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†.

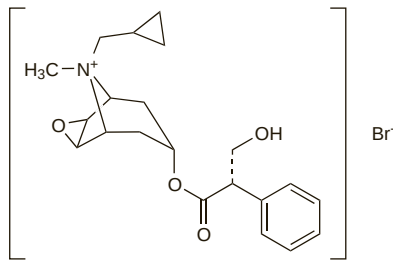
**Multi-ingredient:** ***Neth.:*** Aciflux.

## 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

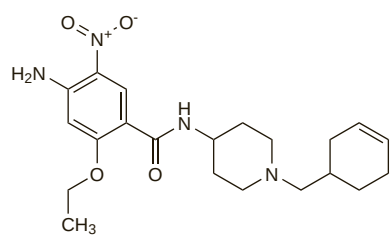
**Proprietary Preparations** (details are given in Part 3)
***Ital.:*** Alginor.

## 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

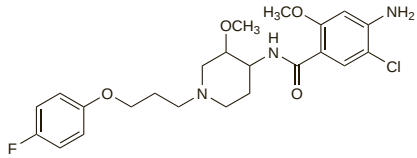
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Cinigest; Paxapride; Rogastril; ***Mex.:*** Pemix; ***Spain:*** Blaston; Cidine.

## 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

interval, as well as in patients with a history of QT interval prolongation, ventricular arrhythmia, or torsade de pointes, or other risk factors for arrhythmia (see Precautions, below). Neonates[4] (especially of low gestational age[5]) are vulnerable to cisapride-induced QT interval prolongation, and the CSM also specifically contra-indicated use in premature neonates[2] and noted that there were insufficient data to support use in children up to the age of 12. Other studies have also noted a prolongation of QT interval in children.[6,7] However, some commentators have questioned the general contra-indication in prematurity,[8] and one retrospective analysis estimated the rate of serious adverse events such as arrhythmia in premature newborns to be less than 1 in 11 000, excluding those cases related to concurrent treatment with a contra-indicated drug or to overdose.[9] Conversely, others emphasise the lack of objective evidence of benefit for cisapride in most paediatric indications.[10] The European Society of Paediatric Gastroenterology, Hepatology and Nutrition has published recommendations on the use of cisapride in paediatric gastro-oesophageal reflux disease,[11] including that the total daily dose of cisapride should rarely exceed 800 micrograms/kg, and that ECG monitoring should be performed before and after 3 days of treatment in certain groups such as premature infants.

The use of cisapride has also been the subject of warnings and restrictions in other countries. In the USA, prescribing information was amended in January 2000 to recommend that all patients should receive an ECG before beginning cisapride therapy and extending the contra-indications to use; the drug was subsequently **withdrawn** from general supply, remaining available only in severely restricted cases. In July 2000 cisapride was also withdrawn completely from the UK market.[12] In Europe, the European Commission decided that cisapride-containing products could be maintained with restricted indications; all patients given cisapride should be enrolled in either a study or registry of clinical safety, or a study of clinical effectiveness.[13] Despite a withdrawal of cisapride from general supply, a retrospective cohort study in South Korea found that it was still in use there up to 2 years later; in many instances cisapride had been given with contra-indicated drugs, which was associated with an increase in the risk of all-cause mortality.[14]


