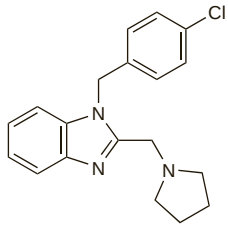
Clemizole Hydrochloride *(BANM, rINNM)*

AL-20; Clémizole, Chlorhydrate de; Clemizoli Hydrochloridum; Hidrocloruro de clemizol. 1-(4-Chlorobenzyl)-2-(pyrrolidin-1-ylmethyl)benzimidazole hydrochloride.

Клемизола Гидрохлорид

$C_{19}H_{20}ClN_3,HCl$ = 362.3.

CAS — 442-52-4 (clemizole); 1163-36-6 (clemizole hydrochloride).



(clemizole)

Profile
Clemizole hydrochloride is a sedating antihistamine (p.561). It has been used for the symptomatic relief of allergic conditions, in pruritic skin disorders, and in combination preparations for the treatment of symptoms of the common cold. Clemizole has also been applied topically as the hexachlorophene, the sodium sulfate, and the undecylate derivatives in topical and rectal preparations combined with corticosteroids and local anaesthetics, although as with other antihistamines, there is a risk of sensitisation.

See p.251 for the use of clemizole penicillin.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Arg.:*** Apracur†; ***Braz.:*** Ultraproct; ***Hong Kong:*** Ultraproct†; ***Indon.:*** Ultraproct; ***Thai.:*** Apracur; Scheriproct†.

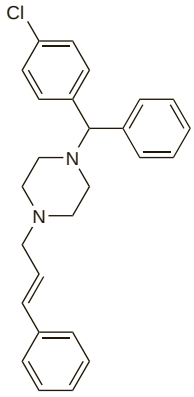
Clocinizine Hydrochloride *(rINNM)*

Chlorcinnazine Dihydrochloride; Clocinizine, Chlorhydrate de; Clocinizini Hydrochloridum; Hidrocloruro de clonizina. 1-(4-Chlorobenzhydryl)-4-cinnamylpiperazine dihydrochloride.

Клоцинизина Гидрохлорид

$C_{26}H_{27}ClN_2,2HCl$ = 475.9.

CAS — 298-55-5 (clocinizine).



(clocinizine)

Profile
Clocinizine hydrochloride, a piperazine derivative, is an antihistamine (p.561) given by mouth in combination preparations for the symptomatic treatment of upper respiratory-tract disorders, often with a decongestant.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Fr.:*** Denoral†; ***Ital.:*** Denoral†; ***Spain:*** Senioral.

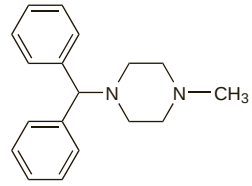
Cyclizine *(BAN, rINN)*

Ciclizina; Cyclizinum; Cyklizin; Siklizin; Syklitsiini. 1-Benzhydryl-4-methylpiperazine.

Циклизин

$C_{18}H_{22}N_2$ = 266.4.

CAS — 82-92-8.
ATC — R06AE03.
ATC Vet — QR06AE03.



Pharmacopoeias. In *Br.*

BP 2008 (Cyclizine). A white or creamy white, crystalline powder. Practically insoluble in water. It dissolves in most organic solvents and in dilute acids. M.p. about 107°. A saturated solution in water has a pH of 7.6 to 8.6.

Cyclizine Hydrochloride *(BANM, rINNM)*

Ciklizin-hidroklorid; Ciklizino hidrochloridas; Cyclizine, chlorhydrate de; Cyclizini hydrochloridum; Cyklizin hydrochlorid; Cyklizinhydroklorid; Hidrocloruro de ciclizina; Syklitsiinihydrokloridi.

Циклизина Гидрохлорид

$C_{18}H_{22}N_2,HCl$ = 302.8.
CAS — 303-25-3.
ATC — R06AE03.
ATC Vet — QR06AE03.

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

Ph. Eur. 6.2 (Cyclizine Hydrochloride). A white or almost white, crystalline powder. Slightly soluble in water and in alcohol. A 2% solution in alcohol 2 vol. and water 3 vol. has a pH of 4.5 to 5.5. Protect from light.

