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.

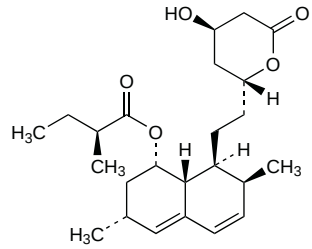
Ловастатин

$C_{24}H_{36}O_5$ = 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-

statin; an initial dose of 10 mg daily is recommended in patients taking *ciclosporin* or *danazol*, and the daily dose should not exceed 20 mg in patients taking *ciclosporin*, *danazol*, *fibric acid derivatives*, or *nicotinic acid*, or 40 mg in those taking *amiodarone* or *verapamil*.

For the use of lovastatin in children, see below.

◊ General reviews.

1. Curran MP, Goa KL. Lovastatin extended release: a review of its use in the management of hypercholesterolaemia. *Drugs* 2003; **63:** 685–99.

Administration in children. Lovastatin reduces plasma-cholesterol concentrations in children and adolescents with heterozygous familial hypercholesterolaemia[1-3] and has been given safely for up to 48 weeks in boys,[2] and up to 24 weeks in girls.[3] In the USA it is licensed in children aged 10 to 17 years and is given orally in an initial dose of 10 to 20 mg once daily, increased at intervals of 4 weeks or more, if necessary, to a maximum dose of 40 mg once daily.

1. Lambert M, *et al.* Canadian Lovastatin in Children Study Group. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. *Pediatrics* 1996; **97:** 619–28.
2. Stein EA, *et al.* Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. *JAMA* 1999; **281:** 137–44.
3. Clauss SB, *et al.* Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia. *Pediatrics* 2005; **116:** 682–8.

Administration in renal impairment. Patients with renal impairment may be at increased risk of myopathy and US licensed product information states that doses of lovastatin above 20 mg daily should be used cautiously in patients with a creatinine clearance below 30 mL/minute.

Adrenoleucodystrophy. A preliminary study[1] has shown that lovastatin may be useful in the treatment of adrenoleucodystrophy (see under Lorenzo's Oil, p.2334). Lovastatin reduced the plasma levels of very-long-chain fatty acids which are known to be elevated in patients with this rare metabolic disorder.

1. Pai GS, *et al.* Lovastatin therapy for X-linked adrenoleukodystrophy: clinical and biochemical observations on 12 patients. *Mol Genet Metab* 2000; **69:** 312–22.

Preparations

USP 31: Lovastatin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Hipovastin; Loriter†; Mevlor; Sivlor†; ***Austria:*** Mevacor; ***Braz.:*** Lipoclin; Lovast†; Lovaton†; Lovax†; Mevacor; Mevalip; Minor†; Neolipid†; Reducol; ***Canad.:*** Mevacor; ***Chile:*** Colevix†; Hiposterol; Lispor; Lovacol; Mevacor†; Nij-Terol†; Sanelor; ***Cz.:*** Holetar; Lovacard†; Medostatin; Mevacor; Rancor; ***Denm.:*** Lovacodan; Mevacor; ***Fin.:*** Lovacol; Mevacor; ***Ger.:*** Lova†; Lovabeta; Lovadura; Lovagamma; Lovahexal; Mevinacor; ***Gr.:*** Aurostatin; B-Lovatin†; Cecural; Ilopar; Liferzit; Lipidless; Lostin; Lovadrug; Lovapen; Lovasten; Lovatex; Lovatop; Lowlipid; Medovascin; Mevacor; Mevastin; Mevinol†; Misodomin; Nabicortin; Terveson; Velkalov; Viking; ***Hong Kong:*** Ellanco; Lofacol†; Lomar; Medostatin; Mevacor; ***Hung.:*** Mevacor; Stoplip; ***India:*** Lovacard; Pro-HDL; Rovacor; ***Indon.:*** Cholvastin; Lipovas; Lofacol; Lotyn; Lovatrol; ***Israel:*** Lovalip†; ***Ital.:*** Lovinacor; Rextat; Tavacor; ***Malaysia:*** Lestric; Lostatin; Lovarem; Lovastin; Medostatin; Mevacor†; ***Mex.:*** Casbame; Dilucid; Liperol; Mevacor; ***Norw.:*** Mevacor; ***Pol.:*** Anlostin; Apo-Lova; Liprox; Lovasterol; Lovastin; ***Port.:*** Flozul; Lipdaune; Lipus; Mevinacor; Mevlor; Tecnolip; ***Rus.:*** Cardiostatin (Кардиостатин); Holetar (Холетар); Lovasterol (Ловастерол); Medostatin (Медостатин); Rovacor (Ровакор); ***S.Afr.:*** Lovachol; ***Singapore:*** Elstatin; Lostatin; Lovastin; Medostatin; Rovacor; ***Spain:*** Aterkey; Colesvir; Lipofren†; Liposcler; Mevacor; Mevasterol; Nergadan; Taucor; ***USA:*** Altoprev; Mevacor; ***Venez.:*** Dislipin†; Levistan; Lostatin†; Lovanil; Lovas†; Mevacor.

