999; **81:** 1356–62.
5. Primrose JN, *et al.* A prospective randomised controlled study of the use of ranitidine in patients with gastric cancer. *Gut* 1998; **42:** 17–19.


**Mastocytosis.** Cimetidine, alone or with an antihistamine (histamine $H_1$-antagonist), has been reported to relieve gastrointestinal symptoms,[1,2] pruritus, and urticaria[3,4] in patients with mastocytosis (p.1138).


1. Hirschowitz BI, Groarke JF. Effect of cimetidine on gastric hypersecretion and diarrhea in systemic mastocytosis. *Ann Intern Med* 1979; **90:** 769–71.
2. Linde R, *et al.* Combination H1 and H2 receptor antagonist therapy in mastocytosis. *Ann Intern Med* 1980; **92:** 716.
3. Simon RA. Treatment of systemic mastocytosis. *N Engl J Med* 1980; **302:** 231.
4. Frieri M, *et al.* Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis: results of a double-blind clinical trial. *Am J Med* 1985; **78:** 9–14.


**Paracetamol toxicity.** It has been suggested that cimetidine might be of use in the treatment of paracetamol poisoning (see p.108) because of its inhibition of the cytochrome P450 system. However, there appears to be no evidence to support the claims of benefit made in some anecdotal reports.[1]


1. Kaufenberg AJ, Shepherd MF. Role of cimetidine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 1998; **55:** 1516–19.


**Porphyria.** There are reports[1-3] of patients with acute intermittent porphyria (p.1448) showing clinical and biochemical improvement during treatment with cimetidine. Cimetidine is, however, considered to be unsafe in patients with porphyria (see under Precautions, above).


1. Baccino E, *et al.* Cimetidine in the treatment of acute intermittent porphyria. *JAMA* 1989; **262:** 3000.
2. Horie Y, *et al.* Clinical usefulness of cimetidine treatment for acute relapse in intermittent porphyria. *Clin Chim Acta* 1995; **234:** 171–5.
3. Cherem JH, *et al.* Cimetidine and acute intermittent porphyria. *Ann Intern Med* 2005; **143:** 694–5.


**Skin disorders.** Cimetidine has been used alone[1-8] or with an antihistamine ($H_1$-antagonist)[5,8,9] in various skin disorders. $H_2$-antagonists such as cimetidine and ranitidine have produced improvement in certain types of *urticaria* (p.1584), especially those associated with cold or angioedema. Their routine use in urticaria is controversial, but in practice their addition to conventional treatment can be tried in resistant cases.[10-12] Little additional benefit has been found with combination therapy in dermographic urticaria.[13] Although they may act by antagonism of $H_2$-receptors on cutaneous blood vessels, other mechanisms of action may be involved.[8] Patients with *pruritus* (p.1582) of various causes may also respond to $H_2$-antagonists,[1,2,6,7,9] but studies in larger groups of patients have demonstrated no benefit.[3-5,14]


1. Easton P, Galbraith PR. Cimetidine treatment of pruritus in polycythemia vera. *N Engl J Med* 1978; **299:** 1134.
2. Hess CE. Cimetidine for the treatment of pruritus. *N Engl J Med* 1979; **300:** 370.
3. Harrison AR, *et al.* Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; **300:** 433–4.
4. Scott GL, Horton RJ. Pruritus, cimetidine and polycythemia. *N Engl J Med* 1979; **300:** 434. Correction. *ibid.*; 936.
5. Zappacosta AR, Hauss D. Cimetidine doesn't help pruritus of uremia. *N Engl J Med* 1979; **300:** 1280.
6. Schapira DV, Bennett JM. Cimetidine for pruritus. *Lancet* 1979; **i:** 726–7.
7. Aymard JP, *et al.* Cimetidine for pruritus in Hodgkin's disease. *BMJ* 1980; **280:** 151–2.
8. Theoharides TC. Histamine (H )-receptor antagonists in the treatment of urticaria. *Drugs* 1989; **37:** 345–55.
9. Deutsch PH. Dermatographism treated with hydroxyzine and cimetidine and ranitidine. *Ann Intern Med* 1984; **101:** 569.
10. Advenier C, Queille-Roussel C. Rational use of antihistamines in allergic dermatological conditions. *Drugs* 1989; **38:** 634–44.
11. Ormerod AD. Urticaria: recognition, causes, and treatment. *Drugs* 1994; **48:** 717–30.
12. Greaves MW. Chronic urticaria. *N Engl J Med* 1995; **332:** 1767–72.
13. Sharpe GR, Shuster S. In dermographic urticaria H receptor antagonists have a small but therapeutically irrelevant additional effect compared with H antagonists alone. *Br J Dermatol* 1993; **129:** 575–9.
14. Raisch DW, *et al.* Evaluation of a non-food and drug administration-approved use of cimetidine: treatment of pruritus resulting from epidural morphine analgesia. *DICP Ann Pharmacother* 1991; **25:** 716–8.


