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.

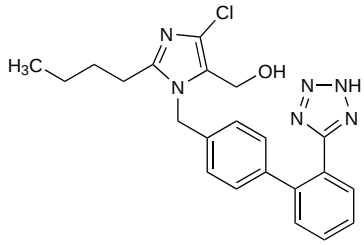
Калия Лозартан

$C_{22}H_{22}ClKN_6O$ = 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-

sion; volume depletion should be corrected before starting therapy, or a low initial dose should be used. Since hyperkalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment, and potassium-sparing diuretics should generally be avoided.

Diabetes mellitus. After reports of reduced awareness of hypoglycaemia in type 1 diabetic patients receiving losartan, a study[1] in healthy subjects found that losartan slightly attenuated the symptomatic and hormonal responses to hypoglycaemia. Although the clinical significance was not established, the authors recommended that losartan should be used with caution in diabetics with reduced awareness of hypoglycaemia. However, losartan and other angiotensin II receptor antagonists may have a role in type 2 diabetics with nephropathy (see Kidney Disorders under Uses, below). There is also some evidence[2-6] that angiotensin II receptor antagonists may prevent the development of diabetes in non-diabetic patients.

1. Deininger E, *et al.* Losartan attenuates symptomatic and hormonal responses to hypoglycemia in humans. *Clin Pharmacol Ther* 2001; **70:** 362–9.
2. Padwal R, Laupacis A. Antihypertensive therapy and incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2004; **27:** 247–55.
3. Gillespie EL, *et al.* The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. *Diabetes Care* 2005; **28:** 2261–6.
4. Abuissa H, *et al.* Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 2005; **46:** 821–6.
5. Yusuf S, *et al.* Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112:** 48–53. Correction. *ibid.*; e292.
6. Aguilar D, Solomon SD. ACE inhibitors and angiotensin receptor antagonists and the incidence of new-onset diabetes mellitus: an emerging theme. *Drugs* 2006; **66:** 1169–77.

Pregnancy. Losartan is contra-indicated in pregnancy since it has been associated with fetal toxicity in *animal* studies and other drugs that act on the renin-angiotensin system, such as ACE inhibitors, have been associated with fetal toxicity in humans (see p.1196). Oligohydramnios with subsequent fetal death occurred in a patient who received losartan during weeks 20 to 31 of pregnancy;[1] the effects on the fetus were similar to those reported with ACE inhibitors. A number of similar cases have subsequently been reported with losartan,[2,3] candesartan,[4] and valsartan.[3,5,6]

1. Saji H, *et al.* Losartan and fetal toxic effects. *Lancet* 2001; **357:** 363.
2. Lambot M-A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; **357:** 1619–20.
3. Martinovic J, *et al.* Fetal toxic effects and angiotensin-II-receptor antagonists. *Lancet* 2001; **358:** 241–2.
4. Hinsberger A, *et al.* Angiotensin-II-receptor inhibitors in pregnancy. *Lancet* 2001; **357:** 1620.
5. Briggs GG, Nageotte MP. Fatal fetal outcome with the combined use of valsartan and atenolol. *Ann Pharmacother* 2001; **35:** 859–61.
6. Bos-Thompson M-A, *et al.* Fetal toxic effects of angiotensin II receptor antagonists: case report and follow-up after birth. *Ann Pharmacother* 2005; **39:** 157–61. Correction. *ibid.*; 389.

Interactions

The antihypertensive effects of losartan may be potentiated by drugs or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalaemia; losartan and potassium-sparing diuretics should not generally be given together. NSAIDs should be used with caution in patients taking losartan as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of NSAIDs may also attenuate the hypotensive effect of losartan. Losartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

Lithium. For reference to a possible interaction between lithium and angiotensin II receptor antagonists, see p.404.

Pharmacokinetics

Losartan is readily absorbed from the gastrointestinal tract after oral doses, but undergoes substantial first-pass metabolism resulting in a systemic bioavailability of about 33%. It is metabolised to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about 1 hour and 3 to 4 hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine and about 6% is excreted in urine as the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

◊ References.