USP 31 (Cyclizine Hydrochloride). A white, odourless, crystalline powder or small colourless crystals. Soluble 1 in 115 of water and of alcohol and 1 in 75 of chloroform; insoluble in ether. pH of a 2% solution in alcohol 2 vol. and water 3 vol. is between 4.5 and 5.5. Store in airtight containers. Protect from light.

Cyclizine Lactate *(BANM, rINNM)*

Cyclizine, Lactate de; Cyclizini Lactas; Lactato de ciclizina.

Циклизина Лактат

$C_{18}H_{22}N_2,C_3H_6O_3$ = 356.5.
CAS — 5897-19-8.
ATC — R06AE03.
ATC Vet — QR06AE03.

Pharmacopoeias. *Br.* includes an injection of cyclizine lactate.

Incompatibility. Cyclizine lactate is reported to be incompatible with oxytetracycline hydrochloride, chlortetracycline hydrochloride, benzylpenicillin, and solutions with a pH of 6.8 or more.

Cyclizine Tartrate *(BANM, rINNM)*

Cyclizine, Tartrate de; Cyclizini Tartras; Tartrato de ciclizina.

Циклизина Тартрат

$C_{18}H_{22}N_2,C_4H_6O_6$ = 416.5.
ATC — R06AE03.
ATC Vet — QR06AE03.

Adverse Effects and Precautions
As for the sedating antihistamines in general, p.561. Cyclizine may aggravate severe heart failure. Hypotension may occur on injection.

Abuse. Cyclizine tablets have been abused either alone or with opioids for their euphoric effects.[1-7] They have been taken by mouth or used to make injections. It has been suggested that cyclizine dependence may occur when it is used with opioids in the treatment of chronic pain.[8]

1. Gott PH. Cyclizine toxicity—intentional drug abuse of a proprietary antihistamine. *N Engl J Med* 1968; **279:** 596.
2. Kahn A, Harvey GJ. Increasing misuse of cyclizine. *Pharm J* 1985; **235:** 706.
3. Atkinson MK. Misuse of cyclizine. *Pharm J* 1985; **235:** 773.
4. Halpin D. Misuse of cyclizine. *Pharm J* 1985; **235:** 773.
5. Council of the Pharmaceutical Society of Great Britain. Sales of preparations containing cyclizine. *Pharm J* 1985; **235:** 797.
6. Ruben SM, *et al.* Cyclizine abuse among a group of opiate dependents receiving methadone. *Br J Addict* 1989; **84:** 929–34.
7. Bassett KE, *et al.* Cyclizine abuse by teenagers in Utah. *Am J Emerg Med* 1996; **14:** 472–4.
8. Hughes AM, Coote J. Cyclizine dependence. *Pharm J* 1986; **236:** 130.

Effects on the blood. Agranulocytosis occurred in a patient after 6 weeks of treatment with cyclizine 50 mg three times daily.[1] The blood count returned to normal once cyclizine was withdrawn.

1. Collier PM. Agranulocytosis associated with oral cyclizine. *BMJ* 1986; **292:** 174.

Effects on the heart. In a study[1] of 11 patients with severe heart failure, cyclizine produced detrimental haemodynamic effects including increased systemic and pulmonary artery pressures and ventricular filling pressures, and negated the vasodilator effects of diamorphine. It was suggested that the use of cyclizine should be avoided in patients with acute myocardial infarction or severe heart failure.

1. Tan LB, *et al.* Detrimental haemodynamic effects of cyclizine in heart failure. *Lancet* 1988; **i:** 560–1.

Effects on the liver. An 8-year-old girl developed jaundice on 2 occasions after taking cyclizine hydrochloride 25 mg daily by mouth. 'Hypersensitivity hepatitis' was considered responsible.[1]

1. Kew MC, *et al.* "Hypersensitivity hepatitis" associated with administration of cyclizine. *BMJ* 1973; **2:** 307.

Pregnancy. For discussion of the use of antihistamines in pregnancy, including studies involving cyclizine, see p.563.

