Lidoflazine *(BAN, USAN, rINN)*

Lidoflazina; Lidoflazinum; McN-JR-7904; Ordiflazine; R-7904. 4-[3-(4,4′-Difluorobenzhydryl)propyl]piperazin-1-ylaceto-2′,6′-xylidide.

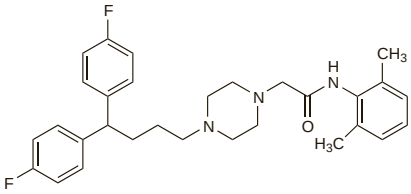
Лидофлазин

$C_{30}H_{35}F_2N_3O$ = 491.6.

CAS — 3416-26-0.

ATC — C08EX01.

ATC Vet — QC08EX01.



Profile

Lidoflazine is a calcium-channel blocker (p.1154) that reduces AV conduction. It has been used in angina pectoris.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Clinium; ***S.Afr.:*** Clinium.

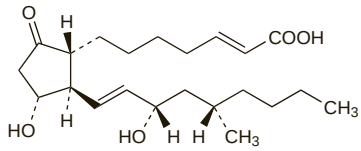
Limaprost *(rINN)*

Limaprostum; ONO-1206; OP-1206. (*E*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-5-oxocyclopentyl}-2-heptenoic acid.

Лимапрост

$C_{22}H_{36}O_5$ = 380.5.

CAS — 74397-12-9 (limaprost); 88852-12-4 (limaprost alfadex).



Pharmacopoeias. *Jpn* includes limaprost alfadex.

Profile

Limaprost is a synthetic analogue of alprostadil (prostaglandin E_1) used in the management of peripheral vascular disease (p.1178). It is given orally as limaprost alfadex, in a dose equivalent to limaprost 15 to 30 micrograms daily in three divided doses.

◊ References.

1. Shono T, Ikeda K. Rapid effect of oral limaprost in Raynaud's disease in childhood. *Lancet* 1989; **i:** 908.
2. Murai C, *et al.* Oral limaprost for Raynaud's phenomenon. *Lancet* 1989; **ii:** 1218.
3. Aoki Y, *et al.* Possible participation of a prostaglandin E1 analogue in the aggravation of diabetic nephropathy. *Diabetes Res Clin Pract* 1992; **16:** 233–8.
4. Sato Y, *et al.* Effect of oral administration of prostaglandin E1 on erectile dysfunction. *Br J Urol* 1997; **80:** 772–5.
5. Swainston Harrison T, Plosker GL. Limaprost. *Drugs* 2007; **67:** 109–18.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Opalmon.

Linsidomine Hydrochloride *(rINNM)*

Hidrocloruro de linsidomina; Linsidomine, Chlorhydrate de; Linsidomini Hydrochloridum. 3-Morpholinosydnonimine hydrochloride.

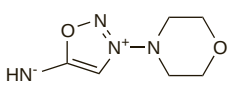
Линсидомина Гидрохлорид

$C_6H_{10}N_4O_2$,HCl = 206.6.

CAS — 33876-97-0 (linsidomine); 16142-27-1 (linsidomine hydrochloride).

ATC — C01DX18.

ATC Vet — QC01DX18.



(linsidomine)

Profile

Linsidomine is a nitrovasodilator and a metabolite of molsidomine (p.1343) and has been given intravenously or via the intracoronary route for coronary vasodilatation.

◊ References.

1. Delonca J, *et al.* Comparative efficacy of the intravenous administration of linsidomine, a direct nitric oxide donor, and isosorbide dinitrate in severe unstable angina: a French multicentre study. *Eur Heart J* 1997; **18:** 1300–6.

Preparations

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

Lisinopril *(BAN, USAN, rINN)*

L-154826; Lisinopriili; Lisinoprilum; Lizinopril; Lizinoprilis; MK-521. *N*-{*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl}-L-proline dihydrate.

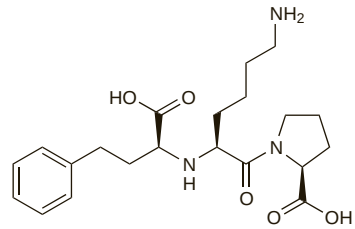
Лизиноприл

$C_{21}H_{31}N_3O_5$,$2H_2O$ = 441.5.

CAS — 76547-98-3 (anhydrous lisinopril); 83915-83-7 (lisinopril dihydrate).

ATC — C09AA03.

ATC Vet — QC09AA03.



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

Ph. Eur. 6.2 (Lisinopril Dihydrate). A white or almost white crystalline powder. Soluble in water; practically insoluble in dehydrated alcohol and in acetone; sparingly soluble in methyl alcohol.

USP 31 (Lisinopril). A white crystalline powder. Soluble 1 in 10 of water and 1 in 70 of methyl alcohol; practically insoluble in alcohol, in acetone, in acetonitrile, in chloroform, and in ether.