1. Olsson S, Edwards IR. Tachycardia during cisapride treatment. *BMJ* 1992; **305:** 748–9.
2. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid): risk of arrhythmias. *Current Problems* 1998; **24:** 11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023231&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
3. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med* 1996; **335:** 290–1.
4. Bernardini S, *et al.* Effect of cisapride on QTc interval in neonates. *Arch Dis Child Fetal Neonatal Ed* 1997; **77:** F241–3.
5. Dubin A, *et al.* Cisapride associated with QTc prolongation in very low birth weight preterm infants. *Pediatrics* 2001; **107:** 1313–16.
6. Hill SL, *et al.* Proarrhythmia associated with cisapride in children. *Pediatrics* 1998; **101:** 1053–6.
7. Khongphatthanayothin A, *et al.* Effects of cisapride on QT interval in children. *J Pediatr* 1998; **133:** 51–6.
8. Lander A, Desai A. The risks and benefits of cisapride in premature neonates, infants, and children. *Arch Dis Child* 1998; **79:** 469–71.
9. Ward RM, *et al.* Cisapride: a survey of the frequency of use and adverse events in premature newborns. *Pediatrics* 1999; **103:** 469–72.
10. Cairns P. The risks and benefits of cisapride. *Arch Dis Child* 1999; **80:** 493.
11. Vandenplas Y, *et al.* The role of cisapride in the treatment of pediatric gastroesophageal reflux: the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 1999; **28:** 518–28.
12. Committee on Safety of Medicines/Medicines Control Agency. Cisapride (Prepulsid) withdrawn. *Current Problems* 2000; **26:** 9–10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
13. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Cisapride: licences cancelled. *Current Problems* 2004; **30:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 14/06/06)
14. Choi N-K, *et al.* Increase in mortality rate following coprescription of cisapride and contraindicated drugs. *Ann Pharmacother* 2007; **41:** 667–73.


**Effects on the respiratory system.** Chest tightness, wheezing, and a fall in peak flow rate occurred in a patient with severe brittle asthma after taking cisapride 10 mg.[1] Four other cases of bronchospasm associated with cisapride were discussed in a subsequent report;[2] in 2 of these cases symptoms resolved on withdrawal and recurred on rechallenge.


1. Nolan P, *et al.* Cisapride and brittle asthma. *Lancet* 1990; **336:** 1443.
2. Pillans P. Bronchospasm associated with cisapride. *BMJ* 1995; **311:** 1472.


**Effects on the urinary tract.** There had been 12 cases of urinary disturbances associated with use of cisapride[1] reported to the Australian Adverse Drug Reactions Advisory Committee between March 1991 and July 1993. Five reports were of urinary incontinence, 8 involved frequency, and individual reports involved cystitis, hesitancy, and urinary retention. The majority of the cases involved women, and most patients were elderly.


1. Boyd IW, Rohan AP. Urinary disorders associated with cisapride. *Med J Aust* 1994; **160:** 579–80.


## Precautions

Cisapride should not be used when stimulation of muscular contractions might adversely affect gastrointestinal conditions as in gastrointestinal haemorrhage, obstruction, perforation, or immediately after surgery.

Cisapride is **contra-indicated** in the following patients:

- those receiving potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 such as macrolide antibacterials, azole antifungals, HIV-protease inhibitors, or nefazodone (see also Interactions, below)
- those taking other drugs that predispose to electrolyte disturbances or that prolong the QT interval
- those with a personal or family history of QT interval prolongation
- those with a history of ventricular arrhythmia or torsade de pointes

Furthermore, it should not be given to those with other risk factors for arrhythmia including:

- clinically significant heart disease
- uncorrected electrolyte disturbances (particularly hypokalaemia and hypomagnesaemia)
- renal failure
- respiratory failure

Use is also contra-indicated in premature infants for up to 3 months after birth.

Cisapride should be used with caution and in reduced doses in patients with hepatic or renal impairment. All patients should have their ECG, serum electrolytes, and renal function monitored before and during treatment.

Care should be taken not to exceed the recommended dose.

**Breast feeding.** No adverse effects have been observed in breast-fed infants whose mothers were receiving cisapride, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.


1. 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)


## Interactions

Cisapride is metabolised by the cytochrome P450 isoenzyme CYP3A4. Use with drugs that significantly inhibit this enzyme is contra-indicated as it may result in increased plasma concentrations of cisapride and hence a greater risk of QT interval prolongation and ventricular arrhythmias. Examples of such drugs include the azole antifungals ketoconazole, fluconazole, itraconazole, and miconazole; the macrolide antibacterials troleandomycin, azithromycin, erythromycin, and clarithromycin; the NNRTIs delavirdine and efavirenz; and the HIV-protease inhibitors. Nefazodone may interact similarly.