1. Sica DA, *et al.* Clinical pharmacokinetics of losartan. *Clin Pharmacokinet* 2005; **44:** 797–814.

Uses and Administration

Losartan is an angiotensin II receptor antagonist with antihypertensive activity due mainly to selective blockade of AT_1 receptors and the consequent reduced pressor effect of angiotensin II. It is used in the management of hypertension (p.1171), particularly in patients who develop cough with ACE inhibitors and to reduce the risk of stroke in patients with left ventricular hypertrophy, and in the treatment of diabetic nephropathy (see Kidney Disorders, below). It has also been tried in heart failure (below) and in myocardial infarction (p.1175).

Losartan is given orally as the potassium salt. The maximum hypotensive effect is achieved in about 3 to 6 weeks after starting treatment.

In **hypertension** the usual dose of losartan potassium is 50 mg once daily. The dose may be increased, if necessary, to 100 mg daily as a single dose or in two divided doses. An initial dose of 25 mg once daily should be given to patients with intravascular fluid depletion, and is recommended in the UK in patients over 75 years of age. Similar reductions may be appropriate in patients with hepatic or renal impairment (but see below).

There are limited data on the use of losartan in children with hypertension. In the UK, the recommended initial dose of losartan potassium for children weighing between 20 and 50 kg is 25 mg once daily; this may be increased to a maximum of 50 mg once daily. In the USA, children aged 6 years or over may be given an initial dose of 700 micrograms/kg once daily, with a maximum of 50 mg, adjusted according to response. There are no data to recommend doses for children with glomerular filtration rate below 30 mL/min per 1.73 m^2, and in the UK losartan should not be given to children with hepatic impairment.

In **diabetic nephropathy** losartan potassium is given in an initial dose of 50 mg once daily, increased to 100 mg once daily depending on the blood pressure.

◊ Reviews.

1. Carr AA, Prisant LM. Losartan: first of a new class of angiotensin antagonists for the management of hypertension. *J Clin Pharmacol* 1996; **36:** 3–12.
2. Goa KL, Wagstaff AJ. Losartan potassium: a review of its pharmacology, clinical efficacy and tolerability in the management of hypertension. *Drugs* 1996; **51:** 820–45.
3. Schaefer KL, Porter JA. Angiotensin II receptor antagonists: the prototype losartan. *Ann Pharmacother* 1996; **30:** 625–36.
4. Burrell LM. A risk-benefit assessment of losartan potassium in the treatment of hypertension. *Drug Safety* 1997; **16:** 56–65.
5. McConnaughey MM, *et al.* Practical considerations of the pharmacology of angiotensin receptor blockers. *J Clin Pharmacol* 1999; **39:** 547–59.
6. Burnier M, Brunner HR. Angiotensin II receptor antagonists. *Lancet* 2000; **355:** 637–45.
7. Dina R, Jafari M. Angiotensin II-receptor antagonists: an overview. *Am J Health-Syst Pharm* 2000; **57:** 1231–41.
8. Rodgers JE, Patterson JH. Angiotensin II-receptor blockers: clinical relevance and therapeutic role. *Am J Health-Syst Pharm* 2001; **58:** 671–81. Correction. *ibid.*; 1658.
9. Moen MD, Wagstaff AJ. Losartan: a review of its use in stroke risk reduction in patients with hypertension and left ventricular hypertrophy. *Drugs* 2005; **65:** 2657–74.

Administration in children. References.

1. Ellis D, *et al.* Long-term antiproteinuric and renoprotective efficacy and safety of losartan in children with proteinuria. *J Pediatr* 2003; **143:** 89–97.
2. Ellis D, *et al.* Antihypertensive and renoprotective efficacy and safety of losartan: a long-term study in children with renal disorders. *Am J Hypertens* 2004; **17:** 928–35.
3. Shahinfar S, *et al.* A double-blind, dose-response study of losartan in hypertensive children. *Am J Hypertens* 2005; **18:** 183–90.
4. Lubrano R, *et al.* Renal and cardiovascular effects of angiotensin-converting enzyme inhibitor plus angiotensin II receptor antagonist therapy in children with proteinuria. Abstract: *Pediatrics* 2006; **118:** e833. Full text: http://pediatrics.aappublications.org/cgi/reprint/118/3/e833 (accessed 13/03/08)

Administration in hepatic or renal impairment. Licensed product information in both the UK and the USA recommend a reduced dose of losartan in patients with hepatic impairment; the suggested initial dose in the USA is 25 mg daily. In the UK an initial dose of 25 mg daily is also recommended in those with moderate to severe renal impairment (creatinine clearance less than 20 mL/minute), but in the USA dosage reduction is considered unnecessary.

