Pharmacopoeias. In *Jpn.*

Profile
Bunazosin is an alpha$_1$-adrenoceptor blocker (p.1153) with general properties similar to those of prazosin (p.1375). It is given orally as the hydrochloride in the management of hypertension; the usual maintenance dose of bunazosin hydrochloride is 3 to 6 mg daily but up to 12 mg daily has been given.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Andante; ***Indon.:*** Detantol; ***Jpn:*** Detantol; ***Thai.:*** Detantol.

Bupranolol Hydrochloride *(rINNM)* ⊗

B-1312; Bupranolol, Chlorhydrate de; Bupranololi Hydrochloridum; Hidrocloruro de bupranolol; KL-255. 1-*tert*-Butylamino-3-(6-chloro-*m*-tolyloxy)propan-2-ol hydrochloride.

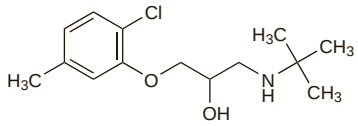
Бупранолола Гидрохлорид

$C_{14}H_{22}ClNO_2$,HCl = 308.2.

CAS — 14556-46-8 (bupranolol); 15148-80-8 (bupranolol hydrochloride).

ATC — C07AA19.

ATC Vet — QC07AA19.



(bupranolol)

Pharmacopoeias. In *Jpn.*

Profile
Bupranolol is a beta blocker (p.1225). It is given as the hydrochloride in usual oral doses of 100 to 400 mg daily in the management of cardiovascular disorders.

Bupranolol eye drops have been used in the management of glaucoma.

Preparations
Proprietary Preparations (details are given in Part 3)
Ger.: Betadrenol.

Multi-ingredient: ***Austria:*** Betamed.

Butalamine Hydrochloride *(BANM, rINNM)*

Butalamine, Chlorhydrate de; Butalamini Hydrochloridum; Hidrocloruro de butalamina; LA-1221. *NN*-Dibutyl-*N′*-(3-phenyl-1,2,4-oxadiazol-5-yl)ethylenediamine hydrochloride.

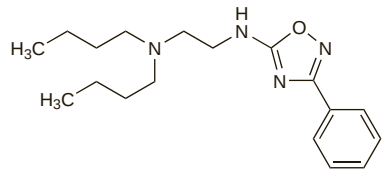
Буталамина Гидрохлорид

$C_{18}H_{28}N_4O$,HCl = 352.9.

CAS — 22131-35-7 (butalamine); 56974-46-0 (butalamine hydrochloride).

ATC — C04AX23.

ATC Vet — QC04AX23.



(butalamine)

Profile
Butalamine hydrochloride is a vasodilator that has been used in the management of peripheral and cerebral vascular disorders.

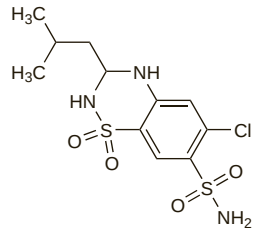
Butizide *(rINN)* ⊗

Buthiazide *(USAN)*; Butitsidi; Butizid; Butizida; Butizidum; Isobutylhydrochlorothiazide; Thiabutazide. 6-Chloro-3,4-dihydro-3-isobutyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Бутизид

$C_{11}H_{16}ClN_3O_4S_2$ = 353.8.

CAS — 2043-38-1.



Profile
Butizide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p.1307). It is used for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Butizide is given orally, usually with spironolactone; the usual maintenance dose for oedema or hypertension is 5 to 10 mg daily. It has also been given with other antihypertensive drugs.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Aldactone Saltucin; Buti-Spirobene; ***Ger.:*** Aldactone Saltucin†; Modenol†; Torrat†; Tri-Torrat†; ***Hong Kong:*** Torrat†; ***Indon.:*** Aldazide; ***Ital.:*** Kadiur; Saludopin; ***Mex.:*** Aldazida; ***Philipp.:*** Aldazide; ***S.Afr.:*** Aldazide; ***Switz.:*** Aldozone; ***Thai.:*** Iso-Triraupin†.