Cisapride should not be used in patients receiving other medication known to prolong the QT interval, including quinine or halofantrine, terfenadine, astemizole, certain antiarrhythmics such as amiodarone or quinidine, some antidepressants such as amitriptyline, phenothiazine antipsychotics, and sertindole. Cimetidine may enhance cisapride bioavailability. Grapefruit juice also increases the bioavailability of cisapride and they should not be taken together. In addition, drugs such as potassium-sparing diuretics, or insulin in acute settings, can result in altered electrolyte balance, and use with cisapride may also increase the risk of arrhythmias.

Antimuscarinics and possibly opioid analgesics may antagonise the gastrointestinal effects of cisapride. Because cisapride increases intestinal motility it may affect the absorption of other drugs, either diminishing absorption from the stomach or enhancing absorption from the small intestine. Prothrombin times may be increased in some patients receiving oral anticoagulants, and the effects of alcohol and some other CNS depressants may be enhanced.

◊ Reviews.


1. Bedford TA, Rowbotham DJ. Cisapride: drug interactions of clinical significance. *Drug Safety* 1996; **15:** 167–75.
2. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet* 2000; **39:** 49–75.


**Cardiovascular drugs.** Near syncope and a prolonged QT interval occurred in a patient taking cisapride and *diltiazem*.[1] Diltiazem may have inhibited the metabolism of cisapride. For mention of cisapride possibly reducing the absorption of *digoxin*, see p.1262.


1. Thomas AR, *et al.* Prolongation of the QT interval related to cisapride-diltiazem interaction. *Pharmacotherapy* 1998; **18:** 381–5.


**$H_2$-antagonists.** *Cimetidine*[1] but not *ranitidine*[2] has been reported to enhance the bioavailability of oral cisapride, possibly by inhibition of cisapride metabolism (cimetidine is an inhibitor of the cytochrome P450 isoenzyme CYP3A4). Cisapride conversely increases the rate of absorption and decreases the oral bioavailability of both cimetidine[1] and ranitidine (see p.1766).


1. Kirch W, *et al.* Cisapride-cimetidine interaction: enhanced cisapride bioavailability and accelerated cimetidine absorption. *Ther Drug Monit* 1989; **11:** 411–14.
2. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–305.


## Pharmacokinetics

Cisapride is readily absorbed from the gastrointestinal tract, with peak plasma concentrations achieved 1 to 2 hours after an oral dose. It undergoes extensive first-pass metabolism in the liver and gut wall, resulting in an absolute bioavailability of 35 to 40%. The main metabolic pathways are oxidative *N*-dealkylation by the cytochrome P450 isoenzyme CYP3A4, producing the major metabolite norcisapride, and aromatic hydroxylation. More than 90% of a dose is excreted as metabolites in the urine and faeces in about equal amounts. A small amount is distributed into breast milk. The elimination half-life is about 10 hours. Cisapride is about 98% bound to plasma proteins.

## Uses and Administration

Cisapride is a substituted benzamide used for its prokinetic properties. It stimulates gastrointestinal motility, probably by increasing the release of acetylcholine in the gut wall at the level of the myenteric plexus, increases the resting tone of the lower oesophageal sphincter, and increases the amplitude of lower oesophageal contractions. Gastric emptying is accelerated and the mouth-to-caecum transit time is reduced. Colonic peristalsis is also increased which decreases colonic transit time. Cisapride apparently lacks antidopaminergic effects (unlike metoclopramide, p.1747, to which it is chemically related) or direct parasympathomimetic activity and it does not affect prolactin release or gastric secretion. It is reported to be an agonist at serotonin-4 ($5\text{-}HT_4$) receptors.

Cisapride has been used mainly in the treatment of gastro-oesophageal reflux disease (p.1696), in disorders associated with decreased gastric motility (p.1694), and in non-ulcer dyspepsia. However, as mentioned under Effects on the Heart, above, its use is severely restricted by its propensity to cause cardiac arrhythmias, and it has been withdrawn completely in many countries, including the UK.

