(p.1171), and for oedema, including that associated with heart failure (p.1165). Other indications include diabetes insipidus (p.2179).

Diuresis begins about 2 hours after an oral dose and lasts for 48 to 72 hours.

The usual dose in the treatment of **hypertension** is 25 mg daily, given either alone or with other antihypertensives, increasing to 50 mg daily if necessary.

In the treatment of **oedema** the usual initial dose is 25 to 50 mg daily. In severe cases a daily dose of 100 to 200 mg may be given. If possible lower doses should be used for maintenance; 25 to 50 mg daily or on alternate days may be adequate.

A dose for children is up to 2 mg/kg on alternate days.

In **diabetes insipidus** an initial dose of 100 mg twice daily has been used, reduced to a maintenance dose of 50 mg daily.

In the US, a preparation is available with improved bioavailability; suggested doses range from 15 to 50 mg daily for hypertension and 30 to 120 mg daily for oedema.

Preparations

BP 2008: Chlortalidone Tablets; Co-tenidone Tablets;
USP 31: Atenolol and Chlorthalidone Tablets; Chlorthalidone Tablets; Clonidine Hydrochloride and Chlorthalidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Euretico; Hygroton; ***Austral.:*** Hygroton; ***Austria:*** Hydrosan; Hygroton; ***Belg.:*** Hygroton; ***Braz.:*** Clordilon†; Clortalil; Clortil; Clorton†; Drenidra; Higroton; Neolidona; Taluron†; ***Cz.:*** Urandil†; ***Ger.:*** Hydrolong†; Hygroton; ***Gr.:*** Hygroton; ***Hong Kong:*** Hygroton†; ***Hung.:*** Hygroton; ***India:*** Hythalton†; Thalizide; ***Indon.:*** Hygroton; ***Israel:*** Aquadon; ***Ital.:*** Igroton; ***Malaysia:*** Hygroton†; ***Mex.:*** Anilid; Bioralin; Diuprol†; Hidrona; Hidropharm; Higroton; Sinhidron; ***Neth.:*** Hygroton; ***NZ:*** Hygroton; ***Pol.:*** Hygroton; Urandil; ***Port.:*** Hygroton; ***S.Afr.:*** Hygroton; ***Spain:*** Higrotona; ***Switz.:*** Hygroton; ***Turk.:*** Hygroton; ***UK:*** Hygroton; ***USA:*** Hygroton; Thalitone; ***Venez.:*** Higroton†.

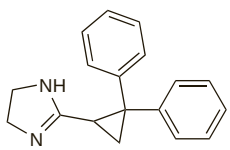
Multi-ingredient: ***Arg.:*** Atel C†; Bemplas; Hygroton-Reserpina†; Prenoretic; ***Austria:*** Arcablock comp; Atenolan comp; Atenolol comp; Atenotyrol comp†; Darebon; Polinorm; Selecturon; Tenoretic; Trasitensin; Trepress; ***Belg.:*** Logroton; Tenoretic; ***Braz.:*** Ablok Plus; Angipress CD; Atenoclor†; Atenoric; Atenuol CRT; Diupress; Higroton Reserpina; Tenoretic; ***Canad.:*** Apo-Atenidone; Tenoretic; ***Chile:*** Tenoretic†; ***Cz.:*** Amicloton; Atedon†; Atenolol Compositum†; Neocrystepin; Tenoretic; Trimecryton†; ***Denm.:*** Tenidon; Tenoretic; ***Fr.:*** Logroton; Tenoretic; Trasitensine; ***Ger.:*** Ate Lich comp; Atehexal comp; Atel; Ateno comp; Atenogamma comp; Atenolol AL comp; Atenolol comp; Blocotenol comp†; Combipresan†; Darebon†; Diu-Atenolol; duratenol comp†; Impresso†; Prelis comp; Sigabloc†; Tenoretic; Trasitensin†; Trepress; TRI-Normin; ***Gr.:*** Apress†; Chlotenor; Hygroton-Reserpine; Obosan; Tenoretic; Trasitensin; Typofen; ***Hong Kong:*** Target; Tenoret; Tenoretic; ***Hung.:*** Atenolol Comp†; Blokium Diu; ***India:*** Atecard-D†; Catapres Diu; Tenoclor; Tenoric; ***Indon.:*** Tenoret; Tenoretic; ***Irl.:*** Atecor CT; Atenetic; Tenoret; Tenoretic; ***Ital.:*** Atenigron; Carmian; Clortanol; Diube; Eupres; Igroseles; Igroton-Lopresor; Igroton-Reserpina; Target; Tenolone†; Tenoretic; Tranduir; Trasitensin; ***Malaysia:*** Apo-Atenidone; Logroton; Pretenol C; Target; Tenoret; Tenoretic; ***Mex.:*** Higroton-Res; Tenoretic; ***Neth.:*** Tenoretic; ***Philipp.:*** Tenoretic; ***Port.:*** Blokium Diu†; Tenoretic; ***Rus.:*** Atehexal Compositum (Атегексал Композитум); Tenoric (Тенорик); Tenorox (Тенороке); ***S.Afr.:*** Adco-Loten; Atenoblok Co†; Hygroton-Reserpine†; Tenchlor; Tenoretic; ***Singapore:*** Tenoret; Tenoretic; ***Spain:*** Aldoleo; Blokium Diu; Higrotensin; Higrotona Reserpina†; Normopresil; Tenoretic; Trasitensin; ***Switz.:*** Atedurex; ateno-basan comp†; Cardaxen plus; Co-Atenolol†; Cotenolol-Neo; Cotesifar†; Hygroton-Reserpine; Logroton; Primatenol Plus†; Sandoretic; Slow-Trasitensine; Tenoretic; ***Thai.:*** Tenoret†; Tenoretic†; ***Turk.:*** Regroton; Tenoretic; ***UK:*** Atenix-Co; Kalspare; Tenchlor; Tenoret; Tenoretic; Totaretic; ***USA:*** Clorpres; Combipres†; Demi-Regroton; Regroton; Tenoretic; ***Venez.:*** Blokiuret; Tenoretic.