Cadralazine *(BAN, rINN)*

Cadralazina; Cadralazinum; CGP-18684/E; ISF-2469; Kadralatsiini; Kadralazin. Ethyl 3-{6-[ethyl(2-hydroxypropyl)amino]pyridazin-3-yl}carbazate.

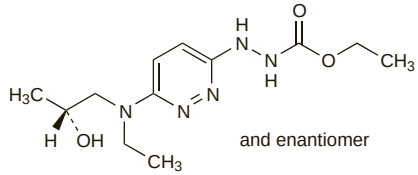
Кадралазин

$C_{12}H_{21}N_5O_3$ = 283.3.

CAS — 64241-34-5.

ATC — C02DB04.

ATC Vet — QC02DB04.



Profile
Cadralazine is a vasodilator with actions and uses similar to those of hydralazine (p.1305). It has been given in oral doses of 10 mg once daily in the management of hypertension (p.1171).

◊ Reviews.

1. McTavish D, *et al.* Cadralazine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the treatment of hypertension. *Drugs* 1990; **40:** 543–60.

ADVERSE EFFECTS. Unlike hydralazine, cadralazine is reported not to produce a lupus-like syndrome.[1,2]

1. Andersson OK. Cadralazine did not produce the SLE-syndrome when hydralazine did. *Eur J Clin Pharmacol* 1987; **31:** 741.
2. Mulder H. Conversion of drug-induced SLE-syndrome by the vasodilating agent cadralazine. *Eur J Clin Pharmacol* 1990; **38:** 303.

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

Cafedrine Hydrochloride *(BANM, pINNM)*

Cafédrine, Chlorhydrate de; Cafedrini Hydrochloridum; H-8351; Hidrocloruro de cafedrina; Kafedrin Hydrochloride. 7-[2-(β-Hydroxy-α-methylphenethylamino)ethyl]theophylline hydrochloride.

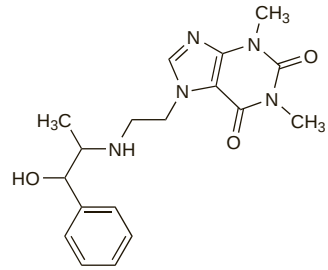
Кафедрина Гидрохлорид

$C_{18}H_{23}N_5O_3$,HCl = 393.9.

CAS — 58166-83-9 (cafedrine); 3039-97-2 (cafedrine hydrochloride).

ATC — C01CA21.

ATC Vet — QC01CA21.



(cafedrine)

Profile
Cafedrine hydrochloride is a derivative of theophylline (p.1140), used mainly in preparations with theodrenaline hydrochloride in the treatment of hypotensive states.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***Austria:*** Akrinor; ***Fr.:*** Praxinor; ***Ger.:*** Akrinor†; ***S.Afr.:*** Akrinor; ***Spain:*** Bifort†.

Calcitonin Gene-related Peptide

CGRP; Péptido relacionado con el gen de la calcitonina.

Profile
Calcitonin gene-related peptide is an endogenous peptide derived from the calcitonin gene. It has vasodilating activity and has been investigated in the management of peripheral vascular disease (Raynaud's syndrome), heart failure, and for ischaemia following neurosurgery for subarachnoid haemorrhage.

◊ References.

1. Johnston FG, *et al.* Effect of calcitonin-gene-related peptide on postoperative neurological deficits after subarachnoid haemorrhage. *Lancet* 1990; **335:** 869–72.
2. Shawkett S, *et al.* Prolonged effect of CGRP in Raynaud's patients: a double-blind randomised comparison with prostacyclin. *Br J Clin Pharmacol* 1991; **32:** 209–13.
3. Shekhar YC, *et al.* Effects of prolonged infusion of human alpha calcitonin gene-related peptide on haemodynamics, renal blood flow and hormone levels in congestive heart failure. *Am J Cardiol* 1991; **67:** 732–6.
4. European CGRP in Subarachnoid Haemorrhage Study Group. Effect of calcitonin-gene-related peptide in patients with delayed postoperative cerebral ischaemia after aneurysmal subarachnoid haemorrhage. *Lancet* 1992; **339:** 831–4.
5. Bunker CB, *et al.* Calcitonin gene-related peptide in treatment of severe peripheral vascular insufficiency in Raynaud's phenomenon. *Lancet* 1993; **342:** 80–2.
6. Feuerstein G, *et al.* Clinical perspectives of calcitonin gene related peptide pharmacology. *Can J Physiol Pharmacol* 1995; **73:** 1070–4.
7. Gherardini G, *et al.* Venous ulcers: improved healing by iontophoretic administration of calcitonin gene-related peptide and vasoactive intestinal peptide. *Plast Reconstr Surg* 1998; **101:** 90–3.