Interactions
As for the sedating antihistamines in general, p.563. Cyclizine may counteract the haemodynamic benefits of opioids (see Effects on the Heart, above) and this should be considered before using preparations that contain a combination of cyclizine and an opioid analgesic.

General anaesthetics. For a possible interaction between cyclizine premedication and *barbiturate anaesthetics* see under Thiopental, p.1795.

Pharmacokinetics
Cyclizine is absorbed from the gastrointestinal tract and has an onset of action within 2 hours. The duration of action is reported to be about 4 hours. Cyclizine is metabolised in the liver to the relatively inactive metabolite, norcyclizine. Both cyclizine and norcyclizine have plasma elimination half-lives of 20 hours. Less than 1% of the total oral dose is eliminated in the urine in 24 hours.

Uses and Administration
Cyclizine, a piperazine derivative, is a sedating antihistamine with antimuscarinic activity, although the sedative effects are not marked.

It is used as an antiemetic in the management of nausea and vomiting (p.564) including motion sickness, postoperative nausea and vomiting, after radiotherapy, and in drug-induced nausea and vomiting. It is included as an antiemetic with some opioids, and in combination preparations for the treatment of migraine attacks (p.616). Cyclizine is also used for the symptomatic treatment of vertigo (p.565) caused by Ménière's disease and other vestibular disturbances.

In the management of nausea and vomiting, cyclizine hydrochloride is given in a usual oral dose of 50 mg up to three times daily, although up to 200 mg may be given in 24 hours if necessary. For the prevention of motion sickness, the first dose should be given about 30 minutes before travelling. Children aged 6 to 12 years may be given 25 mg up to three times daily. Although not licensed in the UK, the *BNFC* suggests that those aged 1 month to 6 years may be given 0.5 to 1 mg/kg (maximum of 25 mg) up to 3 times daily.

Cyclizine is given intramuscularly or intravenously as the lactate. Doses of cyclizine lactate are similar to those of cyclizine hydrochloride given orally. For the prevention of postoperative nausea and vomiting the first dose of cyclizine lactate should be given about 20 minutes before the anticipated end of surgery.

Although not licensed in the UK, cyclizine is also available as suppositories on a named-patient basis. The *BNFC* suggests that children aged 2 to 6 years may be given rectal doses of 12.5 mg; those aged 6 to 12 years, 25 mg; and those aged 12 to 18 years, 50 mg. Doses may be given up to 3 times daily.

Cyclizine salts are used as antiemetics in combination with morphine or dipipanone; the use of such fixed-combination opioid preparations is considered to be

unsuitable for the prolonged treatment that may be required in palliative care. See also under Interactions, above.

Preparations

BP 2008: Cyclizine Injection; Cyclizine Tablets; Dipipanone and Cyclizine Tablets;
USP 31: Cyclizine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austria: Echnatol; ***Denm.:*** Marzine; ***Fin.:*** Marzine; ***Hong Kong:*** Marzine†; Valoid†; ***India:*** Medazine; ***Irl.:*** Valoid; ***Neth.:*** Kruidvat Reistabletten; ***Norw.:*** Marzine; ***NZ:*** Marzine; Nausicalm; Valoid; ***S.Afr.:*** Aculoid; Covamet; Emitex†; Medazine; Nauzine; Norizine†; Triazine; Valoid; ***Singapore:*** Marzine†; ***Swed.:*** Marzine†; ***Switz.:*** Marzine; ***UK:*** Valoid; ***USA:*** Bonine for Kids; Marezine.

Multi-ingredient: ***Austria:*** Echnatol B ; Migril; ***Fin.:*** Vertipam; ***Hong Kong:*** Migril†; Wellconal†; ***Irl.:*** Cyclimorph; Diconal†; Migril†; ***Neth.:*** Ercycof†; ***S.Afr.:*** Cyclimorph; Migril; Wellconal; ***UK:*** Cyclimorph; Diconal; Migril.

