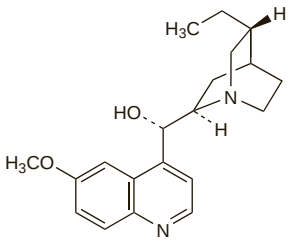
Hydroquinidine Hydrochloride

Dihydrochinidin Hydrochloride; Dihydroquinidine Hydrochloride; Hidrocloruro de dihidroquinidina; Hidroquinidina, hidrocloruro de; Hydroconchinine Hydrochloride. (8*R*,9*S*)-10,11-Dihydro-6′-methoxycinchonan-9-ol hydrochloride.

Гидрохинидина Гидрохлорид

$C_{20}H_{26}N_2O_2$,HCl = 362.9.

CAS — 1435-55-8 (hydroquinidine); 1476-98-8 (hydroquinidine hydrochloride).



(hydroquinidine)

Pharmacopoeias. In *Fr.*

Profile

Hydroquinidine is a class Ia antiarrhythmic with actions and uses similar to those of quinidine (p.1383). It is given orally as the hydrochloride in a usual maintenance dose of 600 mg daily in divided doses.

Hydroquinidine alginate and quinalbital (the hydroquinidine salt of amobarbital) have also been used in the treatment of cardiac arrhythmias.

◊ References.

1. Hermida J-S, *et al.* Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004; **43:** 1853–60.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Serecor; ***Spain:*** Lentoquine.

Ibopamine *(BAN, USAN, rINN)* ⊗

Ibopamina; Ibopaminum; SB-7505; SKF-100168. 4-(2-Methylaminoethyl)-*o*-phenylene di-isobutyrate.

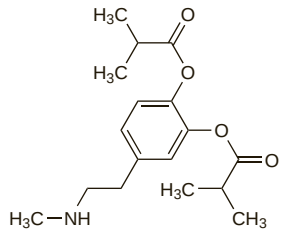
Ибопамин

$C_{17}H_{25}NO_4$ = 307.4.

CAS — 66195-31-1.

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.



Ibopamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de ibopamina; Ibopamiinihydrokloridi; Ibopamine, Chlorhydrate d'; Ibopaminhydroklorid; Ibopamini Hydrochloridum.

Ибопамина Гидрохлорид

$C_{17}H_{25}NO_4$,HCl = 343.8.

ATC — C01CA16; S01FB03.

ATC Vet — QC01CA16; QS01FB03.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Ibopamine should not be used in patients with severe heart failure in whom, similarly to xamoterol (p.1433), it has been reported to increase the risk of death.

Effects on the cardiovascular system. A multicentre study (PRIME II) of the use of ibopamine in patients with severe (NYHA class III or IV) heart failure was stopped early when it was found that the drug was associated with an increased risk of death.[1] Subgroup analysis found that use of an antiarrhythmic drug was independently predictive of an adverse effect in ibopamine-treated patients. Excess mortality in heart failure has also been reported with dobutamine and xamoterol, and with flosequinan and the phosphodiesterase inhibitors amrinone, enoximone, milrinone, and vesnarinone, all of which produce positive inotropic effects through catecholamine-receptor stimulation or post-receptor pathway stimulation.[2] The association with antiarrhythmic therapy in the ibopamine study might reflect an interaction with amiodarone, the most commonly used antiarrhythmic in this study, or might simply be a marker for patients at risk of ibopamine-induced tachyarrhythmias.

1. Hampton JR, *et al.* Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997; **349:** 971–7.
2. Niebauer J, Coats AJS. Treating chronic heart failure: time to take stock. *Lancet* 1997; **349:** 966–7.

Interactions

As for Sympathomimetics, p.1407. It has been recommended that ibopamine should not be given to patients taking amiodarone in the light of the increased mortality seen in the PRIME II study in patients given both drugs (see above), although it is not clear that this represents a genuine interaction.