Multi-ingredient: ***USA:*** Advicor.

Low-molecular-weight Heparins

Depolymerised Heparins; Heparina massae molecularis minoris; Heparinas de bajo peso molecular; Hepariner, lågmolekylära; Héparines de basse masse moléculaire; Hepariny nízkomolekulární; LMW Heparins; Low-molecular-mass Heparins; Mažos molekulinės masės heparinai; Pienimolekyyliset hepariinit.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Heparins, Low-molecular Mass; Low-molecular-weight Heparins BP 2008). Salts of sulfated glucosaminoglycans having a mass-average molecular mass less than 8000. They are obtained by fractionation or depolymerisation of heparin of natural origin and display different chemical structures at the reducing or the non-reducing end of the polysaccharide chains.
The potency is not less than 70 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is not less than 1.5.
A white or almost white hygroscopic powder. Freely soluble in water. A 1% solution in water has a pH of 5.5 to 8.0. Store in airtight containers.

Units

The second International Standard for low-molecular-weight heparin was agreed in 2003 and is used to calibrate products for both anti-factor Xa and anti-factor IIa activities. Potency is expressed in terms of units of anti-factor Xa activity per mg and the ratio of anti-factor Xa to anti-factor IIa activity. This ratio differs for individual low-molecular-weight heparins and neither they nor unfractionated heparin can be used interchangeably unit for unit.

Adverse Effects

As for Heparin, p.1301.

◊ Reviews.

1. Gouin-Thibault I, *et al.* Safety profile of different low-molecular weight heparins used at therapeutic dose. *Drug Safety* 2005; **28:** 333–49.

Effects on the adrenal glands. Hyperkalaemia related to hypoaldosteronism has been reported in patients treated with low-molecular-weight heparins.[1-3] The UK CSM suggests[4] that plasma-potassium concentrations should be monitored in all patients with risk factors for hyperkalaemia, particularly those receiving low-molecular-weight heparins for more than 7 days (see Heparin, p.1301).

1. Levesque H, *et al.* Low molecular weight heparins and hypoaldosteronism. *BMJ* 1990; **300:** 1437–8.
2. Canova CR, *et al.* Effect of low-molecular-weight heparin on serum potassium. *Lancet* 1997; **349:** 1447–8.
3. Wiggam MI, Beringer TRO. Effect of low-molecular-weight heparin on serum concentrations of potassium. *Lancet* 1997; **350:** 292–3.
4. Committee on Safety of Medicines/Medicines Control Agency. Suppression of aldosterone secretion by heparin. *Current Problems* 1999; **25:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023235&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)

Effects on the blood. It was hoped that, because of their higher ratio of anti-factor Xa to anti-thrombin activity compared with heparin, low-molecular-weight heparins might cause less bleeding while maintaining their antithrombotic activity. Some large studies[1,2] have suggested less bleeding with low-molecular-weight heparins than with unfractionated heparin. However, meta-analyses and reviews[3,4] have been unable to confirm a significant reduction in major haemorrhage in patients treated with low-molecular-weight heparins, compared with heparin, for venous thromboembolism, although they confirmed that low-molecular-weight heparins are not associated with an increase in risk. There may be an increased risk of bleeding in patients with renal impairment,[5,6] (see Precautions, below) although the criterion of creatinine clearance 30 mL/minute or less as a guide to selecting patients at increased risk has been questioned;[7] pharmacokinetic response may vary according to the low-molecular-weight heparin used.

Thrombocytopenia has also been reported with low-molecular-weight heparins[8-10] although in one study the incidence was less than with unfractionated heparin.[11]

Thrombocytosis has also been reported.[12,13]