Cyproheptadine Hydrochloride

(BANM, rINNM)

Ciproheptadin-hidroklorid; Ciproheptadino hidrocloridas; Cyproheptadine, chlorhydrate de; Cyproheptadin-hydrochlorid seskvihydrát; Cyproheptadinhydroklorid; Cyproheptadini hydrochloridum; Cyproheptadini Hydrochloridum Sesquihydricum; Hidrocloruro de ciproheptadina; Siproheptadin Hidroklorür; Syproheptadiinihydrokloridi. 4-(5*H*-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride sesquihydrate.

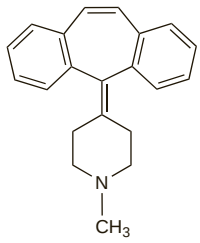
Ципрогептадина Гидрохлорид

$C_{21}H_{21}N,HCl,1/_2H_2O$ = 350.9.

CAS — 129-03-3 (cyproheptadine); 969-33-5 (anhydrous cyproheptadine hydrochloride); 41354-29-4 (cyproheptadine hydrochloride sesquihydrate).

ATC — R06AX02.

ATC Vet — QR06AX02.



(cyproheptadine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Cyproheptadine Hydrochloride). A white or slightly yellow, crystalline powder. Slightly soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.
USP 31 (Cyproheptadine Hydrochloride). A white to slightly yellow, odourless or practically odourless, crystalline powder. Soluble 1 in 275 of water, 1 in 35 of alcohol, 1 in 26 of chloroform, and 1 in 1.5 of methyl alcohol; practically insoluble in ether.

Adverse Effects and Precautions

As for the sedating antihistamines in general, p.561. Increased appetite and weight gain may occur with cyproheptadine.

Abuse. Dependence developed in a patient who took about 180 mg of cyproheptadine daily by mouth for 5 years.[1]

1. Craven JL, Rodin GM. Cyproheptadine dependence associated with an atypical somatoform disorder. *Can J Psychiatry* 1987; **32:** 143–5.

Effects on the nervous system. Antimuscarinic toxicity manifest by hallucinations and agitation developed in a 9-year-old child taking cyproheptadine 4 mg twice daily for migraine prophylaxis.[1]

1. Watemberg NM, *et al*. Central anticholinergic syndrome on therapeutic doses of cyproheptadine. *Pediatrics* 1999; **103:** 158–60.

Interference with diagnostic tests. Cyproheptadine reduced hypoglycaemia-induced growth hormone secretion by between 5 and 97% in 8 healthy subjects.[1] It was suggested that if patients receiving cyproheptadine were given a pituitary function test that used growth hormone response to insulin-induced hypoglycaemia, then cyproheptadine therapy should be stopped before the test.

UK licensed product information states that cyproheptadine may cause a false positive test result for tricyclic antidepressants in urine.

1. Bivens CH, *et al*. Inhibition of hypoglycaemia-induced growth hormone secretion by the serotonin antagonists cyproheptadine and methysergide. *N Engl J Med* 1973; **289:** 236–9.

Interactions

As for the sedating antihistamines in general, p.563.

Antidepressants. For reports suggesting that cyproheptadine can reduce the effectiveness of *SSRIs*, see under Fluoxetine, p.396.

Pharmacokinetics

After absorption from the gastrointestinal tract, cyproheptadine hydrochloride undergoes almost complete metabolism. Metabolites are excreted principally in the urine as conjugates, and also in the faeces.

Uses and Administration

Cyproheptadine, a piperidine derivative, is a sedating antihistamine with antimuscarinic, serotonin-antagonist, and calcium-channel blocking actions. It is used as the hydrochloride for the symptomatic relief of allergic conditions including urticaria and angioedema (p.565), rhinitis (p.565) and conjunctivitis (p.564), and in pruritic skin disorders (p.565). Other uses include the management of migraine (p.564). Cyproheptadine hydrochloride is given as the sesquihydrate although doses are expressed in terms of the anhydrous substance. Anhydrous cyproheptadine hydrochloride 10 mg is equivalent to about 11 mg of cyproheptadine hydrochloride sesquihydrate.