Candesartan Cilexetil *(BANM, USAN, rINNM)*

Candésartan, Cilexétil de; Candesartán cilexetilo; Candesartani Cilexetilum; CV-11974 (candesartan); H-212/91; Kandesartan Sileksetil; TCV-116. Cyclohexyl carbonate ester of (±)-1-hydroxyethyl 2-ethoxy-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-7-benzimidazolecarboxylate.

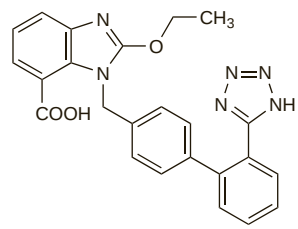
Кандесартана Силексетил

$C_{33}H_{34}N_6O_6$ = 610.7.

CAS — 139481-59-7 (candesartan); 145040-37-5 (candesartan cilexetil).

ATC — C09CA06.

ATC Vet — QC09CA06.



(candesartan)

Adverse Effects and Precautions
As for Losartan Potassium, p.1326.

Interactions
As for Losartan Potassium, p.1327.

Pharmacokinetics
Candesartan cilexetil is an ester prodrug that is hydrolysed during absorption from the gastrointestinal tract to the active form candesartan. The absolute bioavailability for candesartan is about 40% when candesartan cilexetil is given as a solution and about 14% when given as tablets. Peak plasma concentrations of candesartan occur about 3 to 4 hours after oral doses as tablets. Candesartan is more than 99% bound to plasma proteins. It is excreted in urine and bile mainly as unchanged drug and a small amount of inactive metabolites. The terminal elimination half-life is about 9 hours. Candesartan is not removed by haemodialysis.

◊ Reviews.

1. Gleiter CH, Mörike KE. Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* 2002; **41:** 7–17.

Uses and Administration
Candesartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p.1327). It is used in the management of hypertension (p.1171) and may also be used in heart failure in patients with impaired left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors, (see under Losartan Potassium, p.1327).

Candesartan is given orally as the ester prodrug candesartan cilexetil. Onset of antihypertensive action occurs about 2 hours after a dose and the maximum effect is achieved within about 4 weeks of starting therapy.

In the management of **hypertension** the usual initial dose of candesartan cilexetil is 8 mg once daily in the UK, or 16 mg once daily in the USA. The dose should be adjusted according to response; the usual maintenance dose is 8 mg once daily, but doses up to 32 mg daily, as a single dose or in 2 divided doses, may be used. Lower initial doses should be considered in patients with intravascular volume depletion; in the UK an initial dose of 4 mg once daily is suggested. Patients with renal or hepatic impairment may also require lower initial doses (see below).

In **heart failure,** candesartan cilexetil is given in an initial dose of 4 mg once daily; the dose should be doubled at intervals of not less than two weeks up to 32 mg once daily if tolerated.

◊ Reviews.