Uses and Administration

Ibopamine is a prodrug and is rapidly converted to its active metabolite, epinine, which is a peripheral dopamine agonist and sympathomimetic (p.1408). At low doses its dopaminergic effects predominate, leading to vasodilatation and a weak positive inotropic effect; at high concentrations it has a stimulant action on alpha and beta adrenoceptors.

Ibopamine is used in the management of mild heart failure (p.1165). It is given as the hydrochloride but doses are often expressed in terms of the base; 111.9 mg of hydrochloride is equivalent to about 100 mg of base. Doses of 100 to 200 mg orally two or three times daily have been used.

Ibopamine is also used topically as a mydriatic (p.1874) in the form of eye drops containing ibopamine hydrochloride 2%.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Scandine; ***Braz.:*** Escandine†; ***Ital.:*** Scandine; Trazyl; ***Neth.:*** Inopamil; ***Spain:*** Escandine†.

Ibutilide Fumarate *(BANM, USAN, rINNM)*

Fumarato de ibutilida; Ibutilide, Fumarate d'; Ibutilidi Fumaras; U-70226E. (±)-4′-[4-(Ethylheptylamino)-1-hydroxybutyl]methanesulfonanilide fumarate (2:1).

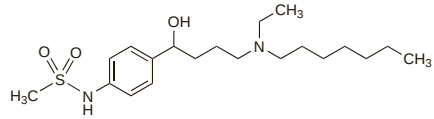
Ибутилида Фумарат

$(C_{20}H_{36}N_2O_3S)_2,C_4H_4O_4$ = 885.2.

CAS — 122647-31-8 (ibutilide); 122647-32-9 (ibutilide fumarate).

ATC — C01BD05.

ATC Vet — QC01BD05.



(ibutilide)

Adverse Effects

Adverse cardiovascular effects associated with ibutilide include heart block, hypotension, hypertension, and bradycardia. It prolongs the QT interval and, like other antiarrhythmics, can cause arrhythmias, including torsade de pointes. Other adverse effects include nausea and vomiting.

Effects on the heart. Ibutilide prolongs the QT interval and has been associated with torsade de pointes, particularly in women.[1] A small study[2] suggested that this effect could be prevented by magnesium sulfate (p.1679), which might therefore be suitable for use as prophylaxis. Although magnesium could theoretically reduce the antiarrhythmic effect of ibutilide as well as the proarrhythmic effect, a retrospective study[3] found that the rate of cardioversion was higher in patients given both ibutilide and magnesium than in those given ibutilide alone, an effect confirmed in a later study.[4]

1. Gowda RM, *et al.* Female preponderance in ibutilide-induced torsade de pointes. *Int J Cardiol* 2004; **95:** 219–22.
2. Caron MF, *et al.* Effects of intravenous magnesium sulfate on the QT interval in patients receiving ibutilide. *Pharmacotherapy* 2003; **23:** 296–300.
3. Kalus JS, *et al.* Impact of prophylactic i.v. magnesium on the efficacy of ibutilide for conversion of atrial fibrillation or flutter. *Am J Health-Syst Pharm* 2003; **60:** 2308–12.
4. Tercius AJ, *et al.* Intravenous magnesium sulfate enhances the ability of intravenous ibutilide to successfully convert atrial fibrillation or flutter. *Pacing Clin Electrophysiol* 2007; **30:** 1331–5.

Effects on the kidneys. Acute renal failure with biopsy evidence of acute tubular necrosis developed in a 52-year-old man shortly after he received 2 doses of ibutilide for an episode of atrial flutter.[1] Renal function returned to normal after 4 sessions of haemodialysis.

1. Franz M, *et al.* Acute renal failure after ibutilide. *Lancet* 1999; **353:** 467.

Precautions

ECG monitoring should be carried out during, and for at least 4 hours after, ibutilide infusion, and the infusion should be stopped if the QT interval becomes markedly prolonged. Electrolyte abnormalities should be corrected before treatment is started.

Interactions

Use of ibutilide with other antiarrhythmics or drugs that prolong the QT interval should be avoided.

Magnesium. For the synergistic effect of magnesium and ibutilide in producing cardioversion, see Effects on the Heart, above.