### Preparations

***BP 2008:*** Cimetidine Injection; Cimetidine Oral Solution; Cimetidine Oral Suspension; Cimetidine Tablets;
***USP 31:*** Cimetidine in Sodium Chloride Injection; Cimetidine Injection; Cimetidine Tablets.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Tagamet†; Ulcerfen; ***Austral.:*** Cimehexal; Magicul; Sigmetadine†; Tagamet; ***Austria:*** Acidex; Cimetag; Neutromed; Neutronorm; Sodexx Cimetidine; Ulcometin; Ulcostad; ***Belg.:*** Doccimeti; Nuardin; Tagamet; ***Braz.:*** Cigamete; Cimetetax†; Cimetidan; Cimetil†; Cimetilab; Cimetin†; Cimetina†; Cimetinax; Cimetival; Cintidina; Cinton†; Climatidine†; Duomet†; Etidine; Gastidin†; Laveran†; Novacimet†; Pristonal; Prometidine; Stomakon†; Tagaliv; Tagamet; Tranimet†; Ulcedine; Ulcenon; Ulcerac; Ulceracid†; Ulcimet; Ulcinax; Ulcitag†; Ulcitrat; ***Canad.:*** Gaviscon Prevent†; Novo-Cimetine; Nu-Cimet; Tagamet†; ***Cz.:*** CimLich†; Lock-2†; Primamet; ***Denm.:*** Aciloc; Acinil; Cimecodan; Hocimin†; Novamet; ***Fr.:*** Stomedine; Tagamet; ***Ger.:*** Azucimet†; Cime; Cimebeta; Cimehexal; Cimet†; CimLich; duraH2†; Gastroprotect; H 2 Blocker; Sigacimet†; Tagamet; ***Gr.:*** Alkastom†; Besidin†; Cimeton†; Gastrolene†; Tagamet; Tamper; ***Hong Kong:*** Cementin; Cimedine; Cimeta; Cimulcer†; Citidine; Gastab; Gastidine; Maritidine; Simaglen; Syncomet; Tagadine†; Tagamet; Ulcomet; ***Hung.:*** Histodil; ***India:*** Cimet†; ***Indon.:*** Cimexol; Corsamet; Licomet; Nulcer; Sanmetidin; Tagamet; Ulcedine; Ulcumet; Ulcusan; Ulsikur; Xepamet; ***Irl.:*** Cedine; Cimagen; Cimeldine; Dyspamet; Galenamet; Geramet; Pinamet; Tagamet; ***Israel:*** Cemidin; Cimetag; Cimi†; Tagamet; ***Ital.:*** Biomag; Brumetidina; Dina†; Etideme; Notul†; Stomet; Tagamet; Temic; Ulcedin; Ulcodina†; Ulcomedina†; Ulis; ***Malaysia:*** Cimulcer; Shintamet; Tagamet; Ulcidine†; Xepamet†; ***Mex.:*** Alcatex†; Antil†; Cimebec; Cimedul; Cimeffer; Cimetase; Colimet; Columina†; Gastrodina; Metidisol†; Procimeti; Sercim; Sinegastrin; Tagamet; Ulcedine†; Ulmarin; Ulserral; ***Neth.:*** Tagamet; ***Norw.:*** Cimal; Tagamet; ***NZ:*** Cytine; ***Philipp.:*** Antag; Ciclem; Cimecid; Cimulcer; Duogastril; Montidin; Tagamet; Ulcenon; ***Pol.:*** Altramet; Cimegast; ***Port.:*** Cim; Evicer†; Tagamet; Ulceridine†; ***Rus.:*** Histodil (Гистодил); ***S.Afr.:*** Aci-Med; Cimlok; Cinadine; Cymi; Hexamet; Lenamet; Secadine; Tagamet; Ulcim; ***Singapore:*** Cementin; Cimulcer; Citidine; Erlmetin†; Gastromet†; Himetin; Shintamet; Tagamet; Xepamet; ***Spain:*** Ali Veg; Fremet; Mansal†; Tagamet; ***Swed.:*** Acinil; Tagamet; ***Switz.:*** Malimed†; Tagamet†; ***Thai.:*** Aidar†; Alserine†; Cencamet; Cidine; Cigamet; Cimet-P†; Cimetine; Cimidine†; Cimulcer†; Citidine; Clinimet; CMD†; Duotric; Gastrodin†; Iwamet; Manomet; Med-Gastramet†; Milamet; Peptica; Pondarmett; Promet; Rinadine; Sertidine; Siamidine; Simaglen; Simex; Tagamet†; Ulcedine; Ulcemet; Ulcimet; Umamett; ***UAE:*** Cimetag; ***UK:*** Acitak†; Dyspamet; Galenamet; Peptimax†; Tagamet; Ultec†; Zita; ***USA:*** Tagamet; ***Venez.:*** Cavimet†; Cimetix†; Gadol; Iscaten†; Mempotal†.

