Profile
Chlorphenoxamine, a congener of diphenhydramine (p.577), has antimuscarinic and antihistaminic properties. It has been used in nausea, vomiting, and vertigo, and was formerly used in the symptomatic treatment of parkinsonism. Chlorphenoxamine has also been used in hypersensitivity reactions.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Systral; ***Hong Kong:*** Systral†; ***Indon.:*** Systral; ***Philipp.:*** Systral; ***Port.:*** Systral; ***Thai.:*** Systral; ***Turk.:*** Sistral; Systral.

Multi-ingredient: ***Austria:*** Spirbon; ***Ger.:*** Systral C†; ***S.Afr.:*** Analgen-SA†.

Cinnarizine *(BAN, USAN, rINN)*

Cinarizin; Cinarizina; Cinarizinas; Cinnarizin; Cinnarizinum; Cynaryzyna; 516-MD; R-516; R-1575; Sinarizin; Sinnaritsiini. 1-Benzhydryl-4-cinnamylpiperazine; (*E*)-1-(Diphenylmethyl)-4-(3-phenylprop-2-enyl)piperazine.

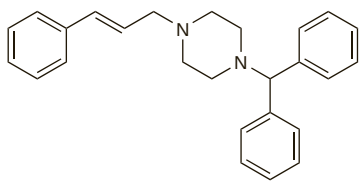
Циннаризин

$C_{26}H_{28}N_2$ = 368.5.

CAS — 298-57-7.

ATC — N07CA02.

ATC Vet — QN07CA02.



Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Cinnarizine). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in dichloromethane. Protect from light.

Adverse Effects and Precautions
As for the sedating antihistamines in general, p.561.

There have been rare reports of extrapyramidal symptoms after taking cinnarizine, sometimes associated with depressive feelings.

High doses of cinnarizine should be used with caution in patients with hypotension because of the possibility of decreasing blood pressure further.

Extrapyramidal disorders. For reference to extrapyramidal disorders associated with the use of cinnarizine, see Flunarizine, p.580.

Hypersensitivity. Immunologically-defined lichen planus pemphigoides has been reported[1] in a 72-year-old woman taking cinnarizine. Lesions began to clear when treatment was stopped but challenge with cinnarizine provoked severe itching and reactivation of pigmented lesions. Another case[2] has also been described.

1. Miyagawa S, *et al.* Lichen planus pemphigoides-like lesions induced by cinnarizine. *Br J Dermatol* 1985; **112:** 607–13.
2. Ramallal M, *et al.* Lichenoid eruption associated with cinnarizine use. *Pharm World Sci* 2002; **24:** 215–16.

Porphyria. Cinnarizine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Tinnitus. The Spanish System of Pharmacovigilance had received reports[1] of tinnitus associated with calcium-channel blockers; some of the reports, including the one relating to cinnarizine, were in patients also receiving other ototoxic drugs. WHO was said to have additional reports of tinnitus associated with calcium-channel blockers including cinnarizine.

1. Narváez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; **343:** 1229–30.

Weight gain. There has been a report[1] of weight gain in 4 patients who had taken cinnarizine for 1 to 2 years; in all cases the weight gain was associated with increased appetite.

1. Navarro-Badenes J, *et al.* Weight-gain associated with cinnarizine. *Ann Pharmacother* 1992; **26:** 928–30.

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

Pharmacokinetics
Cinnarizine is absorbed from the gastrointestinal tract, peak plasma concentrations occurring 2 to 4 hours after oral doses. It undergoes metabolism and has a half-life of 3 to 6 hours. Cinnarizine is excreted in the faeces mainly as unchanged drug, and in the urine predominantly as metabolites.

Uses and Administration
Cinnarizine is a piperazine derivative with antihistamine, sedative, and calcium-channel blocking activity. It is used for the symptomatic treatment of nausea and vertigo caused by Ménière's disease and other vestibular disorders (see Vertigo, p.565) and for the prevention and treatment of motion sickness (p.564). It is also used in the management of various peripheral and cerebral vascular disorders.

In the UK, the usual oral dose for vertigo and vestibular disorders is 30 mg three times daily. For motion sickness a dose of 30 mg is taken 2 hours before the start of the journey and 15 mg every 8 hours during the journey if necessary. Children aged 5 to 12 years are given half the adult dose for both indications. In other European countries, a dose of 75 mg once or twice daily has been given for vertigo and vestibular disorders. Doses of 75 mg have also been given 1 to 3 times daily for cerebrovascular disorders and 2 or 3 times daily for peripheral vascular disorders.

◊ References.