Pharmacokinetics

Ibutilide is widely distributed in the body after intravenous infusion. It has low plasma protein binding (about 40%) and undergoes extensive metabolism in the liver to form several metabolites. Ibutilide is excreted mainly in the urine, as metabolites and a small amount of unchanged drug (about 7%), with about 19% being excreted in the faeces. The elimination half-life is reported to range from 2 to 12 hours.

Uses and Administration

Ibutilide is a class III antiarrhythmic (p.1153) used for the acute treatment of atrial fibrillation or flutter (p.1160).

Ibutilide is given intravenously as the fumarate. For the termination of atrial fibrillation or flutter, ibutilide fumarate is given as a single dose of 1 mg in patients weighing 60 kg and over, or 10 micrograms/kg in patients weighing less than 60 kg, infused over 10 minutes; the infusion should be stopped as soon as the arrhythmia is terminated. If the arrhythmia persists 10 minutes after completion of the infusion, a second infusion of the same dose may be given.

◊ References.

1. Foster RH, *et al.* Ibutilide: a review of its pharmacological properties and clinical potential in the acute management of atrial flutter and fibrillation. *Drugs* 1997; **54:** 312–30.
2. Granberry MC. Ibutilide: a new class III antiarrhythmic agent. *Am J Health-Syst Pharm* 1998; **55:** 255–60.
3. Howard PA. Ibutilide: an antiarrhythmic agent for the treatment of atrial fibrillation or flutter. *Ann Pharmacother* 1999; **33:** 38–47.
4. Doggrell SA, Hancox JC. Ibutilide—recent molecular insights and accumulating evidence for use in atrial flutter and fibrillation. *Expert Opin Invest Drugs* 2005; **14:** 655–69.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Corvert; ***Cz.:*** Corvert†; ***Fin.:*** Corvert; ***Fr.:*** Corvert†; ***Gr.:*** Corvert; ***Ital.:*** Corvert; ***Neth.:*** Corvert; ***Norw.:*** Corvert; ***Swed.:*** Corvert; ***Switz.:*** Corvert; ***USA:*** Corvert.

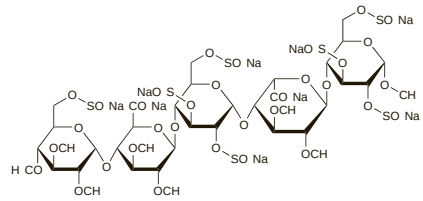
Idraparinux Sodium *(USAN, rINN)*

Idraparinux sódico; Idraparinux Sodique; Idraparinuxum Natricum; Org-34006; SANORG-34006; SR-34006. Methyl *O*-2,3,4-tri-*O*-methyl-6-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-β-D-glucopyranuronosyl-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-*O*-sulfo-α-D-glucopyranoside nonasodium.

Идрапаринукс Натрия

$C_{38}H_{55}Na_9O_{49}S_7$ = 1727.2.

CAS — 162610-17-5 (idraparinux); 149920-56-9 (idraparinux sodium).



Profile
Idraparinux is a factor Xa inhibitor under investigation in the management of thromboembolism.

◊ References.

1. Buller HR, *et al.* van Gogh Investigators. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med* 2007; **357:** 1094–1104.
2. Buller HR, *et al.* van Gogh Investigators. Extended prophylaxis of venous thromboembolism with idraparinux. *N Engl J Med* 2007; **357:** 1105–12.
3. Bousser MG, *et al.* Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *Lancet* 2008; **371:** 315–21.
4. Prandoni P, *et al.* Idraparinux: review of its clinical efficacy and safety for prevention and treatment of thromboembolic disorders. *Expert Opin Invest Drugs* 2008; **17:** 773–7.

Ifenprodil Tartrate *(rINNM)*

Ifenprodil, Tartrate d'; Ifenprodili Tartras; RC-61-91; Tartrato de ifenprodil. (±)-2-(4-Benzylpiperidino)-1-(4-hydroxyphenyl)propan-1-ol tartrate.