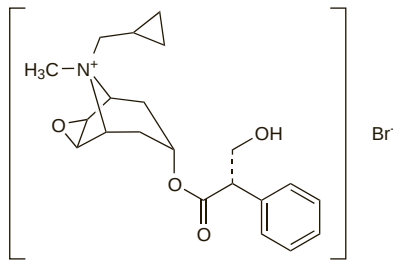
**Multi-ingredient:** ***Neth.:*** Aciflux.

## Cimetropium Bromide *(rINN)*

Bromuro de cimetropio; Cimetropii Bromidum; Cimétropium, Bromure de; DA-3177; Hyoscine-*N*-(cyclopropylmethyl) Bromide. 8-(Cyclopropylmethyl)-6β,7β-epoxy-3α-hydroxy-1α$H$,5α$H$-tropanium bromide, (–)-(*S*)-tropate.

Циметропия Бромид

$C_{21}H_{28}BrNO_4$ = 438.4.
*CAS — 51598-60-8.*
*ATC — A03BB05.*
*ATC Vet — QA03BB05.*



### Profile

Cimetropium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an antispasmodic in the treatment of gastrointestinal disorders, in usual doses of 50 mg two or three times daily orally or by rectal suppository. It has also been given intramuscularly or intravenously in usual doses of 5 mg.

◊ References.


1. Dobrilla G, *et al.* Longterm treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo controlled clinical trial. *Gut* 1990; **31:** 355–8.
2. Marzio L, *et al.* Effect of cimetropium bromide on esophageal motility and transit in patients affected by primary achalasia. *Dig Dis Sci* 1994; **39:** 1389–94.
3. Savino F, *et al.* Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr Gastroenterol Nutr* 2002; **34:** 417–9.


### Preparations

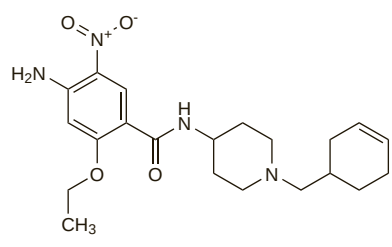
**Proprietary Preparations** (details are given in Part 3)
***Ital.:*** Alginor.

## Cinitapride *(rINN)*

Cinitaprida; Cinitapridum. 4-Amino-*N*-[1-(3-cyclohexen-1-ylmethyl)-4-piperidyl]-2-ethoxy-5-nitrobenzamide.

Цинитаприд

$C_{21}H_{30}N_4O_4$ = 402.5.
*CAS — 66564-14-5.*



### Profile

Cinitapride is a substituted benzamide used for its prokinetic properties. It is given as the acid tartrate in oral doses of 1 mg three times daily before meals in the management of gastroparesis and gastro-oesophageal reflux disease (p.1696).