Cardiac arrhythmias. See under Heart Failure, below.

Cardiovascular risk reduction. The benefits of ACE inhibitors in patients with high cardiovascular risk are well-established (see Cardiovascular Risk Reduction, p.1164) but whether angiotensin II receptor antagonists have comparable effects is less clear. In the LIFE study,[1] losartan reduced cardiovascular events more than a beta blocker (atenolol), despite a similar effect on blood pressure. In VALUE,[2] there was no difference in the incidence of cardiovascular events between valsartan and a calcium-channel blocker (amlodipine), although the calcium-channel blocker reduced blood pressure to a greater extent. However, in hypertensive stroke patients,[3] eprosartan reduced the risk of cardiovascular and cerebrovascular events more than another calcium-channel blocker (nitrendipine); blood pressure reduction was similar with both drugs. A study[4] comparing telmisartan with the ACE inhibitor ramipril, found that both reduced cardiovascular events to a similar extent; there was no additional benefit in patients given both drugs.

Based on the results of VALUE, there has been concern that angiotensin II receptor antagonists may increase the risk of myocardial infarction, but a systematic review[5] was unable to confirm a significant effect.

1. Dahlöf B, *et al.* Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359:** 995–1003.
2. Julius S, *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363:** 2022–31.
3. Schrader J, *et al.* Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke* 2005; **36:** 1218–24.
4. Yusuf S, *et al.* ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358:** 1547–59.
5. McDonald MA, *et al.* Angiotensin receptor blockers and risk of myocardial infarction: systematic review. *BMJ* 2005; **331:** 873–6.

Erythrocytosis. For reference to the use of losartan in the management of secondary erythrocytosis, see under ACE inhibitors, p.1198

Heart failure. Diuretics, ACE inhibitors, and beta blockers are the standard drugs used in the management of heart failure (p.1165). Angiotensin II receptor antagonists have been studied as an alternative to ACE inhibitors since they may be better tolerated. In the ELITE study,[1] which compared losartan with captopril, both drugs had similar effects on renal function but other adverse effects were fewer with losartan and there was also a reduction in mortality in patients receiving losartan. However, the larger ELITE II study[2] failed to confirm any survival benefit with losartan, and studies with losartan[3] and valsartan[4] in patients with heart failure following myocardial infarction have also failed to show superiority over ACE inhibitors. ACE inhibitors therefore remain first-line therapy, although angiotensin II receptor antagonists may be used as an alternative, particularly in patients unable to tolerate ACE inhibitors.[5,6] The combination of angiotensin II receptor antagonists with ACE inhibitors has also shown some benefit.[6] In the ValHeFT study,[7] valsartan was added to standard therapy (including ACE inhibitors in most patients) and reduced the combined end-point of death or hospitalisation for heart failure, although the effect on mortality alone was not significant. In the CHARM-Added trial,[8] addition of candesartan to therapy including an ACE inhibitor also led to a reduction in cardiovascular events. However, in the VALIANT study,[4] no additional benefit was found from using valsartan with captopril. There has been some concern that use of triple therapy with angiotensin II receptor antagonists, ACE inhibitors, and beta blockers, might be detrimental, but this has not been confirmed. In ValHeFT,[7] mortality appeared to be increased in patients receiving all three drug classes, but in both CHARM-Added[8] and VALIANT[4] use of beta blockers had no effect on the results. Use of ACE inhibitors and angiotensin II receptor antagonists together may therefore be considered in patients who remain symptomatic despite standard therapy, including patients receiving beta blockers.[9,10]

There is some evidence[11] that angiotensin II receptor antagonists may reduce the incidence of arrhythmias in patients with heart failure.

1. Pitt B, *et al.* Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; **349:** 747–52.
2. Pitt B, *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355:** 1582–7.

3. Dickstein K, *et al.* Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002; **360:** 752–60.
4. Pfeffer MA, *et al.* Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349:** 1893–1906. Correction. *ibid.* 2004; **350:** 203.
5. Granger CB, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362:** 772–6.
6. Jong P, *et al.* Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2002; **39:** 463–70.
7. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345:** 1667–75.
8. McMurray JJV, *et al.* Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362:** 767–71.
9. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Full version: http://content.onlinejacc.org/cgi/reprint/46/6/e1.pdf (accessed 24/07/08)
10. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Executive summary: *Eur Heart J* 2005; **26:** 1115–40. Full text: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-CHF-FT.pdf (accessed 24/07/08)
11. Healey JS, *et al.* Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. *J Am Coll Cardiol* 2005; **45:** 1832–9.

