Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Buflomedil Hydrochloride). A white or almost white microcrystalline powder. Freely soluble in water; soluble in alcohol; very slightly soluble in acetone. A 5% solution in water has a pH of 5.0 to 6.5.

Adverse Effects
Buflomedil has been reported to cause gastrointestinal disturbances, headache, vertigo, syncope, rash, pruritus, and paraesthesia. Overdosage may produce severe hypotension, tachycardia, and convulsions.

◊ References.

1. Bachand RT, Dubourg AY. A review of long-term safety data with buflomedil. *J Int Med Res* 1990; **18:** 245–52.

Pharmacokinetics
Buflomedil hydrochloride is absorbed from the gastrointestinal tract and peak plasma concentrations are reached 1.5 to 4 hours after oral doses. Buflomedil is subject to first-pass metabolism; bioavailability is reported to be between 50 and 80%.

Buflomedil is widely distributed. Binding to plasma proteins is dose-dependent and varies between 60 and 80% at therapeutic concentrations. Buflomedil is metabolised in the liver and is mainly excreted in the urine both as unchanged drug and metabolites. The elimination half-life is about 2 to 3 hours. Elimination may be impaired in patients with renal or hepatic impairment.

Uses and Administration
Buflomedil hydrochloride is a vasodilator used in the treatment of cerebrovascular (p.1165) and peripheral vascular disease (p.1178). Usual oral doses are 300 to 600 mg daily, doses by intramuscular injection are up to 100 mg daily, by slow intravenous injection up to 200 mg daily, and by intravenous infusion up to 400 mg daily. In patients with hepatic or renal impairment, doses may need to be reduced (see below).

◊ References.

1. Clissold SP, *et al*. Buflomedil: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in peripheral and cerebral vascular diseases. *Drugs* 1987; **33:** 430–60.
2. de Backer TLM, *et al*. Buflomedil for intermittent claudication. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 08/05/08).

Administration in hepatic or renal impairment. The dose of buflomedil should be reduced in patients with hepatic or renal impairment. It should not be used in patients with creatinine clearance (CC) below 30 mL/minute and the maximum oral dose in those with CC between 30 and 80 mL/minute is 150 mg twice daily.

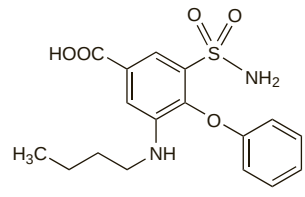
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Arteriol; Buflomed; Lofton; ***Austria:*** Buflohexal; Buflomed; Buftyl; Loftyl; ***Belg.:*** Buflomemed; Buflotop; Docbuflome; Kelomedil; Loftyl; ***Braz.:*** Bufedil; ***Chile:*** Loftyl†; Vaselastic†; ***Fr.:*** Fonzylane; Loftyl†; ***Ger.:*** Bufedil; Buflo; Buflo-POS; Buflo-Puren; Buflohexal; Complamin; Defluina; ***Gr.:*** Bladiron; Botamiral; Buflodil; Chlorofarm-S; Cordimedil; Dialon-T; Dicasin; Farmidil†; Flubir; Gavenil; Gondofil†; Irrodan†; Loftyl; Melirgan†; Ostramont; Penpurin; Spediol†; Sulodil; Thiocodin; Vanogel; Vardolin; Zelian; ***Hong Kong:*** Fonzylane; Irrodan; ***Indon.:*** Loftyl; ***Ital.:*** Buflan; Buflocit; Buflofar†; Flomed; Irrodan; Loftyl; Perfudan†; Pirxane†; ***Mex.:*** Loftyl†; ***Neth.:*** Loftyl; ***Pol.:*** Buflox; Buvasodil; ***Port.:*** Loftyl; ***S.Afr.:*** Loftyl; ***Spain:*** Lofton; Sinoxis†; ***Switz.:*** Loftyl; ***Thai.:*** Irrodan; ***Venez.:*** Loftyl.

Multi-ingredient: ***Arg.:*** Mimixin.

Bumetanide *(BAN, USAN, rINN)* ⊗

Bumetanid; Bumetanida; Bumetanidas; Bumétanide; Bumetanidi; Bumetanidum; Ro-10-6338. 3-Butylamino-4-phenoxy-5-sulphamoylbenzoic acid.

Буметанид
$C_{17}H_{20}N_2O_5S$ = 364.4.
CAS — 28395-03-1.
ATC — C03CA02.
ATC Vet — QC03CA02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Bumetanide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in alcohol and in acetone; slightly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides. Protect from light.
USP 31 (Bumetanide). A practically white powder. Slightly soluble in water; soluble in alkaline solutions. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects
As for Furosemide, p.1292. Bumetanide may cause muscle pain, particularly at high doses.

Effects on the ears. Early reports suggested that bumetanide might be less ototoxic than furosemide.[1] However, both drugs can cause deafness, especially when given in large doses to patients with renal impairment.

1. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; **28:** 426–64.

