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.

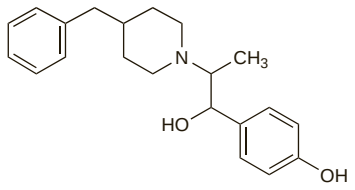
Ифенпродила Тартрат

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

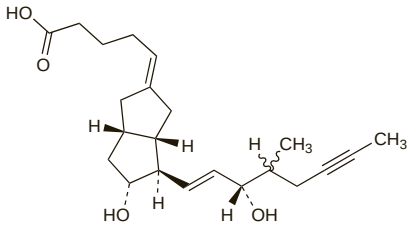
Илопрост

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

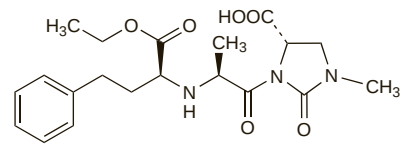
Имидаприла Гидрохлорид

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

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

ATC — C09AA16.

ATC Vet — QC09AA16.



(imidapril)