1. Sever P, Ménard J, eds. Angiotensin II antagonism refined: candesartan cilexetil. *J Hum Hypertens* 1997; **11** (suppl 2): S1–S95.
2. McClellan KJ, Goa KL. Candesartan cilexetil: a review of its use in essential hypertension. *Drugs* 1998; **56:** 847–69.
3. Stoukides CA, *et al.* Candesartan cilexetil: an angiotensin II receptor blocker. *Ann Pharmacother* 1999; **33:** 1287–98.
4. See S, Stirling AL. Candesartan cilexetil: an angiotensin II-receptor blocker. *Am J Health-Syst Pharm* 2000; **57:** 739–46.
5. Easthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. *Drugs* 2002; **62:** 1253–87.
6. Fenton C, Scott LJ. Candesartan cilexetil: a review of its use in the management of chronic heart failure. *Drugs* 2005; **65:** 537–58.
7. McKelvie RS. Candesartan for the management of heart failure: more than an alternative. *Expert Opin Pharmacother* 2006; **7:** 1945–56.
8. Meredith PA. Candesartan cilexetil—a review of effects on cardiovascular complications in hypertension and chronic heart failure. *Curr Med Res Opin* 2007; **23:** 1693–1705.

Administration in hepatic or renal impairment. The elimination of candesartan may be reduced in patients with hepatic or renal impairment and lower doses may therefore be required. Candesartan may also have adverse effects on renal function and regular monitoring is advised in patients with heart failure.

In the UK, candesartan is contra-indicated in severe hepatic impairment and an initial dose of 2 mg once daily is recommended for hypertension in patients with mild to moderate impairment. In the USA, consideration of a lower dose is recommended for moderate hepatic impairment.

For patients with renal impairment, an initial dose of 4 mg once daily is recommended in the UK for hypertension, including for patients on haemodialysis. In the USA, no initial dose adjustment is recommended for mild renal impairment, although dose reduction may be considered if patients are volume depleted. For patients with heart failure, dose reduction or discontinuation of candesartan may be necessary if renal function deteriorates.

Migraine. For reference to the use of angiotensin II receptor antagonists, including candesartan, in the prophylaxis of migraine, see under Losartan, p.1328.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Atacand; Dacten; Tiadyl; ***Austral.:*** Atacand; ***Austria:*** Atacand; Blopress; ***Belg.:*** Atacand; ***Braz.:*** Atacand; Blopress; ***Canad.:*** Atacand; ***Chile:*** Atacand; Bilaten; Blopress; Blox; ***Cz.:*** Atacand; Blopress†; ***Denm.:*** Atacand; ***Fin.:*** Atacand; ***Fr.:*** Atacand; Kenzen; ***Ger.:*** Atacand; Blopress; ***Gr.:*** Atacand; ***Hong Kong:*** Blopress; ***Hung.:*** Atacand; ***India:*** Candesar; ***Indon.:*** Blopress; ***Irl.:*** Atacand; ***Israel:*** Atacand; ***Ital.:*** Blopress; Ratacand; ***Jpn:*** Blopress; ***Malaysia:*** Atacand; Blopress; ***Mex.:*** Atacand; Blopress; ***Neth.:*** Amias; Atacand; Blopress; Ratacand; ***Norw.:*** Atacand; ***NZ:*** Atacand; ***Philipp.:*** Blopress; ***Pol.:*** Atacand; ***Port.:*** Atacand; Blopress; ***Rus.:*** Atacand (Атаканд); ***S.Afr.:*** Atacand; ***Singapore:*** Atacand; ***Spain:*** Atacand; Blopress; Parapres; ***Swed.:*** Atacand; ***Switz.:*** Atacand; Blopress; ***Thai.:*** Blopress; ***Turk.:*** Atacand; Ayra; ***UK:*** Amias; ***USA:*** Atacand; Candepressin; ***Venez.:*** Atacand; Blopress.