Cisapride is given as the monohydrate, but doses are calculated in terms of the anhydrous substance. Cisapride monohydrate 10.39 mg is equivalent to about 10 mg of anhydrous cisapride. It is taken orally 15 to 30 minutes before a meal and at bedtime, if necessary. Where still licensed, a usual oral dose is 5 to 10 mg three to four times daily up to a maximum daily dose of 40 mg. For discussion of dosage and use in children, see below.

Doses of cisapride should be reduced in patients with hepatic or renal impairment (see below).

**Administration in children.** Where still licensed, neonates, infants, and children have been given cisapride 200 micrograms/kg orally three or four times daily up to a maximum daily dose of 800 micrograms/kg. However, there are particular safety concerns over the use of cisapride in children because of the risk of cardiac arrhythmias (see Effects on the Heart, above). Special care is needed in neonates and cisapride is contra-indicated in premature neonates for 3 months after birth due to the increased risk of QT interval prolongation in this patient group.

Its efficacy has also been questioned and a systematic review[1] of the use of cisapride in children found no clear evidence that cisapride had a statistically significant effect in reducing symptoms of gastro-oesophageal reflux disease compared with placebo.


1. Augood C, *et al.* Cisapride treatment for gastro-oesophageal reflux in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 10/01/07).


**Administration in hepatic or renal impairment.** In patients with hepatic impairment the dose of cisapride should be half the usual dose, followed by adjustment depending on clinical response. In cases where renal impairment is not considered to contra-indicate the use of cisapride, a similar reduction in dose has been recommended.

## Preparations

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Cisap†; Cispride†; Digenormotil†; Etacri†; Fabrapride; Kinetizine†; Prepulsid†; Pulsar; Regalisa†; ***Austral.:*** Prepulsid†; ***Austria:*** Prepulsid†; ***Belg.:*** Prepulsid; ***Braz.:*** Prepulsid; ***Chile:*** Gastrokin†; Gastromet; Marovil†; Ondax; Prepulsid†; Tono-Cis†; ***Cz.:*** Prepulsid†; ***Denm.:*** Prepulsid†; ***Fin.:*** Prepulsid†; ***Fr.:*** Prepulsid; ***Gr.:*** Alimix†; Bozaktral; Cefanyl†; Cevilor†; Cisaprid†; Dolyzinax†; Elpegon†; Epasan†; Gastridol†; Kinussen†; Lamafer†; Lasapride†; Lirebin†; Lycalin†; Minsk†; Nastilox†; Oferin†; Ruvetine†; Saprimix†; Spabucol†; Systilan†; ***Hong Kong:*** Prepulsid†; ***Hung.:*** Coordinax†; ***India:*** Alipride; Cisalone†; Gastro; ***Indon.:*** Acpulsif; Disflux; Ethiprid; Guarposid; Pridesia; Stimulit; ***Irl.:*** Prepulsid†; ***Israel:*** Prepulsid; ***Mex.:*** Aposada; Cepriser; Enteropride; Eriken; Expril; Kinestase; Maprilex; Mavisid; Nodrix; Prepulsid†; Presistin; Profercol; Sapriken; Unamol; ***Neth.:*** Prepulsid; ***Norw.:*** Prepulsid†; ***NZ:*** Prepulsid†; ***Pol.:*** Gasprid; Gastronax; ***Port.:*** Prepulsid; ***S.Afr.:*** Prepulsid; ***Spain:*** Arcasin†; Fisiogastrol†; Kelosal†; Prepulsid†; ***Swed.:*** Prepulsid†; ***Switz.:*** Prepulsid†; ***Thai.:*** Cipasid; Cipride†; Cisapin†; Cisaride; Esorid†; Metison†; Palcid†; Prepulsid†; Pri-De-Sid†; ***Venez.:*** Adamin†; Cisamod; Isaprid†; Motilar†.

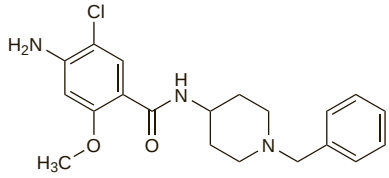
**Multi-ingredient:** ***Arg.:*** Digenormotil Plus†; Gastrimet Enzimatico†; Gastrimet†; Pulsar Enzimatico†; Pulsar Plus†; ***India:*** Gastro MPS; ***Mex.:*** Ergex.