Effects on the lungs. Alveolitis, presenting as haemoptysis and steadily increasing dyspnoea in a 79-year-old man, was found to coincide with the use of bumetanide for congestive heart failure.[1] When the diuretic was replaced with furosemide the condition gradually resolved.

1. van Tellingen C. Suspension of disbelief - or the bumetanide paradox. *Neth Heart J* 2007; **15:** 31–2.

Effects on the muscles. Bumetanide, particularly in high doses in patients with chronic renal impairment, may cause severe musculoskeletal pain. A curious muscle stiffness distinct from cramp, with tenderness to compression and pain on movement, was noted in 4 patients with end-stage renal failure.[1] The calf muscles were the first to be affected; shoulder girdle and thigh muscle tenderness also occurred in 2 patients, and 1 patient also had neck stiffness. The adverse effect appeared to be dose-related for the individual patients.

1. Barclay JE, Lee HA. Clinical and pharmacokinetic studies on bumetanide in chronic renal failure. *Postgrad Med J* 1975; **51** (suppl 6): 43–6.

Effects on the skin. Bullous pemphigoid developed in a patient about 6 weeks after starting bumetanide.[1] Healing occurred after withdrawal without the need for corticosteroids.

1. Boulinguez S, *et al.* Bullous pemphigoid induced by bumetanide. *Br J Dermatol* 1998; **138:** 548–9.

Precautions
Bumetanide's precautions and contra-indications are generally dependent on its effects on fluid and electrolyte balance and are similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1309).

Interactions
As for Furosemide, p.1293.

Pharmacokinetics
Bumetanide is almost completely and fairly rapidly absorbed from the gastrointestinal tract; the bioavailability is reported to be about 80 to 95%. It has a plasma elimination half-life of about 1 to 2 hours. It is about 95% bound to plasma proteins. About 80% of the dose is excreted in the urine, about 50% as unchanged drug, and 10 to 20% in the faeces.

◊ References to the pharmacokinetics of bumetanide in healthy subjects.

1. Halladay SC, *et al*. Diuretic effect and metabolism of bumetanide in man. *Clin Pharmacol Ther* 1977; **22:** 179–87.
2. Pentikäinen PJ, *et al*. Fate of [C]-bumetanide in man. *Br J Clin Pharmacol* 1977; **4:** 39–44.
3. Holazo AA, *et al*. Pharmacokinetics of bumetanide following intravenous, intramuscular, and oral administrations to normal subjects. *J Pharm Sci* 1984; **73:** 1108–13.
4. Ward A, Heel RC. Bumetanide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic use. *Drugs* 1984; **28:** 426–64.
5. McCrindle JL, *et al*. Effect of food on the absorption of frusemide and bumetanide in man. *Br J Clin Pharmacol* 1996; **42:** 743–6.

Hepatic impairment. In a study of 8 patients with chronic hepatic disease,[1] the diuretic response to bumetanide 1 mg was impaired but bumetanide excretion rates were normal.

1. Marcantonio LA, *et al.* The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; **15:** 245–52.

Renal impairment. Renal excretion of bumetanide has been shown to be reduced in patients with chronic renal impairment with a subsequent attenuation of diuretic effect.[1-3] The cumulative pharmacodynamic effects of oral and intravenous doses were essentially similar in patients with renal impairment and transition from intravenous to oral maintenance regimens should pose no special problems.[2]

1. Marcantonio LA, *et al.* The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in hepatic and renal disease. *Br J Clin Pharmacol* 1983; **15:** 245–52.
2. Lau HSH, *et al.* Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with chronic renal failure. *Clin Pharmacol Ther* 1986; **39:** 635–45.
3. Howlett MR, *et al.* Metabolism of the diuretic bumetanide in healthy subjects and patients with renal impairment. *Eur J Clin Pharmacol* 1990; **38:** 583–6.

Uses and Administration
Although chemically unrelated, bumetanide is a loop diuretic with actions and uses similar to those of furosemide (p.1294). Bumetanide is used in the treatment of oedema associated with heart failure (p.1165) and with renal and hepatic disorders. It is given in high doses in the management of oliguria due to renal failure or insufficiency. Bumetanide has also been used in hypertension (p.1171).

Diuresis starts within about 30 minutes to an hour after an oral dose, reaches a maximum at 1 to 2 hours, and lasts for about 4 hours but may be prolonged to 6 hours after high doses; after intravenous injection its effects are evident within a few minutes and last for about 2 hours. As a general guide bumetanide 1 mg produces a diuretic effect similar to furosemide 40 mg although this should not be used for direct substitution at higher doses.

In the treatment of **oedema** the usual oral dose is 1 mg in the morning or early evening; a second dose may be given 6 to 8 hours later if necessary. A dose of 500 micrograms daily may be adequate in some elderly patients.