1. Shupak A, *et al.* Cinnarizine in the prophylaxis of seasickness: laboratory vestibular evaluation and sea study. *Clin Pharmacol Ther* 1994; **55:** 670–80.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Dismaren; Fabracin; Folcodal; Iroplex†; Natropas; Stugeron; ***Austria:*** Cinnabene; Pericephal; Stutgeron; ***Belg.:*** Stugeron; ***Braz.:*** Antigeron; Cinaran; Cinarivert†; Cinarix†; Cinazin†; Cinazon; Civertim; Cronogeron; Fluxon; Laberitin†; Labigeron; Nerizina†; Stugerina†; Stugeron; Vertigeron; Verzum; Vessel†; ***Chile:*** Cinergil; Siridone; Stugeron; ***Cz.:*** Cinedil†; Cinnabene; Stugeron; ***Denm.:*** Sepan; ***Gr.:*** Derozin; Stugeron; ***Hong Kong:*** Celenid†; Medozine; Stugeron; ***Hung.:*** Stugeron; ***India:*** Avidazine; Cintigo; Diziron; Stugeron; Vertiron; ***Indon.:*** Merron; Nariz; Penfas; Stugeron; Vertizine; ***Irl.:*** Stugeron; ***Israel:*** Stunarone; ***Ital.:*** Cinazyn; Stugeron; Toliman; ***Malaysia:*** Celenid†; Cereron†; Cinna; Cinnaron; Stugeron; Uphageron; ***Mex.:*** Bulasan; Cisaken; Dilateron-F; Dilper-INA; Karilex; Oblant; Stugeron; Venoxil; Winpar; ***Philipp.:*** Dizzinon; Niziran; Stugeron; Vertisin; ***Port.:*** Cinon; Stugeron; ***Rus.:*** Phezam (Фезам); Stugeron (Структум); ***S.Afr.:*** Purazine; Stugeron; ***Singapore:*** Celenid; Cinna; Cinnar; Cinnaron; Stugeron†; Urizine†; ***Spain:*** Stugeron; ***Switz.:*** Cerepar; Cinnageron; Cinnamed†; Stugeron; ***Thai.:*** C-Pela†; Celenid; Cenai; Cerebroad; Ceremin; Cinerine; Cinna; Cinnar; Cinnaza; Cinrizine; CN-25†; Linazine; Manoron; Med-Circuron†; Medozine; Siarizine; Silicin; Sorebral; Stugeron; Stugin; Stuno; Urizine; Vernarin; ***Turk.:*** Sefal; ***UK:*** Arlevert; Cinaziere†; Stugeron; ***Venez.:*** Cinaren; Cinarin; Sinver; Stugeron; Vericin.

Multi-ingredient: ***Arg.:*** Cadencial Plus; Cinacris; Difusil; Ribex; Vasodual†; ***Austria:*** Cinnarplus; ***Belg.:*** Touristil; ***Braz.:*** Coldrin; Exit; Forgrip†; Sureptil; ***Cz.:*** Arlevert; ***Fin.:*** Rinomar; ***Ger.:*** Arlevert; ***Hong Kong:*** C-Sik†; ***Hung.:*** Arlevert; ***India:*** Vertigil; ***Neth.:*** Primatour; ***Rus.:*** Omaron (Омарон); Piracezine (Пирацезин); ***Spain:*** Clinadil; Clinadil Compositum; Diclamina; ***Swed.:*** Rinomar.

Clemastine Fumarate
(BANM, USAN, rINNM)

Clémastine, fumarate de; Clemastini fumaras; Fumarato de clemastina; HS-592 (clemastine); Klemastiinifumaraatti; Klemastin fumarát; Klemastin Hidrojen Fumarat; Klemastinfumarat; Klemastino fumaratas; Klemastyny fumaran; Klemasztin-fumarát; Meclastine Fumarate; Mecloprodine Fumarate. (+)-(2*R*)-2-{2-[(*R*)-4-Chloro-α-methylbenzhydryloxy]ethyl}-1-methylpyrrolidine hydrogen fumarate.

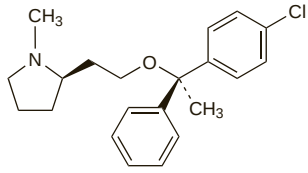
Клемастина Фумарат

$C_{21}H_{26}ClNO,C_4H_4O_4$ = 460.0.

CAS — 15686-51-8 (clemastine); 14976-57-9 (clemastine fumarate).

ATC — D04AA14; R06AA04.

ATC Vet — QD04AA14; QR06AA04.



(clemastine)

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Clemastine Fumarate). A white or almost white, crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol (70%); slightly soluble in alcohol (50%) and in methyl alcohol. A 10% suspension in water has a pH of 3.2 to 4.2.
USP 31 (Clemastine Fumarate). A colourless to faintly yellow, odourless, crystalline powder. Very slightly soluble in water; very slightly soluble in chloroform; slightly soluble in methyl alcohol. pH of a 10% suspension in water is between 3.2 to 4.2. Store in airtight containers at a temperature not exceeding 25°. Protect from light.