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

Cleboprida; Clébopride; Clebopridum; LAS-9273. 4-Amino-*N*-(1-benzyl-4-piperidyl)-5-chloro-*o*-anisamide.

Клебоприд

$C_{20}H_{24}ClN_3O_2$ = 373.9.
*CAS — 55905-53-8.*
*ATC — A03FA06.*
*ATC Vet — QA03FA06.*



## Clebopride Malate *(BANM, rINNM)*

Clébopride, malate de; Clebopridi malas; Kleboprid malát; Klebopridimalaatti; Klebopridmalat; Kleboprid-malát; Kleboprido malatas; Malato de clebopride.

Клебоприда Малат

$C_{20}H_{24}ClN_3O_2,C_4H_6O_5$ = 508.0.
*CAS — 57645-91-7.*
*ATC — A03FA06.*
*ATC Vet — QA03FA06.*

**Pharmacopoeias.** In *Eur.* (see p.vii)
**Ph. Eur. 6.2** (Clebopride Malate). A white or almost white, crystalline powder. Sparingly soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in dichloromethane. The pH of a 1% solution in water is 3.8 to 4.2. Protect from light.

### Profile
Clebopride is a substituted benzamide similar to metoclopramide (p.1747), that is used for its antiemetic and prokinetic actions in nausea and vomiting (p.1700) and various other gastrointestinal disorders. It is given as the malate but doses are expressed in terms of the base. Clebopride malate 679 micrograms is equivalent to about 500 micrograms of clebopride.

Clebopride malate is given in a usual oral dose equivalent to clebopride 0.5 mg three times daily before meals or 0.5 to 1 mg by intramuscular or intravenous injection for acute symptoms. For dosage in children see below.

**Administration in children.** Adolescents aged 12 to 20 years may be given clebopride malate orally in a dose equivalent to clebopride 250 micrograms three times daily. An oral dose of 15 to 20 micrograms/kg daily in 3 divided doses may be used for children under 12; the following doses have been recommended:

- 1 to 4 years: 50 micrograms 3 times daily
- 4 to 8 years: 100 micrograms 3 times daily
- 8 to 10 years: 150 micrograms 3 times daily
- 10 to 12 years: 200 micrograms 3 times daily

### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Gastridin; ***Indon.:*** Clast; ***Ital.:*** Motilex; ***Port.:*** Clebofex; Clebutec; ***Spain:*** Cleboril.

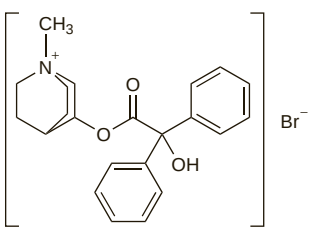
**Multi-ingredient: *Arg.:*** Eudon; Gastridin-E; Somasedan; ***Spain:*** Clanzoflat; Flatoril.

## Clidinium Bromide *(BAN, USAN, rINN)*

Bromuro de clidinio; Clidinii Bromidum; Clidinium, Bromure de; Klidiniumbromid; Klidiniumbromidi; Klidinyum Bromür; Ro-2-3773. 3-Benziloyloxy-1-methylquinuclidinium bromide.

Клидиния Бромид

$C_{22}H_{26}BrNO_3$ = 432.4.
*CAS — 7020-55-5 (clidinium); 3485-62-9 (clidinium bromide).*



**Pharmacopoeias.** In *US.*
**USP 31** (Clidinium Bromide). A white or nearly white, practically odourless, crystalline powder. Soluble in water and in alcohol; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

### Profile
Clidinium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used alone or more often with chlordiazepoxide in the symptomatic treatment of peptic ulcer disease and other gastrointestinal disorders.