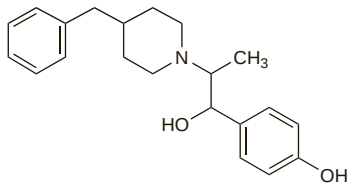
Ифенпродила Тартрат

$(C_{21}H_{27}NO_2)_2,C_4H_6O_6$ = 801.0.

CAS — 23210-56-2 (ifenprodil); 23210-58-4 (ifenprodil tartrate).

ATC — C04AX28.

ATC Vet — QC04AX28.



(ifenprodil)

Pharmacopoeias. In *Jpn.*

Profile
Ifenprodil tartrate is a vasodilator, with alpha-adrenoceptor blocking properties, used in peripheral vascular disease (p.1178). It is given in usual oral doses of 40 to 60 mg daily, and has also been given by deep intramuscular injection, slow intravenous injection, or intravenous infusion.

Preparations
Proprietary Preparations (details are given in Part 3)
Fr.: Vadilex.

Iloprost *(BAN, USAN, rINN)*

Ciloprost; Iloprosti; Iloprostum; ZK-36374; ZK-00036374. (*E*)-(3a*S*,4*R*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H)}$-pentalenevaleric acid.

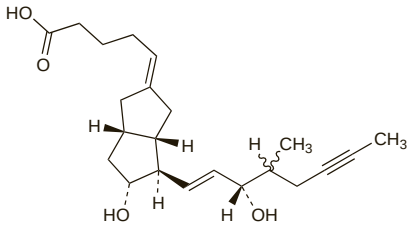
Илопрост

$C_{22}H_{32}O_4$ = 360.5.

CAS — 73873-87-7; 78919-13-8.

ATC — B01AC11.

ATC Vet — QB01AC11.



Iloprost Trometamol *(BANM, rINNM)*

Ciloprost Tromethamine; Iloprost Trométamol; Iloprost Tromethamine; Iloprostum Trometamolum.

Илопрост Трометамол

$C_{22}H_{32}O_4,C_4H_{11}NO_3$ = 481.6.

ATC — B01AC11.

ATC Vet — QB01AC11.

Adverse Effects and Precautions
As for Epoprostenol, p.1279. Inhaled iloprost may cause cough.

Effects on the cardiovascular system. Hypotension was observed[1] in 2 of 6 patients given iloprost. Both patients recovered rapidly when iloprost was stopped, although one required intravenous atropine to correct sinus bradycardia.

Evidence of myocardial ischaemia was reported in 4 of 33 patients with coronary artery disease during iloprost infusion.[2] The same authors[3] noted a similar effect in 4 of 28 patients with stable angina in a subsequent study. According to one study,[4] there might be an increased risk of thromboembolism in some patients given iloprost, due to platelet activation and enhanced coagulation.

1. Upward JW, *et al.* Hypotension in response to iloprost, a prostacyclin analogue. *Br J Clin Pharmacol* 1986; **21:** 241–3.
2. Bugiardini R, *et al.* Myocardial ischemia induced by prostacyclin and iloprost. *Clin Pharmacol Ther* 1985; **38:** 101–8.
3. Bugiardini R, *et al.* Effects of iloprost, a stable prostacyclin analog, on exercise capacity and platelet aggregation in stable angina pectoris. *Am J Cardiol* 1986; **58:** 453–9.
4. Kovacs IB, *et al.* Infusion of a stable prostacyclin analogue, iloprost, to patients with peripheral vascular disease: lack of antiplatelet effect but risk of thromboembolism. *Am J Med* 1991; **90:** 41–6.

Pregnancy. For reference to the successful use of iloprost in pregnancy see Pulmonary Hypertension, under Uses and Administration, below.

Interactions
Iloprost may increase the effect of other vasodilators and antihypertensives. The use of iloprost with other inhibitors of platelet aggregation may increase the risk of bleeding.

Pharmacokinetics
On intravenous infusion iloprost is rapidly cleared from the plasma by oxidation. About 80% of the metabolites are excreted in urine and 20% in the bile.