Kidney disorders. ACE inhibitors have an established role in the management of type 1 and type 2 diabetics with nephropathy, whether or not they are hypertensive, and may also slow the progression of nephropathy in diabetics with microalbuminuria (see p.1199). A number of studies have investigated the effects of angiotensin II receptor antagonists in type 2 diabetics with varying degrees of nephropathy (see Diabetic Complications, p.433). Irbesartan,[1,2] losartan,[3,4] and valsartan[5] have all been reported to reduce the progression of nephropathy independently of their effect on blood pressure. The magnitude of the benefit in retarding progression of nephropathy seems to be similar with angiotensin II receptor antagonists and ACE inhibitors,[6-8] and the American Diabetes Association considers them equal first choices in the management of the condition.[9]

Angiotensin II receptor antagonists have also reduced urinary albumin excretion in non-diabetic patients, including those with hypertension,[10] and those with IgA nephropathy.[11]

A study[12] in diabetics using a combination of candesartan with lisinopril found that blood pressure and microalbuminuria were reduced more with combination therapy than with either drug alone. Benefit has also been reported[13] with a combination of losartan and trandolapril in patients with non-diabetic renal disease.

1. Lewis EJ, *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345:** 851–60.
2. Parving H-H, *et al.* The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345:** 870–8.
3. Brenner BM, *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345:** 861–9.
4. Zandbergen AAM, *et al.* Effect of losartan on microalbuminuria in normotensive patients with type 2 diabetes mellitus: a randomized clinical trial. *Ann Intern Med* 2003; **139:** 90–6.
5. Viberti G, Wheeldon NM. MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 2002; **106:** 672–8.
6. Strippoli GFM, *et al.* Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004; **329:** 828–31.
7. Barnett AH, *et al.* Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; **351:** 1952–61. Correction. *ibid.* 2005; **352:** 1731.
8. Kunz R, *et al.* Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease. *Ann Intern Med* 2008; **148:** 30–48.
9. American Diabetes Association. Nephropathy in diabetes. *Diabetes Care* 2004; **27** (suppl 1): S79–S83. Also available at: http://care.diabetesjournals.org/cgi/reprint/27/suppl_1/s79.pdf (accessed 01/08/05)
10. Vogt L, *et al.* Angiotensin II Receptor Antagonist Telmisartan Micardis in Isolated Systolic Hypertension (ARAMIS) Study Group. The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. *J Hypertens* 2005; **23:** 2055–61.
11. Li PK-T, *et al.* Hong Kong study using valsartan in IgA nephropathy (HKVIN): a double-blind, randomized, placebo-controlled study. *Am J Kidney Dis* 2006; **47:** 751–60.
12. Mogensen CE, *et al.* Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000; **321:** 1440–4.
13. Nakao N, *et al.* Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet* 2003; **361:** 117–24. Correction. *ibid.*; 1230.

Migraine. Angiotensin II receptor antagonists may reduce the incidence of headache. A randomised trial[1] in 60 patients with migraine suggested that candesartan might be effective for prophylaxis, and beneficial results have also been reported[2] with olmesartan. However, there has been a report of migraine caused by an angiotensin II receptor antagonist (see under Adverse Effects, above).

1. Tronvik E, *et al.* Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. *JAMA* 2003; **289:** 65–9.
2. Charles JA, *et al.* Prevention of migraine with olmesartan in patients with hypertension/prehypertension. *Headache* 2006; **46:** 503–7.

Uricosuric action. Losartan has been found to increase urinary uric acid excretion and reduce serum uric acid concentrations in healthy subjects[1] and in hypertensive patients.[2,3] However, the effect is generally small and the clinical significance is not clear. Other angiotensin II receptor antagonists do not appear to have such an effect.[2,3]