In refractory oedema higher doses may be necessary. An initial dose of 5 mg daily has been advocated, increased by 5 mg every 12 to 24 hours as required; however other sources have suggested a maximum total dose of 10 mg daily. Twice daily dosing may be preferred at higher doses. For maintenance therapy doses may be given daily or intermittently. In an emergency or when oral therapy cannot be given 0.5 to 1 mg may be given by intramuscular or slow intravenous injection, subsequently adjusted according to response. A dose for pulmonary oedema is 1 to 2 mg by intravenous injection, repeated 20 minutes later if necessary. Alternatively, 2 to 5 mg may be given over 30 to 60 minutes in 500 mL of a suitable infusion fluid.

In the treatment of **hypertension** bumetanide has been given in oral doses of 0.5 to 1 mg daily, although higher doses have been used.

When very high doses of bumetanide are used careful laboratory control is essential as described under the uses for furosemide (see, p.1294; high-dose therapy).

Preparations
BP 2008: Bumetanide and Prolonged-release Potassium Tablets; Bumetanide Injection; Bumetanide Oral Solution; Bumetanide Tablets;
USP 31: Bumetanide Injection; Bumetanide Tablets.

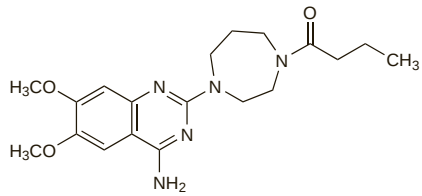
Proprietary Preparations (details are given in Part 3)
Arg.: Butinat†; ***Austral.:*** Burinex; ***Austria:*** Burinex; ***Belg.:*** Burinex; ***Braz.:*** Burinax; ***Canad.:*** Burinex; ***Denm.:*** Burinex; ***Fr.:*** Burinex; ***Ger.:*** Burinex; ***Gr.:*** Burinex; ***Hong Kong:*** Burinex; ***Irl.:*** Burinex; ***Malaysia:*** Burinex; ***Mex.:*** Bumedyl†; Drenural; Miccil; ***Neth.:*** Burinex; ***Norw.:*** Burinex; ***NZ:*** Burinex; ***Philipp.:*** Burinex; ***S.Afr.:*** Burinex; ***Singapore:*** Burinex; ***Spain:*** Fordiuran; ***Swed.:*** Burinex; ***Switz.:*** Burinex; ***Thai.:*** Burinex†; ***UK:*** Burinex; ***USA:*** Bumex; ***Venez.:*** Biulan†; Bumelex; Takomen†.

Multi-ingredient: ***Denm.:*** Buram; Burinex med kaliumklorid; ***Irl.:*** Buram; Burinex K†; ***Malaysia:*** Burinex K†; ***Norw.:*** Burinex K; ***S.Afr.:*** Burinex K; ***Singapore:*** Burinex K; ***UK:*** Burinex A; Burinex K†.

Bunazosin Hydrochloride *(rINNM)*

Bunazosine, Chlorhydrate de; Bunazosini Hydrochloridum; E-643; Hidrocloruro de bunazosina. 1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-butyrylhexahydro-1*H*-1,4-diazepine monohydrochloride.

Буназозина Гидрохлорид
$C_{19}H_{27}N_5O_3$,HCl = 409.9.
CAS — 80755-51-7 (bunazosin); 52712-76-2 (bunazosin hydrochloride).



(bunazosin)

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.

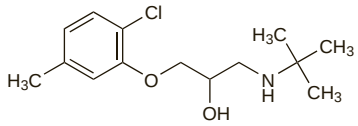
Бупранолола Гидрохлорид

$C_{14}H_{22}ClNO_2$,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.

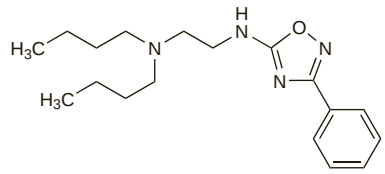
Буталамина Гидрохлорид

$C_{18}H_{28}N_4O$,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.

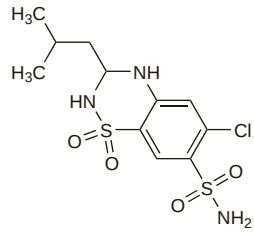
Butizide *(rINN)* ⊗

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.

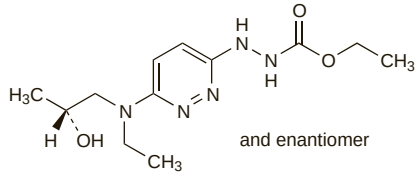
Кадралазин

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

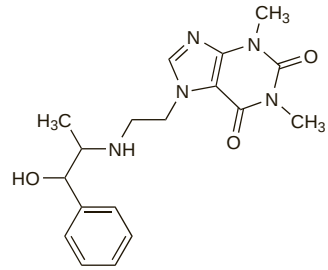
Кафедрина Гидрохлорид

$C_{18}H_{23}N_5O_3$,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.

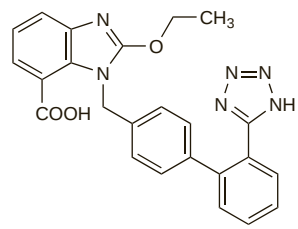
Кандесартана Силексетил

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

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

ATC — C09CA06.

ATC Vet — QC09CA06.



(candesartan)