Uses and Administration
Iloprost, a vasodilator and platelet aggregation inhibitor, is a stable analogue of the prostaglandin epoprostenol (prostacyclin). It is given as the trometamol salt in the treatment of peripheral vascular disease and pulmonary hypertension but doses are described in terms of iloprost; 1.3 nanograms of iloprost trometamol is equivalent to about 1 nanogram of iloprost.

The usual dose for peripheral vascular disease is the equivalent of iloprost 0.5 to 2 nanograms/kg per minute for 6 hours daily by intravenous infusion. The course of treatment may be up to 4 weeks. For pulmonary hypertension, the dose is 1 to 8 nanograms/kg per minute for 6 hours daily; alternatively, iloprost may be given by nebulised solution at a dose of 2.5 or 5 micrograms inhaled 6 to 9 times daily. Doses should be reduced in patients with hepatic or renal impairment (see below).

Oral iloprost is under investigation.

◊ Reviews.

1. Grant SM, Goa KL. Iloprost: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in peripheral vascular disease, myocardial ischaemia and extracorporeal circulation procedures. *Drugs* 1992; **43:** 889–924.

Administration in hepatic or renal impairment. The dose of intravenous iloprost should be reduced, and may need to be halved, in patients with liver cirrhosis or renal impairment requiring dialysis. In hepatic impairment, the initial dose of inhaled iloprost should be 2.5 micrograms given at intervals of at least 3 hours to a maximum of 6 times daily; the dose may be cautiously increased or given more frequently according to patient response.

Peripheral vascular disease. Prostaglandins, including iloprost,[1-10] have been used in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188), but do not constitute mainline therapy. Systematic review[10] suggests that intravenous iloprost produces prolonged benefit in Raynaud's phenomenon secondary to scleroderma. The benefits of oral iloprost are less clear. It is also unclear whether iloprost infusion is of benefit in occlusive peripheral arterial disease due to atherosclerosis: although a meta-analysis of (conflicting) controlled trials did suggest an effect,[6] firm conclusions are difficult.

1. Waller PC, *et al.* Placebo controlled trial of iloprost in patients with stable intermittent claudication. *Br J Clin Pharmacol* 1986; **21:** 562P–563P.
2. Rademaker M, *et al.* Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ* 1989; **298:** 561–4.
3. Fiessinger JN, Schäfer M. Trial of iloprost versus aspirin treatment for critical limb ischaemia of thromboangiitis obliterans. *Lancet* 1990; **335:** 555–7.
4. Zahavi J, *et al.* Ischaemic necrotic toes associated with antiphospholipid syndrome and treated with iloprost. *Lancet* 1993; **342:** 862.
5. Tait IS, *et al.* Management of intra-arterial injection injury with iloprost. *Lancet* 1994; **343:** 419.
6. Loosemore TM, *et al.* A meta-analysis of randomized placebo control trials in Fontaine stages III and IV peripheral occlusive arterial disease. *Int Angiol* 1994; **13:** 133–42.
7. Wigley FM, *et al.* Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. *Arthritis Rheum* 1998; **41:** 670–7.
8. Black CM, *et al.* Oral iloprost in Raynaud's phenomenon secondary to systemic sclerosis: a multicentre, placebo-controlled, dose-comparison study. *Br J Rheumatol* 1998; **37:** 952–60.
9. Scorza R, *et al.* Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon: a randomized, controlled study. *Clin Exp Rheumatol* 2001; **19:** 503–8.
10. Pope J, *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 16/06/05).

Pulmonary hypertension. Epoprostenol is an accepted part of the management of pulmonary hypertension (p.1179) and the use of iloprost, a stable analogue, has been studied. Inhaled iloprost may have a role;[1] it was found[2] to improve walking-test distances, reduce severity of heart failure, and stabilise haemodynamic measures in a 12-week study of patients with severe pulmonary hypertension, while long-term treatment of at least 1 year has been reported to have sustained beneficial effects.[3] Iloprost has also been used successfully in a few cases to manage pulmonary hypertension in pregnant women.[4] There are also reports of effective combination therapy using inhaled iloprost with intravenous epoprostenol,[5] oral sildenafil,[6] or oral bosentan.[7] Continuous intravenous infusion[8] has also been tried with beneficial results over several weeks, and short-term intravenous infusion for 7 days[9] has been successfully used for pulmonary hypertension after pulmonary thromboendarterectomy.