1. Levine MN, *et al.* Prevention of deep vein thrombosis after elective hip surgery: a randomized trial comparing low molecular weight heparin with standard unfractionated heparin. *Ann Intern Med* 1991; **114:** 545–51.
2. Hull RD, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; **326:** 975–82. Correction. *ibid.* **327:** 140.
3. Gould MK, *et al.* Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999; **130:** 800–809.
4. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 257S–298S.
5. Cestac P, *et al.* Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Safety* 2003; **26:** 197–207.
6. Lim W, *et al.* Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006; **144:** 673–84.
7. Nagge J, *et al.* Is impaired renal function a contraindication to the use of low-molecular-weight heparin? *Arch Intern Med* 2002; **162:** 2605–9.
8. Eichinger S, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **337:** 1425–6.
9. Lecompte T, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **338:** 1217.
10. Tardy B, *et al.* Thrombocytopenia associated with low-molecular-weight heparin. *Lancet* 1991; **338:** 1217.
11. Warkentin TE, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; **332:** 1330–5.
12. Rizzieri DA, *et al.* Thrombocytosis associated with low-molecular-weight heparin. *Ann Intern Med* 1996; **125:** 157.
13. Liautard C, *et al.* Low-molecular-weight heparins and thrombocytosis. *Ann Pharmacother* 2002; **36**: 1351–4.

Effects on the skin. Adverse effects of low-molecular-weight heparins on the skin have been reviewed[1] and are estimated to be rare. Most low-molecular-weight heparins have been implicated. Urticarial rash or immediate hypersensitivity has been reported (see below). Delayed hypersensitivity skin reactions have occurred mainly in women. These women were generally postmenopausal, pregnant, or in the postpartum period, suggesting a hormonal influence on pathogenesis. About half of these patients also had a history of allergy to unfractionated heparin.

Skin necrosis reactions are usually localised to the subcutaneous injection site, although distant lesions have also been reported. There has been a report[2] of diffuse skin necrosis leading to fatality in a patient given enoxaparin.

1. Wütschert R, *et al.* Adverse skin reactions to low molecular weight heparins: frequency, management and prevention. *Drug Safety* 1999; **20:** 515–25.
2. Nadir Y, *et al.* A fatal case of enoxaparin induced skin necrosis and thrombophilia. *Eur J Haematol* 2006; **77:** 166–8.

Hypersensitivity. Reports of hypersensitivity reactions associated with low-molecular-weight heparins are rare. However, a patient being treated with enoxaparin 20 mg subcutaneously daily developed a widespread pruritic urticaria and swelling of lips and tongue after 3 days of treatment.[1] Antihistamines and prednisone given with enoxaparin failed to control the reaction and enoxaparin was stopped after a further 3 days. Urticaria and angioedema rapidly resolved on withdrawal.

Delayed hypersensitivity skin reactions have also been reported (see above).

1. Odeh M, Oliven A. Urticaria and angioedema induced by low-molecular-weight heparin. *Lancet* 1992; **340:** 972–3.

Treatment of Adverse Effects

Severe bleeding with low-molecular-weight heparins, usually caused by accidental overdosage, may be reduced by the slow intravenous injection of protamine sulfate (p.1461). The recommended doses of protamine sulfate are given in the individual monographs and should completely neutralise the anti-thrombin effect of the low-molecular-weight heparin but will only partially neutralise the anti-factor-Xa effect. Not more than 50 mg of protamine sulfate should be injected for any one dose.

Precautions

As for Heparin, p.1303.

Low-molecular-weight heparins should not be given to patients who have developed thrombocytopenia with heparin and who have a positive *in-vitro* platelet aggregation test (that is, cross-reactivity) with the particular low-molecular-weight heparin to be used.

Monitoring of plasma-anti-factor-Xa activity may be considered in patients with an increased risk of bleeding, for example the elderly or those with renal impairment or extremes of body-weight, and in patients with active bleeding.

Licensed product information for some low-molecular-weight heparins contra-indicates their use in patients with prosthetic heart valves as they may not provide adequate prophylaxis against thromboembolism even at high doses (but see under Valvular Heart Disease, p.1187, for references to their use).

Spinal anaesthesia. Spinal and epidural haematomas, sometimes leading to paralysis, have occurred in patients receiving low-molecular-weight heparins with spinal or epidural anaesthesia or analgesia (see p.1303).

Interactions

As for Heparin, p.1303.

Pharmacokinetics

Although the precise pharmacokinetic parameters of different low-molecular-weight heparins vary (see individual monographs), they generally have a greater bioavailability after subcutaneous injection and a longer half-life than heparin.

◊ References.

1. Kandrotas RJ. Heparin pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 1992; **22:** 359–74.
2. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. *Semin Thromb Hemost* 2000; **26** (suppl 1): 31–8.

Uses and Administration

Low-molecular-weight heparins are salts of fragments of heparin produced by chemical or enzymatic depolymerisation of the heparin molecule. Commercially available low-molecular-weight heparins differ in their method of production, molecular-weight range, and degree of sulfation. Those included in *Martindale* are:

- Ardeparin, p.1216
- Bemiparin, p.1223
- Certoparin, p.1242