Lidoflazine *(BAN, USAN, rINN)*

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

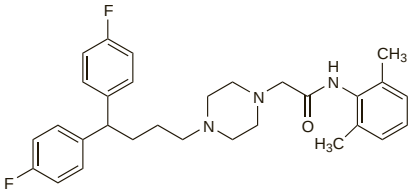
Лидофлазин

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

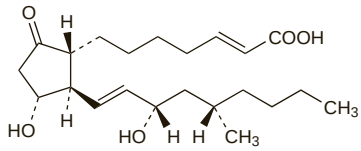
Limaprost *(rINN)*

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.

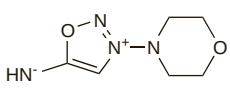
Линсидомина Гидрохлорид

$C_6H_{10}N_4O_2$,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.

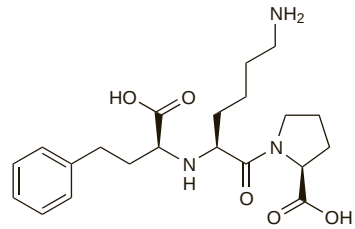
Лизиноприл

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

mends an initial dose of 2.5 mg daily increased as necessary to a maximum of 40 mg daily.

In the treatment of heart failure in children between 12 and 18 years of age the *BNFC* recommends an initial dose of 2.5 mg daily increased as necessary to a usual maintenance dose of 5 to 20 mg daily.

1. Soffer B, *et al.* A double-blind, placebo-controlled, dose-response study of the effectiveness and safety of lisinopril for children with hypertension. *Am J Hypertens* 2003; **16:** 795–800.
2. Raes A, *et al.* Lisinopril in paediatric medicine: a retrospective chart review of long-term treatment in children. *J Renin Angiotensin Aldosterone Syst* 2007; **8:** 3–12.

Administration in renal impairment. In *adult* patients with renal impairment, the initial dose of lisinopril should be reduced depending on the creatinine clearance (CC) as follows:

- CC 31 to 80 mL/minute: 5 to 10 mg once daily
- CC 10 to 30 mL/minute: 2.5 to 5 mg once daily
- CC less than 10 mL/minute or on dialysis: 2.5 mg once daily

The dose should be adjusted according to response, to a maximum of 40 mg once daily.

US licensed prescribing information states that lisinopril should not be given to *children* with a glomerular filtration rate of less than 30 mL/minute per 1.73 m^2 but gives no guidance on dosage in other children with renal impairment.