1. Baker SE, Hockman RH. Inhaled iloprost in pulmonary arterial hypertension. *Ann Pharmacother* 2005; **39:** 1265–73.
2. Olschewski H, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; **347:** 322–9.
3. Hoeper MM, *et al.* Long-term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue. *N Engl J Med* 2000; **342:** 1866–70.
4. Elliot CA, *et al.* The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. *Eur Respir J* 2005; **26:** 168–73.
5. Petkov V, *et al.* Aerosolised iloprost improves pulmonary haemodynamics in patients with primary pulmonary hypertension receiving continuous epoprostenol treatment. *Thorax* 2001; **56:** 734–6.
6. Ghofrani HA, *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* 2002; **136:** 515–22.
7. McLaughlin VV, *et al.* Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2006; **174:** 1257–63.
8. Higenbottam TW, *et al.* Treatment of pulmonary hypertension with the continuous infusion of a prostacyclin analogue, iloprost. *Heart* 1998; **79:** 175–9.
9. Hsu H-H, *et al.* Short-term intravenous iloprost for treatment of reperfusion lung oedema after pulmonary thromboendarterectomy. *Thorax* 2007; **62:** 459–61.

Thrombotic microangiopathies. For reports of the use of iloprost in patients with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura, see under Epoprostenol, p.1281.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Ilomedine†; Ventavis†; ***Austria:*** Ilomedin; ***Chile:*** Ventavis; ***Cz.:*** Ilomedin; Ventavis; ***Denm.:*** Ilomedin; Ventavis; ***Fin.:*** Ilomedin; Ventavis; ***Fr.:*** Ilomedine; Ventavis; ***Ger.:*** Ilomedin; Ventavis; ***Gr.:*** Ilomedin; Ventavis; ***Hong Kong:*** Ilomedin; Ventavis; ***Hung.:*** Ilomedin; Ventavis; ***Indon.:*** Ventavis; ***Irl.:*** Ventavis; ***Israel:*** Ilomedin; ***Ital.:*** Endoprost; Ventavis; ***Malaysia:*** Ilomedin†; ***Neth.:*** Ilomedine; Ventavis; ***Norw.:*** Ilomedin; Ventavis; ***NZ:*** Ilomedin; ***Pol.:*** Ilomedin; Ventavis; ***Port.:*** Ilomedin; Ventavis; ***Singapore:*** Ventavis; ***Spain:*** Ilocit; Ilomedin; Ventavis; ***Swed.:*** Ilomedin; Ventavis; ***Switz.:*** Ilomedin; ***Thai.:*** Ilomedin; ***Turk.:*** Ilomedin; ***UK:*** Ventavis; ***USA:*** Ventavis.

Imidapril Hydrochloride *(BANM, rINNM)*

Hidrocloruro de imidapril; Imidaprilihydrokloridi; Imidapril, Chlorhydrate d'; Imidaprilhydroklorid; Imidaprili Hydrochloridum; TA-6366. (*S*)-3-{*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl}-1-methyl-2-oxoimidazoline-4-carboxylic acid hydrochloride.

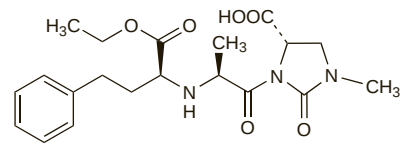
Имидаприла Гидрохлорид

$C_{20}H_{27}N_3O_6$,HCl = 441.9.

CAS — 89371-37-9 (imidapril); 89396-94-1 (imidapril hydrochloride).

ATC — C09AA16.

ATC Vet — QC09AA16.



(imidapril)