Cibenzoline *(BAN, rINN)*

Cibenzolina; Cibenzolinum; Cifenline *(USAN)*; Ro-22-7796; Ro-22-7796/001 (cibenzoline succinate); UP-339-01. (±)-2-(2,2-Diphenylcyclopropyl)-2-imidazoline.

Цибензолин

$C_{18}H_{18}N_2$ = 262.3.
CAS — 53267-01-9 (cibenzoline); 100678-32-8 (cibenzoline succinate).
ATC — C01BG07.
ATC Vet — QC01BG07.



Adverse Effects and Precautions

Cibenzoline may cause neurological and gastrointestinal adverse effects including vertigo, tremor, nausea, vomiting, and diarrhoea. Other adverse effects include fatigue, visual disturbances, and hypoglycaemia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias. It also has a negative inotropic effect and may reduce blood pressure.

Cibenzoline is contra-indicated in patients with heart block and severe heart failure. It should be used with caution in the elderly and in renal impairment, and doses should be reduced.

Effects on the neuromuscular system. Myasthenia-like symptoms have been reported[1-3] in patients with renal impairment taking cibenzoline, including severe respiratory depression in some cases.[2,3]

1. Kasuga A, *et al.* Myasthenia-like syndrome induced by overdosage of cibenzoline. *Intern Med* 1996; **35:** 512–14.
2. Similowski T, *et al.* Neuromuscular blockade with acute respiratory failure in a patient receiving cibenzoline. *Thorax* 1997; **52:** 582–4.
3. Inada K, *et al.* A case of severe respiratory depression due to cibenzoline overdosage induced by a transient renal dysfunction. *Int J Cardiol* 2002; **82:** 177–8.

Hypoglycaemia. Cibenzoline therapy was associated with severe hypoglycaemia in a 67-year-old patient.[1] The plasma-cibenzoline concentration was 1800 nanograms/mL which would probably be considered toxic since the accepted therapeutic trough range is 200 to 600 nanograms/mL. A case-control study[2] also suggested that the risk of hypoglycaemia is increased by cibenzoline.

1. Hilleman DE, *et al.* Cibenzoline-induced hypoglycemia. *Drug Intell Clin Pharm* 1987; **21:** 38–40.
2. Takada M, *et al.* The relationship between risk of hypoglycemia and use of cibenzoline and disopyramide. *Eur J Clin Pharmacol* 2000; **56:** 335–42.

Interactions

Cibenzoline should not be used with other drugs that prolong the QT interval since the risk of arrhythmias may be increased.

Histamine H_2-antagonists. Increased blood concentrations and prolonged half-lives of cibenzoline occurred in healthy subjects given *cimetidine* but the clinical importance of this was unknown.[1] The interaction did not occur with *ranitidine*.

1. Massarella JW. The effects of cimetidine and ranitidine on the pharmacokinetics of cifenline. *Br J Clin Pharmacol* 1991; **31:** 481–3.

Pharmacokinetics

Cibenzoline is well absorbed from the gastrointestinal tract after oral use, with a bioavailability of about 90%. It is about 50 to 60% bound to plasma proteins. About 60% of a dose is excreted unchanged in the urine and the elimination half-life is reported to be about 7 hours.

Uses and Administration

Cibenzoline is a class I antiarrhythmic (p.1153) that has been classified as either Ia or Ic; it also has some class III and class IV properties. It is used in the management of ventricular and supraventricular arrhythmias (p.1160). Cibenzoline is given by mouth as the succinate or intravenously as a mixture of the base and succinate, but doses for both routes are expressed in terms of the base; 145 mg of cibenzoline succinate is equivalent to about 100 mg of base. The usual oral dose of cibenzoline succinate is the equivalent of 260 to 390 mg cibenzoline daily. The usual intravenous dose is the equivalent of 1 mg/kg cibenzoline base given over 2 to 5 minutes. Dosage should be reduced in the elderly (below), and in renal impairment (below).