Multi-ingredient: ***Arg.:*** Atacand-D; Dacten D; Tiadyl Plus; ***Austral.:*** Atacand Plus; ***Austria:*** Atacand Plus; Blopress Plus; ***Belg.:*** Atacand Plus; ***Braz.:*** Atacand HCT; ***Canad.:*** Atacand Plus; ***Chile:*** Bilaten-D; Blopress D; Blox-D; ***Cz.:*** Atacand Plus; ***Denm.:*** AtacandZid; Atazid; ***Fin.:*** Atacand Plus; ***Fr.:*** Cokenzen; Hytacand; ***Ger.:*** Atacand Plus; Blopress Plus; ***Gr.:*** Atacand Plus; ***Hong Kong:*** Blopress Plus; ***Hung.:*** Atacand Plus; ***Indon.:*** Blopress Plus; ***Irl.:*** Atacand Plus; ***Israel:*** Atacand Plus; ***Ital.:*** Blopresid; Ratacand Plus; ***Malaysia:*** Atacand Plus; ***Mex.:*** Atacand Plus; Blopress Plus; ***Neth.:*** Atacand Plus; Blopresid; ***Norw.:*** Atacand Plus; ***Philipp.:*** Blopress Plus; ***Port.:*** Blopress 16 mg + 12,5 mg; Blopress Comp; Hytacand; ***S.Afr.:*** Atacand Plus; ***Singapore:*** Atacand Plus; ***Spain:*** Atacand Plus; Parapres Plus; ***Swed.:*** Atacand Plus; ***Switz.:*** Atacand Plus; Blopress Plus; ***Thai.:*** Blopress Plus; ***Turk.:*** Atacand Plus; ***USA:*** Atacand HCT; Candepressin Plus; ***Venez.:*** Atacand Plus; Blopress Plus.

Canrenone *(USAN, pINN)* ⊗
Canrenona; Canrénone; Canrenonum; SC-9376. 17-Hydroxy-3-oxo-17α-pregna-4,6-diene-21-carboxylic acid γ-lactone.

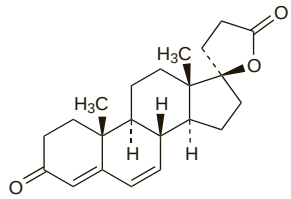
Канренон

$C_{22}H_{28}O_3$ = 340.5.

CAS — 976-71-6.

ATC — C03DA03.

ATC Vet — QC03DA03.



Profile
Canrenone is a potassium-sparing diuretic with properties similar to those of spironolactone (p.1400) and is given orally in the treatment of refractory oedema associated with heart failure (p.1165), renal, or hepatic disease, and in hypertension (p.1171). It is a metabolite of both spironolactone and potassium canrenoate (p.1374). It is given in usual doses of 50 to 200 mg daily. Doses of up to 300 mg daily may be required in some patients.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Contaren†; ***Ital.:*** Luvion.

Captopril *(BAN, USAN, rINN)*
Captoprilum; Kaptopriili; Kaptopril; Kaptoprilis; SQ-14225. 1-[(2*S*)-3-Mercapto-2-methylpropionyl]-L-proline.

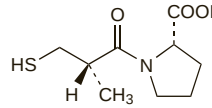
Каптоприл

$C_9H_{15}NO_3S$ = 217.3.

CAS — 62571-86-2.

ATC — C09AA01.

ATC Vet — QC09AA01.



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

- Co-zidocapt (*BAN*)—captopril 2 parts and hydrochlorothiazide 1 part (w/w).

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

Ph. Eur. 6.2 (Captopril). A white or almost white crystalline powder. Freely soluble in water, in dichloromethane, and in methyl alcohol. It dissolves in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 2.0 to 2.6. Store in airtight containers.

USP 31 (Captopril). A white or off-white crystalline powder which may have a characteristic sulfide-like odour. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers.

Stability. Although captopril itself is relatively stable[1] at temperatures up to 50°, and extemporaneously prepared powders (made by triturating the tablets with lactose) have been reported to be stable for at least 12 weeks at room temperature,[2] aqueous solutions are subject to oxidative degradation, mainly to captopril disulfide,[1] which increases[3] with increase in pH above 4. The manufacturers report that a liquid form of captopril prepared from pulverised tablets in distilled water containing 1 mg/mL retained 96.6% of the original concentration of drug after storage at room temperature for 5 days, but they advise that since it contains no preservative it should be used within 2 days of preparation.[4] Others have reported wide variations in stability depending upon the formulation. In one study[5] the shelf-life of a solution of captopril 1 mg/mL prepared from crushed tablets and tap water was estimated to be 27 days when stored at 5°. However, in another study[6] captopril was much less stable; in sterile water for irrigation captopril was stable for at least 3 days when stored at 5°, but in tap water it disappeared at a much faster rate. Increased stability has been reported after the addition of sodium ascorbate to the solution,[7] and with captopril powder rather than crushed tablets.[8] A 1 mg/mL preparation made with crushed tablets and undiluted syrup has also been reported to be stable for 30 days at 5° and may be more palatable than aqueous formulations.[9]