Adverse Effects and Precautions
As for the sedating antihistamines in general, p.561.

Breast feeding. The American Academy of Pediatrics[1] considers that clemastine should be given with caution to breast-feeding mothers, since it has been associated with adverse effects in the infant. Drowsiness, irritability, a high-pitched cry, neck stiffness, and refusal to feed in a 10-week-old breast-fed baby occurred 12 hours after her mother started treatment with clemastine.[2] Clemastine was detected in the mother's breast milk. The baby recovered and was feeding normally on the day after the drug was stopped.

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 08/04/04)
2. Kok THHG, *et al.* Drowsiness due to clemastine transmitted in breast milk. *Lancet* 1982; **i:** 914–15.

Porphyria. Clemastine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

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

Pharmacokinetics
Clemastine fumarate is rapidly and almost completely absorbed from the gastrointestinal tract; peak plasma concentrations are achieved in 2 to 4 hours. Unchanged drug and metabolites are excreted principally in the urine. An elimination half-life of about 21 hours has been reported. Clemastine is distributed into breast milk.

◊ References.

1. Schran HF, *et al.* The pharmacokinetics and bioavailability of clemastine and phenylpropanolamine in single-component and combination formulations. *J Clin Pharmacol* 1996; **36:** 911–22.

Uses and Administration
Clemastine fumarate, a monoethanolamine derivative, is a sedating antihistamine with antimuscarinic and moderate sedative properties. It has been reported to have a duration of action of about 10 to 12 hours. It is used 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).

Clemastine is given as the fumarate although doses are expressed in terms of the base. Clemastine fumarate 1.34 mg is equivalent to about 1 mg of clemastine base. The usual oral dose is 1 mg twice daily. Up to 6 mg daily has been given, particularly for urticaria and angioedema. Children aged 1 to 3 years may be given 250 to 500 micrograms twice daily; those aged 3 to 6 years, 500 micrograms twice daily; and those aged 6 to 12 years, 0.5 to 1 mg twice daily.

Clemastine fumarate may be given by intramuscular or slow intravenous injection in a total daily dose equivalent to 4 mg of clemastine for acute allergic reactions; for prophylaxis 2 mg is given by intravenous injection. The dose for children is 25 micrograms/kg daily in two divided doses by intramuscular injection.

Clemastine fumarate has also been used topically, although as with other antihistamines, there is a risk of sensitisation.

Preparations
BP 2008: Clemastine Oral Solution; Clemastine Tablets;
USP 31: Clemastine Fumarate Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Tavegyl; ***Braz.:*** Agasten; ***Canad.:*** Tavist; ***Cz.:*** Tavegyl; ***Denm.:*** Tavegyl; ***Ger.:*** Tavegil; ***India:*** Clamist; ***Indon.:*** Tavegyl; ***Ital.:*** Tavegil†; ***Mex.:*** Tavist; ***Neth.:*** Tavegil; ***Philipp.:*** Marsthine; Tavegyl; Tavist; ***Port.:*** Tavegyl; Tavist; ***Rus.:*** Tavegyl (Тавегил); ***S.Afr.:*** Tavegyl; ***Spain:*** Tavegil; ***Swed.:*** Tavegyl; ***Switz.:*** Tavegyl; ***Turk.:*** Tavegyl; ***UK:*** Tavegil; ***USA:*** Contac 12 Hour Allergy; Dayhist-1; Tavist Allergy.

Multi-ingredient: ***Braz.:*** Emistin; ***Ger.:*** Corto-Tavegil†; ***Mex.:*** Tavist-D†; ***Spain:*** Dexa Tavegil.

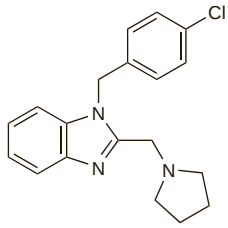
Clemizole Hydrochloride *(BANM, rINNM)*

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†.

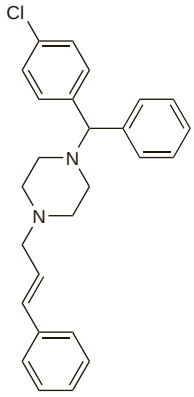
Clocinizine Hydrochloride *(rINNM)*

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.

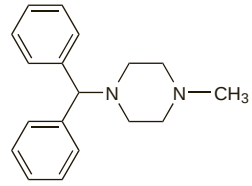
Cyclizine *(BAN, rINN)*

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