Suspension. The US licensed prescribing information provides the following method for making 200 mL of a suspension containing lisinopril 1 mg/mL. Add 10 mL of purified water to a polyethylene terephthalate bottle containing ten 20-mg tablets (*Prinivil, Merck* or *Zestril, AstraZeneca*) and shake for at least 1 minute. Add 30 mL of *Bicitra* (*Alza, USA*) and 160 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and gently shake for several seconds. The suspension should be stored at or below 25° and can be stored for up to 4 weeks. Studies of the characteristics of this and other liquid dosage forms of lisinopril have been published.[1,2]

1. Thompson KC, *et al.* Characterization of an extemporaneous liquid formulation of lisinopril. *Am J Health-Syst Pharm* 2003; **60:** 69–74.
2. Nahata MC, Morosco RS. Stability of lisinopril in two liquid dosage forms. *Ann Pharmacother* 2004; **38:** 396–9.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p.1193.

Porphyria. Lisinopril has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for ACE inhibitors, p.1196.

Pharmacokinetics

Lisinopril is slowly and incompletely absorbed after oral doses. About 25% of a dose is absorbed on average, but the absorption varies considerably between individuals, ranging from about 6 to 60%. It is already an active diacid and does not need to be metabolised *in vivo*. Peak concentrations in plasma are reported to occur after about 7 hours. Lisinopril is reported not to be significantly bound to plasma proteins. It is excreted unchanged in the urine. The effective half-life for accumulation after multiple doses is 12 hours in patients with normal renal function. Lisinopril is removed by haemodialysis.

◊ References.

1. Till AE, *et al.* The pharmacokinetics of lisinopril in hospitalized patients with congestive heart failure. *Br J Clin Pharmacol* 1989; **27:** 199–204.
2. Neubeck M, *et al.* Pharmacokinetics and pharmacodynamics of lisinopril in advanced renal failure: consequence of dose adjustment. *Eur J Clin Pharmacol* 1994; **46:** 537–43.

Uses and Administration

Lisinopril is an ACE inhibitor (p.1193). It is used in the treatment of hypertension (p.1171) and heart failure (p.1165), prophylactically after myocardial infarction (p.1175), and in diabetic nephropathy (see Kidney Disorders, p.1199).

The haemodynamic effects of lisinopril are seen within 1 to 2 hours of a single oral dose and the maximum effect occurs after about 6 hours, although the full effect may not develop for several weeks during chronic dosing. The haemodynamic action lasts for about 24 hours after once-daily dosing. Lisinopril is given orally as the dihydrate, but doses are expressed in terms of the anhydrous substance. Lisinopril 2.72 mg as the dihydrate is equivalent to about 2.5 mg of anhydrous lisinopril. The dose of lisinopril should be reduced in patients with renal impairment (see below).

In the treatment of **hypertension**, the usual initial dose is 10 mg daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. Hypotension is particularly likely in patients with renovascular hypertension, volume depletion, heart failure, or severe hypertension and such patients should be given a lower initial dose of 2.5 to 5 mg once daily. Patients taking diuretics should have the diuretic withdrawn 2 or 3 days before lisinopril is started and resumed later if required; if this is not possible, an initial dose of 5 mg once daily should be given. The usual maintenance dose is 20 mg given once daily, though up to 80 mg daily may be given if necessary.

In the management of **heart failure**, severe first-dose hypotension on introduction of an ACE inhibitor is common in patients on loop diuretics, but their temporary withdrawal may cause rebound pulmonary oedema. Thus treatment should be started with a low dose under close medical supervision. Lisinopril is given in an initial dose of 2.5 mg daily. In the USA an initial dose of 5 mg daily is suggested. Usual maintenance doses range from 5 to 40 mg daily.

After **myocardial infarction**, treatment with lisinopril may be started within 24 hours of the onset of symptoms in an initial dose of 5 mg once daily for two days, then increased to 10 mg once daily. An initial dose of 2.5 mg once daily is recommended for patients with a low systolic blood pressure.

In the management of **diabetic nephropathy**, hypertensive type 2 diabetics with microalbuminuria may be given a dose of 10 mg once daily, increased if necessary to 20 mg once daily to achieve a sitting diastolic blood pressure below 90 mmHg.

◊ Reviews.

1. Lancaster SG, Todd PA. Lisinopril: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 1988; **35:** 646–69.
2. Goa KL, *et al.* Lisinopril: a review of its pharmacology and clinical efficacy in the early management of acute myocardial infarction. *Drugs* 1996; **52:** 564–88.
3. Goa KL, *et al.* Lisinopril: a review of its pharmacology and use in the management of the complications of diabetes mellitus. *Drugs* 1997; **53:** 1081–1105.
4. Simpson K, Jarvis B. Lisinopril: a review of its use in congestive heart failure. *Drugs* 2000; **59:** 1149–67.

Administration in children. Lisinopril has been reported to be an effective and well-tolerated antihypertensive in children 6 years of age and older,[1] although it has been used successfully in younger children.[2] US licensed product information recommends an oral starting dose for lisinopril of 70 micrograms/kg (up to 5 mg) once daily for children 6 years of age and older (but see also Administration in Renal Impairment, below). The *BNFC* recommends similar doses for children aged 6 to 12 years and states that this dose may be increased at intervals of 1 to 2 weeks to a maximum of 600 micrograms/kg or 40 mg once daily. For children between 12 and 18 years of age the *BNFC* recom-