1. Lund W, Cowe HJ. Stability of dry powder formulations. *Pharm J* 1986; **237:** 179–80.
2. Taketomo CK, *et al.* Stability of captopril in powder papers under three storage conditions. *Am J Hosp Pharm* 1990; **47:** 1799–1801.
3. Timmins P, *et al.* Factors affecting captopril stability in aqueous solution. *Int J Pharmaceutics* 1982; **11:** 329–36.
4. Andrews CD, Essex A. Captopril suspension. *Pharm J* 1986; **237:** 734–5.
5. Pereira CM, Tam YK. Stability of captopril in tap water. *Am J Hosp Pharm* 1992; **49:** 612–15.
6. Anaizi NH, Swenson C. Instability of aqueous captopril solutions. *Am J Hosp Pharm* 1993; **50:** 486–8.
7. Nahata MC, *et al.* Stability of captopril in three liquid dosage forms. *Am J Hosp Pharm* 1994; **51:** 95–6.
8. Chan DS, *et al.* Degradation of captopril in solutions compounded from tablets and standard powder. *Am J Hosp Pharm* 1994; **51:** 1205–7.
9. Lye MYF, *et al.* Effects of ingredients on stability of captopril in extemporaneously prepared oral liquids. *Am J Health-Syst Pharm* 1997; **54:** 2483–7.

Adverse Effects, Treatment, and Precautions
As for ACE inhibitors, p.1193.

Captopril has been reported to cause false positive results in tests for acetone in urine.

Incidence of adverse effects. Results of postmarketing surveillance[1] in 30 515 hypertensive patients taking captopril showed that 4.9% had their therapy stopped because of adverse effects thought to be due to the drug. The mean initial daily dose was 46 mg; at final evaluation the mean daily dose was 58 mg. The adverse effect most commonly reported was headache (in 1.8%); others included dizziness (1.6%), rashes (1.1%), nausea (1.0%), taste disturbances (0.9%), and cough (0.8%). This study excluded patients with renal impairment but an earlier survey[2] in 6737 patients taking captopril alone or in combination found that rash and dysgeusia were more frequent in patients with renal impairment (occurring in 6.2% and 3.2% respectively of those receiving 150 mg daily or less of captopril) than in those with normal serum creatinine (4.3% and 2.2%). The frequency of both symptoms was somewhat higher in those given higher doses. Symptoms of hypotension occurred in about 5% of patients and were not influenced by dose or renal function. The cumulative frequency of withdrawal due to adverse effects was estimated at 5.8% in this study, which is similar to that in the larger survey. In another postmarketing surveillance study[3] involving more than 60 000 patients, captopril was withdrawn in 8.9% because of adverse effects.

For further reference to some of these adverse effects, see under ACE Inhibitors, p.1193.

1. Schoenberger JA, *et al.* Efficacy, safety, and quality-of-life assessment of captopril antihypertensive therapy in clinical practice. *Arch Intern Med* 1990; **150:** 301–6.
2. Jenkins AC, *et al.* Captopril in hypertension: seven years later. *J Cardiovasc Pharmacol* 1985; **7** (suppl 1): S96–S101.
3. Chalmers D, *et al.* Postmarketing surveillance of captopril for hypertension. *Br J Clin Pharmacol* 1992; **34:** 215–23.

Breast feeding. Captopril is distributed into breast milk and licensed product information advises that breast feeding should be avoided. However, a study[1] in 12 women found that the concentration of captopril in breast milk was about 1% of maternal blood concentrations, suggesting that the amount ingested by the