### Preparations

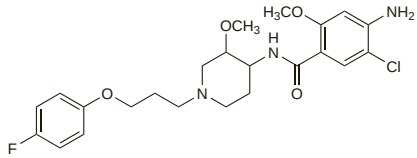
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Cinigest; Paxapride; Rogastril; ***Mex.:*** Pemix; ***Spain:*** Blaston; Cidine.

## Cisapride *(BAN, USAN, rINN)*

Cisaprid; Cisaprida; Cisapridas; Cisapride monohydraté; Cisapridum; Cisapridum monohydricum; Ciszaprid; Cyzapryd jednowodny; R-51619; Sisapridi. *cis*-4-Amino-5-chloro-*N*-{1-[3-(4-fluorophenoxy)propyl]-3-methoxy-4-piperidyl}-2-methoxybenzamide monohydrate.

Цизаприд

$C_{23}H_{29}ClFN_3O_4.H_2O$ = 484.0.
*CAS — 81098-60-4 (anhydrous cisapride).*
*ATC — A03FA02.*
*ATC Vet — QA03FA02.*



**Pharmacopoeias.** In *Eur.* (see p.vii).
**Ph. Eur. 6.2** (Cisapride Monohydrate; Cisapride BP 2008). A white or almost white powder; it exhibits polymorphism. Practically insoluble in water; soluble in dichloromethane; freely soluble in dimethylformamide; sparingly soluble in methyl alcohol. Protect from light.

## Cisapride Tartrate *(BANM, rINNM)*

Cisapride, tartrate de; Cisapridi tartras; Cisaprido tartratas; Cisaprid-tartarát; Cisapridtartrat; Ciszaprid-tartarát; Sisapridi-tartraatti; Tartrato de cisaprida.

Цизаприда Тартрат

$C_{27}H_{35}ClFN_3O_{10}$ = 616.0.

**Pharmacopoeias.** In *Eur.* (see p.vii).
**Ph. Eur. 6.2** (Cisapride Tartrate). A white or almost white powder. It exhibits polymorphism. Slightly soluble in water and in methyl alcohol; very slightly soluble in alcohol; freely soluble in dimethylformamide. Protect from light.

### Adverse Effects

The most commonly reported adverse effects with cisapride are gastrointestinal disturbances including abdominal cramps, borborygmi, and diarrhoea. Headache and lightheadedness may also occur. Hypersensitivity (including rash, pruritus, and bronchospasm), convulsions, extrapyramidal effects, and increased urinary frequency, have occasionally been reported. Cases of arrhythmia, including ventricular tachycardia, ventricular fibrillation, torsade de pointes, and QT interval prolongation have occurred rarely; fatalities have resulted, and have led to severe restrictions on its use (see Effects on the Heart, below). There have been a few cases of disturbances in liver function among patients receiving cisapride.

**Incidence of adverse effects.** A comparison of data from prescription-event monitoring in over 13 000 recipients of cisapride and from a further 9726 recipients involved in a controlled study showed that diarrhoea, in about 2 to 4% of patients, was the commonest adverse effect reported.[1] Other relatively common adverse effects were headache, abdominal pain, nausea and vomiting, and constipation, all in around 1 to 1.5% of patients. There were 46 reports in the prescription-event monitoring data of increased urinary frequency (plus a further 20 among the controlled study patients), and 5 reports of arrhythmias.


1. Wager E, *et al.* A comparison of two cohort studies evaluating the safety of cisapride: prescription-event monitoring and a large phase IV study. *Eur J Clin Pharmacol* 1997; **52:** 87–94.


**Effects on the heart.** Seven reports[1] of cardiac effects associated with cisapride were submitted to the WHO Programme for International Drug Monitoring between 1989 and 1991. They included palpitations in 4, tachycardia and hypertension in 1, and extrasystole in 2. Subsequent reports implicated cisapride in the development of prolonged QT interval and torsade de pointes or ventricular fibrillation or both.[2,3] By December 1999 the FDA had received 341 reports of heart rhythm abnormalities associated with cisapride use, including 80 reports of deaths. Most patients were either receiving other drugs known to impair cisapride metabolism (see Interactions, below) or had other factors predisposing to arrhythmias. In the light of earlier reports of cardiac effects and of evidence for a direct effect of cisapride on the heart at therapeutic concentrations, in 1998 the UK CSM **contra-indicated**[2] the use of cisapride in patients receiving drugs that could inhibit cisapride metabolism or that prolong the QT