1. Nakashima M, *et al.* Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol* 1992; **42:** 333–5.
2. Puig JG, *et al.* Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens* 1999; **17:** 1033–9.
3. Würzner G, *et al.* Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens* 2001; **19:** 1855–60.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Cartan; Cliarvas†; Corticosan; Cozaarex; Enromic; Fensartan; Klosartan; Loctenk; Loplac; Losacor; Losargal; Losarlan; Niten; Paxon; Prelertan†; Presinor; Tacardia; Tacicul; Temisartan; Tenopres†; ***Austral.:*** Cozaar; ***Austria:*** Cosaar; ***Belg.:*** Cozaar; Loortan; ***Braz.:*** Aradois; Corus; Cozaar; Lanzacor; Lorsacor†; Losartec; Losatal†; Redupress†; Torlos; Valtrian; Zaarpress; ***Canad.:*** Cozaar; ***Chile:*** Aratan; Corodin; Cozaar; Losapres; Sanipresin; Simperten; ***Cz.:*** Arionecs; Cozaar†; Giovax; Lakea; Lorista; Losartic; Lozap; Nopretens; ***Denm.:*** Cozaar; ***Fin.:*** Cozaar; ***Fr.:*** Cozaar; ***Ger.:*** Lorzaar; ***Gr.:*** Cozaar; Hypozar; Lorfast; Mozartan; Rabolan; Rapifast; ***Hong Kong:*** Cozaar; ***Hung.:*** Cozaar; Lavestra; Portiron; Tervalon; ***India:*** Alsartan; Covance; Lara; Losacar; Losanorm†; Losium; Lozitan; Zaart; ***Indon.:*** Acetensa; Angioten; Cozaar; Insaar; Sartaxal; Tensaar; ***Irl.:*** Cozaar; ***Israel:*** Ocsaar; ***Ital.:*** Lortaan; Losaprex; Neo-Lotan; ***Jpn:*** Nu-Lotan; ***Malaysia:*** Cozaar; ***Mex.:*** Bimidal; Cozaar; ***Neth.:*** Cozaar; Jalvase; ***Norw.:*** Cozaar; ***NZ:*** Cozaar; ***Philipp.:*** Bepsar; Cozaar; Lifezar; Normoten; ***Pol.:*** Cozaar; Lakea; Lorista; Losacor; Lozap; Xartan; ***Port.:*** Cozaar; Lortaan; Tarnasol; Tiasar; ***Rus.:*** Cozaar (Козаар); Lozap (Лозап); Presartan (Презартан); ***S.Afr.:*** Cozaar; ***Singapore:*** Cozaar; ***Spain:*** Cozaar; ***Swed.:*** Cozaar; ***Switz.:*** Cosaar; ***Thai.:*** Cozaar; ***Turk.:*** Cozaar; Eklips; ***UK:*** Cozaar; ***USA:*** Cozaar; ***Venez.:*** Biortan; Cormac; Cozaar; Hyzaar; Nefrotal; Presartan; Sortal; Tenserpil†.

Multi-ingredient: ***Arg.:*** Cozaarex D; Fensartan D; Klosartan D; Loctenk D; Loplac-D; Losacor D; Niten D; Paxon-D; Presinor D; Tacardia D; Tenopres D†; ***Austria:*** Cosaar Plus; ***Belg.:*** Cozaar Plus; Loortan Plus; ***Braz.:*** Aradois H; Corus H; Hyzaar; Lorsar + HCT†; Neopress; Torlos H; ***Canad.:*** Hyzaar; ***Chile:*** Aratan D; Corodin D; Hyzaar; Losapres-D; Sanipresin-D; Simperten-D; ***Cz.:*** Giovax plus H; Hyzaar†; Lorista H; Losaratio Plus H; Lozap H; Nopretens Plus H; ***Denm.:*** Cozaar Comp; Fortzaar; ***Fin.:*** Cozaar Comp; ***Fr.:*** Fortzaar; Hyzaar; ***Ger.:*** Fortzaar; Lorzaar plus; ***Gr.:*** Hyzaar; ***Hong Kong:*** Hyzaar; ***Hung.:*** Hyzaar; ***India:*** Alsartan-AM; Alsartan-H; Amlopres Z; Covance-D; Losacar-H; Zaart-H; ***Irl.:*** Cozaar Comp; ***Israel:*** Ocsaar Plus; ***Ital.:*** Forzaar; Hizaar; Losazid; Neo-Lotan Plus; ***Malaysia:*** Fortzaar; Hyzaar; ***Mex.:*** Hyzaar; ***Neth.:*** Cozaar Plus; Fortzaar; Hyzaar; Losazid; ***Norw.:*** Cozaar Comp; ***NZ:*** Hyzaar; ***Philipp.:*** Combizar; Hyzaar; ***Pol.:*** Hyzaar; Lorista H; ***Port.:*** Cozaar Plus; Fortzaar; Lortaan Plus; Siaara; ***Rus.:*** Hyzaar (Гизаар); Lozap Plus (Лозап Плюс); ***S.Afr.:*** Cozaar Comp; Fortzaar; ***Singapore:*** Hyzaar; ***Spain:*** Cozaar Plus; Fortzaar; ***Swed.:*** Cozaar Comp; ***Switz.:*** Cosaar Plus; ***Thai.:*** Fortzaar; Hyzaar; ***Turk.:*** Eklips Plus; Hyzaar; ***UK:*** Cozaar Comp; ***USA:*** Hyzaar; ***Venez.:*** Cormatic; Hyzaar Plus; Nefrotal H.