### Preparations
***USP 31:*** Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules.

**Proprietary Preparations** (details are given in Part 3)
**Multi-ingredient: *Arg.:*** Libraxin; ***Canad.:*** Apo-Chlorax; Librax; ***Chile:*** Gastrolen; Lerogin; Libraxin; Lironex†; Sedogastrol†; Tensoliv; ***Fin.:*** Librax; ***Fr.:*** Librax; ***Gr.:*** Distedon; Librax; ***Hong Kong:*** Bralix; Librax; Medocalum†; ***India:*** Equirex; Normaxin; Spasrax; ***Indon.:*** Braxidin; Cliad; Klidibrax; Librax; Melidox; Renagas; ***Israel:*** Nirvaxal; ***Ital.:*** Librax; ***Malaysia:*** Apo-Chlorax†; Liblan; ***Port.:*** Librax; ***S.Afr.:*** Librax; ***Singapore:*** Apo-Chlorax; Chlobax; Librax; Medocalum; ***Switz.:*** Librax; Librocol; ***Thai.:*** Kenspa; Librax; Pobrax†; Tumax; Zepobrax†; ***Turk.:*** Klipaks; Librax; ***USA:*** Clindex; Librax; ***Venez.:*** Librax.

## Colocynth

Bitter Apple; Bitter Cucumber; Colocinto; Colocynth Pulp; Colocynthis; Coloquinte; Coloquintidas; Koloquinthen.

Колоцинт

NOTE. The synonym Bitter Apple has also been applied to the fruits of *Solanum incanum*.

### Profile
Colocynth is the dried pulp of the fruit of *Citrullus colocynthis* (Cucurbitaceae). It has a drastic purgative and irritant action and has been superseded by less toxic laxatives.

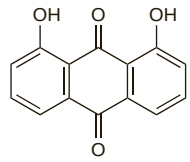
**Homoeopathy.** Colocynth has been used in homoeopathic medicines under the following names: Colocynthis; Coloc.

## Dantron *(BAN, rINN)*

Antrapurol; Chrysazin; Danthron; Dantrón; Dantrone; Dantroni; Dantronum; Dianthon; Dioxyanthrachinonum. 1,8-Dihydroxyanthraquinone.

Дантрон

$C_{14}H_8O_4$ = 240.2.
*CAS — 117-10-2.*
*ATC — A06AB03.*
*ATC Vet — QA06AB03.*



NOTE. Compounded preparations of dantron may be represented by the following names:

- Co-danthramer *x*/*y* (*BAN*)—where *x* and *y* are the strengths in milligrams of dantron and poloxamer respectively
- Co-danthrusate (*BAN*)—dantron 5 parts and docusate sodium 6 parts (w/w).

**Pharmacopoeias.** In *Br.*
**BP 2008** (Dantron). An orange, odourless or almost odourless, crystalline powder. Practically insoluble in water; very slightly soluble in alcohol; soluble in chloroform; slightly soluble in ether; dissolves in solutions of alkali hydroxides.

### Adverse Effects and Precautions
As for Senna, p.1769. Dantron may colour the urine pink or red. Discoloration and superficial sloughing of perianal skin can occur after prolonged contact, therefore dantron should not be used in infants wearing nappies (diapers) and should be used with caution in incontinent patients. The mucosa of the large intestine may be discoloured with prolonged use or high dosage.

In *rodents*, dantron has been associated with the development of intestinal and liver tumours. Consequently, its use has been restricted, see Uses and Administration, below.

◊ References to adverse effects occurring with dantron-containing laxatives include individual cases of leucopenia with liver damage,[1] greyish-blue skin discoloration,[2] and orange vaginal discharge.[3] There has also been a report of intestinal sarcoma in an 18-year-old girl with a history of prolonged use of a dantron-containing laxative.[4] In May 2000 the UK CSM restricted the use of dantron to terminally ill patients on the grounds that pre-clinical evidence had increased and dantron was now established as a potential human carcinogen.[5]