Preparations

BP 2008: Lisinopril Tablets;
USP 31: Lisinopril Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Doxapril; Lisinal; Sedotensil; Tensopril; Tersif; Zestril; ***Austral.:*** Fibsol; Liprace; Lisinobell; Lisodur; Prinivil; Zestril; ***Austria:*** Acemin; Acetan; Lisihexal; Lisinostad; Lisinotyrol†; Prinivil; ***Belg.:*** Novatec; Zestril; ***Braz.:*** Lisopril; Listril; Lonipril; Prilcor; Prinivil; Prinopril; Vasojet; Zestril; Zinopril; ***Canad.:*** Prinivil; Zestril; ***Chile:*** Acerdil; Lipreren; Presokin; Tonotensil; Zestril†; ***Cz.:*** Dapril; Diroton; Irumed†; Lipribela; Lisigamma; Lisipril; Listril†; Prinivil; ***Denm.:*** Acepril†; Lanatin†; Lisinogen; Vivatec†; Zestril; ***Fin.:*** Lisipril; Vivatec; Zestril†; ***Fr.:*** Prinivil; Zestril; ***Ger.:*** Acerbon; Coric; Lisi; Lisi Lich; Lisi-Puren; Lisibeta; Lisidoc; Lisigamma; Lisihexal; Lisodura; ***Gr.:*** Adicanil; Axelvin; Gnostoval; Hyperliz; Icoran; Landolaxin†; Leruze; Lisinospes; Lisodinol; Mealis; Nafordyl; Perenal; Press-12; Pressuril; Prinivil; Terolinal; Thriusedon; Tivirlon; Vercol; Veroxil; Z-Bec; Zestril; ***Hong Kong:*** Acepril; Cipril; Prinivil; Zestril; ***Hung.:*** Conpres; Lisdene; Lisopress; Press-12; ***India:*** Biopril; Cipril; Linoril; Linvas; Lipril; Lisoril; Normopril; ***Indon.:*** Interpril; Linoxal; Noperten; Nopril; Odace; Zestril; ***Irl.:*** ByZestra; Carace; Lisopress; Lispril; Zesger; Zestan; Zestril; ***Israel:*** Tensopril; ***Ital.:*** Alapril; Prinivil; Zestril; ***Jpn:*** Longes; ***Malaysia:*** Acepril; Dapril; Prinivil†; Ranopril; Zestril; ***Mex.:*** Alfaken; Dosteril; Linospril; Priniser; Prinivil; Zestril; ***Neth.:*** Novatec; Zestril; ***Norw.:*** Vivatec; Zestril; ***NZ:*** Prinivil; Zestril†; ***Philipp.:*** Sinolip; Zestril; ***Pol.:*** Diroton; Lisdene; Lisihexal; Lisinoratio; Lisiprol; Prinivil; ***Port.:*** Benzin; Ecapril; Farpresse; Lipril; Lisinol; Lisopress; Prinivil; Zestril; ***Rus.:*** Dapril (Даприл); Diroton (Диротон); Irumed (Ирумед); Lisinoton (Лизинотон); Lisoril (Лизорил); Listril (Листрил); Liten (Литэн); Sinopril (Синоприл); ***S.Afr.:*** Prilosin†; Prinivil; Renotens†; Sinopren; Zemax; Zeprosil; Zestril; Zetomax; ***Singapore:*** Dapril; Lisdene; Lisoril; Prinivil; Zestril; ***Spain:*** Doneka; Iricil; Likenil; Prinivil; Secubar†; Tensikey; Zestril; ***Swed.:*** Vivatec†; Zestril; ***Switz.:*** Corprilin; Lisitril; Lisopril; Prinil; Tobicor; Zestril; ***Thai.:*** Lisdene; Lispril; Zestril; ***Turk.:*** Acerilin; Rilace; Sinopryl; Zestril; ***UAE:*** Lisotec; ***UK:*** Carace; Zestril; ***USA:*** Prinivil; Zestril; ***Venez.:*** Cotensil; Lisilet; Prinivil; Rantex; Tonoten.