For allergic conditions and pruritus the oral dose in adults is initially 4 mg three times daily, adjusted as necessary. The average dose requirement is 12 to 16 mg daily in three or four divided doses, but up to 32 mg daily may occasionally be necessary. The dose for children aged 2 to 6 years is 2 mg two or three times daily increasing to a maximum of 12 mg daily and for children aged 7 to 14 years, 4 mg two or three times daily up to a maximum of 16 mg daily. Cyproheptadine is not recommended in debilitated elderly patients.

A dose of 4 mg is used for both prophylaxis and treatment of migraine and other vascular headaches and may be repeated after 30 minutes; patients who respond usually obtain relief with 8 mg, and this dose should not be exceeded within a 4- to 6-hour period. A maintenance dose of 4 mg may be given every 4 to 6 hours.

Other cyproheptadine salts that have been given orally include the acetylaspartate, aspartate, cyclamate, orotate, acefyllinate (7-theophyllineacetate), and the pyridoxal phosphate salt (dihexazine).

Abdominal migraine. Cyproheptadine has been tried in the prophylactic treatment of children with abdominal migraine (see Pizotifen, p.624).

Angina pectoris. Cyproheptadine was used successfully to treat 2 patients with Prinzmetal's angina (p.1157) refractory to standard treatment with calcium-channel blockers and nitrates.[1] Serotonin is an important endocrine mediator of coronary vasospasm and the beneficial effects of cyproheptadine were attributed to its activity as a serotonin antagonist.

1. Schecter AD, *et al*. Refractory Prinzmetal angina treated with cyproheptadine. *Ann Intern Med* 1994; **121:** 113–14.

Appetite disorders. Cyproheptadine has been widely used as an appetite stimulant, including for anorexia nervosa and cachexia (see under Megestrol, p.2115), but in the long-term appears to have little value in producing weight gain and such use is no longer generally recommended. There has been concern that cyproheptadine was being promoted and used inappropriately as an appetite stimulant in some developing countries.[1]

1. Anonymous. Cyproheptadine: no longer promoted as an appetite stimulant. *WHO Drug Inf* 1994; **8:** 66.

Carcinoid syndrome. The management of carcinoid tumours (p.643) is largely symptomatic. Cyproheptadine hydrochloride, a serotonin antagonist, has had limited success in relieving symptoms such as diarrhoea but somatostatin analogues may now be preferred.[1] It has been used successfully with fenclonine, aprotinin, methylprednisolone, and antibacterials to prevent complications arising from release of tumour metabolites during hepatic embolisation, a procedure sometimes used to relieve the symptoms of carcinoid syndrome.[2] There have been a few reports of tumour regression, in addition to symptomatic control, after treatment of carcinoid tumours with cyproheptadine.[3,4]

1. Caplin ME, *et al*. Carcinoid tumour. *Lancet* 1998; **352:** 799–805.
2. Maton PN, *et al*. Role of hepatic arterial embolisation in the carcinoid syndrome. *BMJ* 1983; **287:** 932–5. Correction to dosage. ibid.; 1664.
3. Harris AL, Smith IE. Regression of carcinoid tumour with cyproheptadine. *BMJ* 1982; **285:** 475.
4. Leitner SP, *et al*. Partial remission of carcinoid tumor in response to cyproheptadine. *Ann Intern Med* 1989; **111:** 760–1.

Serotonin syndrome. Cyproheptadine has been successfully used to treat the serotonin syndrome (p.416) in patients who have developed the syndrome after overdoses involving serotonergic drugs or who have had their antidepressant therapy changed without an adequate wash-out period.[1,2]

1. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med* 1994; **331:** 1021–2.
2. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother* 2001; **35:** 870–3.

Sexual dysfunction. Cyproheptadine has been tried in the management of sexual dysfunction induced by SSRIs (see Effects on Sexual Function under Fluoxetine, p.393) but may possibly reduce the effectiveness of the SSRI.