1. Tolman KG, *et al*. Possible hepatotoxicity of Doxidan. *Ann Intern Med* 1976; **84:** 290–2.
2. Darke CS, Cooper RG. Unusual case of skin discoloration. *BMJ* 1978; **1:** 1188–9.
3. Greer IA. Orange periods. *BMJ* 1984; **289:** 323.
4. Patel PM, *et al*. Anthraquinone laxatives and human cancer: an association in one case. *Postgrad Med J* 1989; **65:** 216–17.
5. Committee on Safety of Medicines/Medicine Control Agency. Danthron restricted to constipation in the terminally ill. *Current Problems* 2000; **26:** 4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007462&RevisionSelectionMethod=LatestReleased (accessed 08/11/06)


**Breast feeding.** The American Academy of Pediatrics[1] state that, although usually compatible with breast feeding, use of dantron by breast-feeding mothers has been reported to cause increased bowel activity in the infant.


1. 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 08/11/06)


### Pharmacokinetics
Dantron is metabolised by bacteria in the colon. Dantron or its metabolites are absorbed from the gastrointestinal tract, as indicated by discoloration of urine in some patients. Dantron or its metabolites are excreted in the faeces and the urine, and also in other secretions including breast milk.

### Uses and Administration
Dantron is an anthraquinone stimulant laxative but, unlike senna (p.1769), it is not a glycoside. It is given orally to treat constipation (p.1693) and is effective within 6 to 12 hours. However, because of concern over *rodent* carcinogenicity it has been withdrawn in some countries, and its use restricted in others. In the UK, it may be used only in terminally ill patients.

Dantron is given in doses of 25 to 75 mg when given with poloxamer 188 (p.1918) as co-danthramer, and in doses of 50 to 150 mg when given with docusate sodium (p.1725) as co-danthrusate. Doses are usually given at bedtime. For doses in children, see below.

**Administration in children.** Children under 12 years have been given dantron 12.5 to 25 mg orally as co-danthramer or 50 mg as co-danthrusate. Doses are usually given at bedtime. Children aged 12 years and over may be treated with the adult dose (see Uses and Administration, above).

The *BNFC* recommends similar doses to these, but restricts the use of co-danthramer to children aged 2 years and over, and the use of co-danthrusate to those aged 6 years and over.

Dantron should not be used in infants wearing nappies (diapers) as it may cause discoloration and superficial sloughing of the skin.

### Preparations
***BP 2008:*** Co-danthrusate Capsules.

**Proprietary Preparations** (details are given in Part 3)
**Multi-ingredient: *Braz.:*** Fenogar†; ***Chile:*** Modane; ***Irl.:*** Ailax; Codalax; Cotron; ***Mex.:*** Modaton; ***NZ:*** Codalax†; Conthram†; ***UK:*** Ailax†; Capsuvac; Codalax; Danlax; Normax.

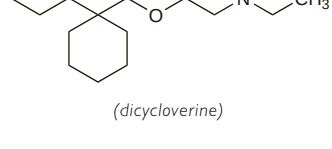
# Dicycloverine Hydrochloride

*(BANM, rINNM)*

Cloridrato de Diciclоverina; Dicikloverin-hidroklorid; Dicikloverino hidrochloridas; Dicyclomine Hydrochloride; Dicyclovérine, chlorhydrate de; Dicycloverini hydrochloridum; Dicykloverin-hydrochlorid; Dicykloverinhydroklorid; Disykloveriinihydrokloridi; Hidrocloruro de diciclоverina. 2-Diethylaminoethyl bicyclohexyl-1-carboxylate hydrochloride.

Дицикловерина Гидрохлорид

$C_{19}H_{35}NO_2$,HCl = 345.9.
*CAS — 77-19-0 (dicycloverine); 67-92-5 (dicycloverine hydrochloride).*
*ATC — A03AA07.*
*ATC Vet — QA03AA07.*



*(dicycloverine)*

**Pharmacopoeias.** In *Eur.* (see p.vii) and *US.*
**Ph. Eur. 6.2** (Dicycloverine Hydrochloride). A white or almost white, crystalline powder. It shows polymorphism. Soluble in water; freely soluble in alcohol and in dichloromethane. A 1% solution in water has a pH of 5.0 to 5.5.