Multi-ingredient: ***Arg.:*** Tensopril D; Zestoretic; ***Austria:*** Acecomb; Acelisino comp; Co-Acetan; Co-Hypomed; Co-Lisinostad; Lisihexal comb; Lisinocomp; Lisinopril comp; Zestoretic; ***Belg.:*** Co-Lisinopril; Merck-Co-Lisinopril; Novazyd†; Zestoretic; ***Braz.:*** Lisinoretic†; Lisodor; Lisonotec†; Lonipril-H; Prinzide; Zestoretic; ***Canad.:*** Prinzide; Zestoretic; ***Chile:*** Acerdil-D; Tonotensil D; Zestoretic†; ***Cz.:*** Lipribela plus H; ***Denm.:*** Lisinoplus; Vivazid†; Zestoretic; ***Fin.:*** Acercomp†; Lisipril Comp; Vivatec Comp; ***Fr.:*** Prinzide; Zestoretic; ***Ger.:*** Acercomp; Coric Plus; Lisi-Puren comp; Lisibeta comp; Lisigamma HCT; LisiLich comp; Lisinopril comp; Lisinopril HCT; Lisiplus; Lisodura plus; ***Gr.:*** Prinzide; Z-Bec Plus; Zestoretic; ***Hong Kong:*** Zestoretic; ***Hung.:*** Lisonorm; ***India:*** Amlopres L; Amlosafe-LS†; Biopril-AM†; Calchek L; Cipril-H; Lisoril-5HT; ***Indon.:*** Zestoretic; ***Irl.:*** Carace Plus; Lispril-hydrochlorothiazide; Zesger Plus; Zestoretic; ***Ital.:*** Nalapres; Prinzide; Zestoretic; ***Mex.:*** Prinzide; Zestoretic; ***Neth.:*** Lisidigal HCT; Novazyd; Zestoretic; ***Norw.:*** Vivatec Comp; Zestoretic; ***Philipp.:*** Zestoretic; ***Port.:*** Ecamais; Lisoplus; Prinzide; Tiazinol; Zestoretic; ***Rus.:*** Iruzid (Ирузид); Lisoretic (Лизоретик); Sinorezid (Синорезид); ***S.Afr.:*** Lisoretic; Zestoretic; Zetomax Co; ***Spain:*** Doneka Plus; Iricil Plus; Prinivil Plus; Secubar Diu; Tensikey Complex; Zestoretic; ***Swed.:*** Zestoretic; ***Switz.:*** Co-Lisinopril; Corpriretic; Lisitril comp; Lisopril plus; Prinzide; Tobicor Plus; Zestoretic; ***Turk.:*** Rilace Plus; Sinoretik; Zestoretic; ***UK:*** Carace Plus; Caralpha; Lisicostad; Zestoretic; ***USA:*** Prinzide; Zestoretic; ***Venez.:*** Lisiletic.

Losartan Potassium *(BANM, USAN, rINNM)*

DuP-753; E-3340; Kalii Losartanum; Losartaanikalium; Losartán potásico; Losartan potassique; Losartan Potasyum; Losartankalium; Losartanum kalicum; MK-0954. 2-Butyl-4-chloro-1-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol potassium.

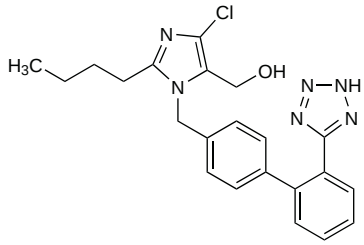
Калия Лозартан

$C_{22}H_{22}ClKN_6O$ = 461.0.

CAS — 114798-26-4 (losartan); 124750-99-8 (losartan potassium).

ATC — C09CA01.

ATC Vet — QC09CA01.



(losartan)

Pharmacopoeias. In *US.*
USP 31 (Losartan Potassium). A white to off-white powder. Freely soluble in water; slightly soluble in acetonitrile; soluble in isopropyl alcohol.

Adverse Effects

Adverse effects of losartan have been reported to be usually mild and transient, and include dizziness, headache, and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received high-dose diuretics). Impaired renal function and, rarely, rash, urticaria, pruritus, angioedema, and raised liver enzyme values may occur. Hyperkalaemia, myalgia, and arthralgia have been reported. Losartan appears less likely than ACE inhibitors to cause cough. Other adverse effects that have been reported with angiotensin II receptor antagonists include respiratory-tract disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia. Rhabdomyolysis has been reported rarely.

◊ Reviews.

1. Mazzolai L, Burnier M. Comparative safety and tolerability of angiotensin II receptor antagonists. *Drug Safety* 1999; **21:** 23–33.