Preparations

BP 2008: Cyproheptadine Tablets;
USP 31: Cyproheptadine Hydrochloride Syrup; Cyproheptadine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)

Austral.: Periactin; ***Austria:*** Periactin; ***Belg.:*** Periactin; ***Braz.:*** Periatin; Preptin†; ***Chile:*** Viternum; ***Cz.:*** Peritol; ***Denm.:*** Periactin†; ***Fr.:*** Periactine; ***Ger.:*** Peritol; ***Hong Kong:*** Cyprogin; ***Hung.:*** Peritol; ***India:*** Apenorm†; Ciplactin; Peritol; Practin; ***Indon.:*** Alphahist; Apeton; Cydifar; Cylat; Ennamax; Esprocy; Glocyp; Heptasan; Lexahist; Poncohist; Profut; Prohessen; Pronicy; Sinapdin; ***Irl.:*** Periactin; ***Ital.:*** Periactin; ***Mex.:*** Viternum; ***Neth.:*** Periactin; ***NZ:*** Periactin; ***Pol.:*** Peritol; ***Port.:*** Trimetabol†; Viternum; ***Rus.:*** Peritol (Перитол); ***S.Afr.:*** Cipla-Actin; Periactin; ***Singapore:*** Cyprotin; ***Spain:*** Klarivitina†; Periactin; Viternum; ***Swed.:*** Periactin; ***Switz.:*** Periactin†; ***Thai.:*** Cyheptine; Cyprogin; Cyprono; Cyprosian; Cyprotec; Hepdine; Periactin; Polytab; ***Turk.:*** Prakten; Sipraktin; ***UK:*** Periactin; ***Venez.:*** Cyprodin; Eptacor†; Periactin†.

Multi-ingredient: ***Arg.:*** Apeplus; Apetitol Forte; Ciprocort; Ciprovit Calcio; Ciprovit Energizante; Ciprovit Magnesico; Mikesan; Nipiol†; Potencil; Sudevil Vita; ***Braz.:*** Apetivit BC; Apetiviton BC; Apevitin BC; Apmed; Bonapetit†; Cobactin; Cobaglobal; Cobavit; Cobavital; Polivitam†; Trimetabol; ***Chile:*** Apetrol; Grisetin Con Carnitina†; Orodina; Peracon; Revil; Rodepan; Viternum Vitaminado; ***Hong Kong:*** Petina Compound; Tres Orix Forte; ***Ital.:*** Carpantin†; ***Mex.:*** Cipro-Dexol†; Ciprolisina; Pangavit Pediatrico; Rocavit; ***Spain:*** Anti Anorex Triple; Childrevit†; Covitasa B12; Desarrol; Enoton; Glotone; Medenorex; Pantobamin; Pranzo; Stolina; Tonico Juventus; Tres Orix Forte†; Trimetabol; Troforex Pepsico; Vita Menal; ***Venez.:*** Cipromet†; Cyprodex.

Deptropine Citrate *(BANM, rINNM)*

Citrato de deptropina; Deptropiinisitraatti; Deptropincitrat; Deptropin-citrát; Deptropine, citrate de; Deptropini citras; Deptropino citratas; Dibenzheptropine Citrate. (1*R*,3*r*,5*S*)-3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yloxy)tropane dihydrogen citrate.

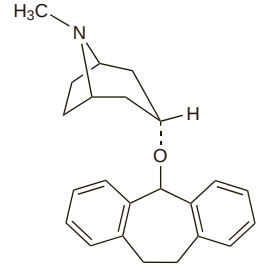
Дептропина Цитрат

$C_{23}H_{27}NO,C_6H_8O_7$ = 525.6.

CAS — 604-51-3 (deptropine); 2169-75-7 (deptropine citrate).

ATC — R06AX16.

ATC Vet — QR06AX16.



(deptropine)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Deptropine Citrate). A white or almost white, microcrystalline powder. Very slightly soluble in water and in dehydrated alcohol; practically insoluble in dichloromethane. A saturated solution in water has a pH of 3.7 to 4.5. Protect from light.

Profile

Deptropine citrate is a sedating antihistamine (p.561) with a marked antimuscarinic action. It was given by mouth mainly in the treatment of respiratory-tract disorders.