◊ Reviews.

1. Harron DW, *et al.* Cibenzoline: a review of its pharmacological properties and therapeutic potential in arrhythmias. *Drugs* 1992; **43:** 734–59.

Administration in the elderly. The renal and non-renal clearance of cibenzoline was found to decrease with increasing age in healthy subjects.[1] The mean elimination half-life was 7 hours in the 20- to 30-year age group and 10.5 hours in the 70- to 80-year age group. The reduction in renal clearance was considered to be related to the decrease in creatinine clearance with increasing age. The results suggested that older patients may need lower doses than younger patients to maintain therapeutic plasma-cibenzoline concentrations. Licensed product information recommends a dosage of 130 mg daily in two divided doses in elderly patients.

1. Brazzell RK, *et al.* Age and cibenzoline disposition. *Clin Pharmacol Ther* 1984; **36:** 613–19.

Administration in renal impairment. A study[1] in patients with normal or impaired renal function has suggested that in renal impairment initial loading doses of cibenzoline may be equivalent to those used in normal renal function although maintenance doses should be reduced to about two-thirds of normal. Oral doses recommended in licensed product information, based on creatinine clearance (CC), are as follows:

- CC 20 to 40 mL/min: the equivalent of 3 mg/kg daily
- CC 10 to 20 mL/min: the equivalent of 2.5 mg/kg daily

1. Aronoff G, *et al.* Bioavailability and kinetics of cibenzoline in patients with normal and impaired renal function. *J Clin Pharmacol* 1991; **31:** 38–44.

Preparations

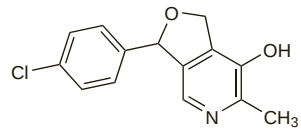
Proprietary Preparations (details are given in Part 3)
Belg.: Cipralan; ***Fr.:*** Cipralan; Exacor; ***Jpn:*** Cibenol.

Cicletanine *(BAN, USAN, rINN)* ⊗

(±)-BN-1270; Cicletanina; Ciclétanine; Cicletaninum; (±)-Cycletanide; Win-90000. (±)-3-(*p*-Chlorophenyl)-1,3-dihydro-6-methylfuro[3,4-*c*]pyridin-7-ol.

Циклетанин

$C_{14}H_{12}ClNO_2$ = 261.7.
CAS — 89943-82-8;.
ATC — C03BX03.
ATC Vet — QC03BX03.



Cicletanine Hydrochloride *(BANM, rINNM)* ⊗

Ciclétanine, Chlorhydrate de; Cicletanini Hydrochloridum; Hidrocloruro de cicletanina.

Циклетанина Гидрохлорид

$C_{14}H_{12}ClNO_2$,HCl = 298.2.
CAS — 89943-82-8;.
ATC — C03BX03.
ATC Vet — QC03BX03.

Profile

Cicletanine hydrochloride is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307). It is used in the treatment of hypertension (p.1171) in a usual oral dose of 50 to 100 mg daily.

Preparations

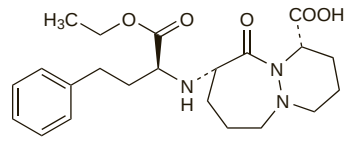
Proprietary Preparations (details are given in Part 3)
Cz.: Tenstaten†; ***Fr.:*** Tenstaten; ***Ger.:*** Justar.

Cilazapril *(BAN, USAN, rINN)*

Cilazapril monohydrát; Cilazaprilis; Cilazaprilum; Cilazaprilum Monohydricum; Ro-31-2848 (anhydrous cilazapril); Ro-31-2848/006 (cilazapril monohydrate); Silatsapriili; Silazapril. (1*S*,9*S*)-9-[(*S*)-1-Ethoxycarbonyl-3-phenylpropylamino]-10-oxoperhydropyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid monohydrate.

Цилазаприл

$C_{22}H_{31}N_3O_5$,H_2O = 435.5.
CAS — 88768-40-5 (anhydrous cilazapril); 92077-78-6 (cilazapril monohydrate).
ATC — C09AA08.
ATC Vet — QC09AA08.



Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Cilazapril). A white or almost white crystalline powder. Slightly soluble in water; freely soluble in dichloromethane and in methyl alcohol. Protect from light.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Cilazapril acts as a prodrug of the diacid cilazaprilat, its active metabolite. After oral dosage and absorption of cilazapril it is rapidly metabolised in the liver to cilazaprilat, the bioavailability of which is about 60%. Peak plasma concentrations of cilazaprilat occur within 2 hours of an oral dose of cilazapril. Cilazaprilat is elim-