Angioedema. Angioedema is a recognised adverse effect of ACE inhibitors and is thought to be due to accumulation of bradykinins. Although angiotensin II receptor antagonists were thought to lack effects on bradykinin, several have been associated with reports[1-6] of angioedema, and increased levels of bradykinin have been shown[7] with losartan. In some cases patients had previously experienced angioedema with ACE inhibitors and caution is advised when using angiotensin II receptor antagonists in such patients.[4,8]

1. Acker CG, Greenberg A. Angioedema induced by the angiotensin II blocker losartan. *N Engl J Med* 1995; **333:** 1572.
2. van Rijnsoever EW, *et al.* Angioneurotic edema attributed to the use of losartan. *Arch Intern Med* 1998; **158:** 2063–5.
3. Adverse Drug Reactions Advisory Committee. Angiotensin II receptor antagonists. *Aust Adverse Drug React Bull* 1999; **18:** 2. Available at: http://www.tga.gov.au/adr/aadrb/aadr9902.pdf (accessed 13/03/08)
4. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? *Drug Safety* 2002; **25:** 73–6.
5. Irons BK, Kumar A. Valsartan-induced angioedema. *Ann Pharmacother* 2003; **37:** 1024–7.
6. Nykamp D, Winter EE. Olmesartan medoxomil-induced angioedema. *Ann Pharmacother* 2007; **41:** 518–20.
7. Campbell DJ, *et al.* Losartan increases bradykinin levels in hypertensive humans. *Circulation* 2005; **111:** 315–20.
8. Warner KK, *et al.* Angiotensin II receptor blockers in patients with ACE inhibitor-induced angioedema. *Ann Pharmacother* 2000; **34:** 526–8.

Effects on the blood. Symptomatic anaemia occurred[1] in a patient with a renal transplant 6 weeks after starting therapy with losartan. Decreased haemoglobin concentrations have also been reported[2] in patients with severe renal impairment undergoing haemodialysis.

Immune thrombocytopenia has been reported[3] in a patient shortly after starting losartan.

1. Horn S, *et al.* Losartan and renal transplantation. *Lancet* 1998; **351:** 111.
2. Schwarzbeck A, *et al.* Anaemia in dialysis patients as a side-effect of sartanes. *Lancet* 1998; **352:** 286.
3. Ada S, *et al.* Immune thrombocytopenia after losartan therapy. *Ann Intern Med* 2002; **137:** 704.

Effects on the liver. Raised liver enzyme values have occurred rarely in patients receiving losartan. Severe, acute hepatotoxicity developed in a patient 1 month after losartan was substituted for enalapril because of ACE inhibitor-induced cough.[1] The patient recovered when losartan was withdrawn but symptoms and raised liver enzyme concentrations recurred following rechallenge. Acute, reversible hepatotoxicity also occurred in a patient who had been taking losartan 150 mg daily for 6 weeks.[2] A case of cholestatic jaundice associated with irbesartan therapy has also been reported;[3] the jaundice resolved slowly once irbesartan was withdrawn.

1. Bosch X. Losartan-induced hepatotoxicity. *JAMA* 1997; **278:** 1572.
2. Andrade RJ, *et al.* Hepatic injury associated with losartan. *Ann Pharmacother* 1998; **32:** 1371.
3. Hariraj R, *et al.* Prolonged cholestasis associated with irbesartan. *BMJ* 2000; **321:** 547.

Effects on the skin. Atypical cutaneous lymphoid infiltrates developed in 2 patients receiving losartan for hypertension.[1] In both cases the lesions disappeared within a few weeks of stopping the drug.

Henoch-Schönlein purpura has been reported[2,3] in patients taking losartan; in 1 case[2] the reaction recurred on rechallenge. A purpuric rash with evidence of vasculitis has been reported with candesartan;[4] the patient also developed acute nephritis.

A polycyclic rash associated with systemic illness developed in a patient who had been taking irbesartan for 2 years;[5] improvement occurred within 2 days of stopping the drug.

There has also been a report[6] of a number of patients in whom psoriasis either developed or was exacerbated following treatment with an angiotensin II receptor antagonist; the drugs involved included candesartan, irbesartan, losartan, and valsartan. In most cases the lesions regressed after the drug was withdrawn.