Lovastatin *(BAN, USAN, rINN)*

L-154803; Lovastatiini; Lovastatina; Lovastatinas; Lovastatine; Lovastatinum; Lovasztatin; MB-530B; 6α-Methylcompactin; Mevinolin; MK-803; Monacolin K; MSD-803. (3*R*,5*R*)-7-{(1*S*,2*S*,6*R*,8*S*,8a*R*)-1,2,6,7,8,8a-Hexahydro-2,6-dimethyl-8-[(*S*)-2-methylbutyryloxy]-1-naphthyl}-3-hydroxyheptan-5-olide.

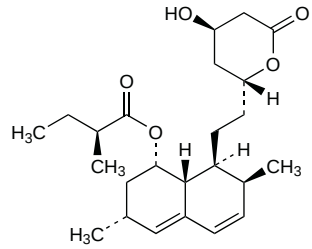
Ловастатин

$C_{24}H_{36}O_5$ = 404.5.

CAS — 75330-75-5.

ATC — C10AA02.

ATC Vet — QC10AA02.



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

Ph. Eur. 6.2 (Lovastatin). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone. Store under nitrogen at a temperature of 2° to 8°.

USP 31 (Lovastatin). A white to off-white crystalline powder. Insoluble in water; sparingly soluble in alcohol; practically insoluble in petroleum spirit; freely soluble in chloroform; soluble in acetone, in acetonitrile, and in methyl alcohol. Store under nitrogen in airtight containers at a temperature not exceeding 8°.

Adverse Effects and Precautions

As for Simvastatin, p.1390.

Incidence of adverse effects. Adverse effects led to withdrawal of lovastatin in 21 of 745 patients receiving the drug for about 5 years.[1] They included asymptomatic elevation of hepatic aminotransferases in 10 patients, gastrointestinal symptoms in 3, rash in 2, myopathy in 2, myalgia in 1, arthralgia in 1, insomnia in 1, and weight gain in 1.

1. Lovastatin Study Groups. Lovastatin 5-year safety and efficacy study: Lovastatin Study Groups I through IV. *Arch Intern Med* 1993; **153:** 1079–87.

Interactions

As for Simvastatin, p.1392.

For specific dosage reductions in patients taking lovastatin with interacting drugs, see Uses and Administration, below.

Pharmacokinetics

Lovastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Three other metabolites have also been isolated. Lovastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action; less than 5% of an oral dose has been reported to reach the circulation. Peak plasma concentrations occur within 2 to 4 hours, and steady-state concentrations are achieved after 2 to 3 days with daily dosage. Both lovastatin and its β-hydroxyacid metabolite are more than 95% bound to plasma proteins. Lovastatin is mainly excreted in the bile as metabolites; about 85% of a dose has been recovered from the faeces and about 10% from the urine. The half-life of the active metabolite is 1 to 2 hours.

◊ General reviews.

1. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; **31:** 348–71.
2. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; **32:** 403–25.

Uses and Administration

Lovastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin), is a lipid regulating drug with actions on plasma lipids similar to those of simvastatin (p.1394).

Lovastatin is used to reduce cholesterol in the treatment of hyperlipidaemias (p.1169), particularly in type IIa and IIb hyperlipoproteinaemias. It is also given for cardiovascular risk reduction (p.1164) in both primary and secondary prevention of ischaemic heart disease.

Lovastatin is given in an initial oral dose of 10 to 20 mg daily in the evening with food, increased, if necessary, at intervals of 4 weeks or more to 80 mg daily as a single dose or in 2 divided doses. Lower doses of lovastatin should be used in patients at risk of myopathy, including patients with severe renal impairment (see below) and those taking drugs that interact with lova-