1. Viraben R, *et al.* Losartan-associated atypical cutaneous lymphoid hyperplasia. *Lancet* 1997; **350:** 1366.
2. Bosch X. Henoch-Schönlein purpura induced by losartan therapy. *Arch Intern Med* 1998; **158:** 191–2.
3. Brouard M, *et al.* Schönlein-Henoch purpura associated with losartan treatment and presence of antineutrophil cytoplasmic antibodies of x specificity. *Br J Dermatol* 2001; **145:** 362–3.
4. Morton A, *et al.* Rash and acute nephritic syndrome due to candesartan. *BMJ* 2004; **328:** 25.
5. Constable S, *et al.* Systemic illness with skin eruption, fever and positive lymphocyte transformation test in a patient on irbesartan. *Br J Dermatol* 2006; **155:** 491–3.
6. Marquart-Elbaz C, *et al.* Sartans, angiotensin II receptor antagonists, can induce psoriasis. *Br J Dermatol* 2002; **147:** 617–8.

Effects on taste. Taste disturbances, in some cases progressing to complete taste loss, have occurred[1,2] in patients receiving losartan for hypertension. In each case taste returned to normal after stopping losartan therapy. Taste impairment has also been reported with both candesartan[3,4] and valsartan[4] in healthy subjects.

1. Schlienger RG, *et al.* Reversible ageusia associated with losartan. *Lancet* 1996; **347:** 471–2.
2. Heeringa M, van Puijenbroek EP. Reversible dysgeusia attributed to losartan. *Ann Intern Med* 1998; **129:** 72.
3. Tsuruoka S, *et al.* Subclinical alteration of taste sensitivity induced by candesartan in healthy subjects. *Br J Clin Pharmacol* 2004; **57:** 807–12.
4. Tsuruoka S, *et al.* Angiotensin II receptor blocker-induces blunted taste sensitivity: comparison of candesartan and valsartan. *Br J Clin Pharmacol* 2005; **60:** 204–7.

Hypersensitivity. See Angioedema,and Effects on the Skin, above.

Migraine. Severe migraine has been reported[1] in a patient after use of losartan. The patient had no history of migraine and symptoms recurred on rechallenge. However, angiotensin II receptor antagonists have also been reported to reduce the incidence of migraine (see under Uses and Administration, below).

1. Ahmad S. Losartan and severe migraine. *JAMA* 1995; **274:** 1266–7.

Pancreatitis. Acute pancreatitis has been reported[1,2] in 2 patients receiving losartan. However, 1 of the patients subsequently developed pancreatitis unrelated to losartan.[3] The other patient[2] had also developed acute pancreatitis during enalapril therapy. Acute pancreatitis has also been reported[4] with irbesartan; the patient was also taking hydrochlorothiazide but in a dose lower than that usually associated with thiazide-induced pancreatitis. Biochemical alterations suggestive of acute pancreatitis have been reported after telmisartan overdosage.[5]

1. Bosch X. Losartan-induced acute pancreatitis. *Ann Intern Med* 1997; **127:** 1043–4.
2. Birck R, *et al.* Pancreatitis after losartan. *Lancet* 1998; **351:** 1178.
3. Bosch X. Correction: losartan, pancreatitis, and microlithiasis. *Ann Intern Med* 1998; **129:** 755.
4. Fisher AA, Bassett ML. Acute pancreatitis associated with angiotensin II receptor antagonists. *Ann Pharmacother* 2002; **36:** 1883–6.
5. Baffoni L, *et al.* Acute pancreatitis induced by telmisartan overdose. *Ann Pharmacother* 2004; **38:** 1088.

Vasculitis. For mention of the development of Henoch-Schönlein purpura and other vasculitic disorders in patients receiving angiotensin II receptor antagonists see Effects on the Skin, above.

Precautions

Losartan is contra-indicated in pregnancy (see below). It should be used with caution in patients with renal artery stenosis. Losartan is excreted in urine and in bile and reduced doses may therefore be required in patients with renal impairment and should be considered in patients with hepatic impairment. Patients with volume depletion (for example those who have received high-dose diuretic therapy) may experience hypoten-