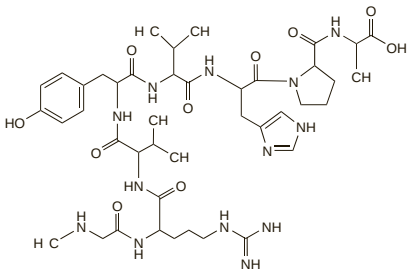
Saralasin Acetate *(BANM, USAN, rINNM)*

Acetato de sarasalina; P-113; Saralasine, Acétate de; Saralasini Acetas; The acetate of 1-Sar-8-Ala-angiotensin II. The hydrated acetate of Sar-Arg-Val-Tyr-Val-His-Pro-Ala; [1-(*N*-Methylglycine)-5-L-valine-8-L-alanine]-angiotensin II acetate hydrate.

Саралазина Ацетат

$C_{42}H_{65}N_{13}O_{10}$, xCH_3COOH,xH_2O = 912.0 (saralasin).

CAS — 34273-10-4 (saralasin); 54194-01-3 (anhydrous saralasin); 39698-78-7 (saralasin acetate hydrate).



(saralasin)

Profile

Saralasin acetate is a competitive antagonist of angiotensin II and thus blocks its pressor action. It is also a partial agonist and causes a transient initial rise in blood pressure. Saralasin has a short half-life and has been used in the differential diagnosis of renovascular hypertension but its use has largely been superseded.

Sarpogrelate Hydrochloride *(rINNM)*

Hidrocloruro de sarpogrelato; MCI-9042; Sarpogrélate, Chlorhydrate de; Sarpogrelati Hydrochloridum. (±)-2-(Dimethylamino)-1-{[o-(*m*-methoxyphenethyl)phenoxy]methyl}ethyl hydrogen succinate hydrochloride.

Сарпогрелата Гидрохлорид

$C_{24}H_{31}NO_6$,HCl = 466.0.

CAS — 125926-17-2 (sarpogrelate); 135159-51-2 (sarpogrelate hydrochloride).

Profile

Sarpogrelate is a serotonin 5-HT_2-receptor antagonist used as an inhibitor of platelet aggregation in thromboembolic disorders. It is given for occlusive arterial disease (see Peripheral Vascular Disease, p.1178) in oral doses of 100 mg of the hydrochloride three times daily.

Preparations

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

Saruplase *(BAN, rINN)*

Prourokinase, Non-glycosylated; Recombinant Human Single-Chain Urokinase-type Plasminogen Activator; Saruplasa; Saruplasum; scuPA. Prourokinase (enzyme-activating) (human clone pUK4/pUK18), non-glycosylated.

Саруплаза

$C_{2031}H_{3121}N_{585}O_{601}S_{31}$ = 46343.1.

CAS — 99149-95-8.
ATC — B01AD08.
ATC Vet — QB01AD08.

NOTE. The term prourokinase has been used for both saruplase and nasaruplase (p.1346).

Profile

Saruplase is a thrombolytic drug. It is a urokinase-type plasminogen activator with a single chain structure prepared via recombinant DNA technology and is converted to urokinase (p.1420) in the body by plasmin. It also has some intrinsic plasminogen-activating properties. Saruplase has been investigated in acute myocardial infarction.

◊ References.

1. Tebbe U, *et al.* Randomized, double-blind study comparing saruplase with streptokinase therapy in acute myocardial infarction: the COMPASS equivalence trial. *J Am Coll Cardiol* 1998; **31:** 487–93.

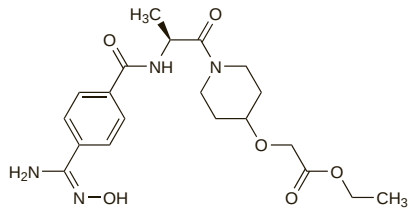
Sibrafiban *(BAN, USAN, rINN)*

G-7333; Ro-48-3657/001; Sibrafibán; Sibrafibanum. Ethyl (*Z*)-[(1-{*N*-[(*p*-hydroxyamidino)benzoyl]-L-alanyl}-4-piperidyl)oxy] acetate.

Сибрафибан

$C_{20}H_{28}N_4O_6$ = 420.5.

CAS — 172927-65-0.



Profile

Sibrafiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug in unstable angina and myocardial infarction but results have been disappointing.

◊ References.

1. Cannon CP, *et al.* Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. *Circulation* 1998; **97:** 340–9.
2. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. *Lancet* 2000; **355:** 337–45.
3. Second SYMPHONY Investigators. Randomized trial of aspirin, sibrafiban, or both for secondary prevention after acute coronary syndromes. *Circulation* 2001; **103:** 1727–33.

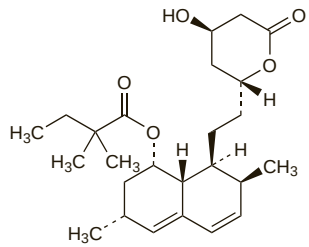
Simvastatin *(BAN, USAN, rINN)*

L-644128-000U; MK-733; Simvastatiini; Simvastatina; Simvastatinas; Simvastatine; Simvastatinum; Sinvinolina; Synvinolin; Szimvasztatin; Velastatin; Velastatina. (1*S*,3*R*,7*S*,8*S*,8a*R*)-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl-8-{2-[(2*R*,4*R*)-tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl]ethyl}-1-naphthyl 2,2-dimethylbutyrate.

Симвастатин

$C_{25}H_{38}O_5$ = 418.6.

CAS — 79902-63-9.
ATC — C10AA01.
ATC Vet — QC10AA01.



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

Ph. Eur. 6.2 (Simvastatin). A white or almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store under nitrogen in airtight containers. Protect from light.

USP 31 (Simvastatin). A white to off-white powder. Practically insoluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in propylene glycol; very slightly soluble in petroleum spirit. Store at a temperature between 15° and 30°, or at 2° to 8°.

Adverse Effects

The commonest adverse effects of therapy with simvastatin and other statins are gastrointestinal disturbances. Other adverse effects reported include headache, skin rashes, dizziness, blurred vision, insomnia, and dysgeusia. Reversible increases in serum-aminotransferase concentrations may occur and liver function should be monitored (see Precautions, below). Hepatitis and pancreatitis have been reported. Hypersensitivity reactions including anaphylaxis and angioedema have also occurred. Myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported, especially in patients also taking ciclosporin, fibric acid derivatives, or nicotinic acid. Rarely, rhabdomyolysis with acute renal failure may develop.

◊ General references.

1. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Safety* 2000; **23:** 197–213.
2. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs* 2001; **61:** 197–206.
3. Pasternak RC, *et al.* ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002; **106:** 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 29/05/08)
4. Karthikeyan VJ. Adverse effects of statins: an update. *Adverse Drug React Bull* 2005; (Aug): 895–8.
5. McKenney JM, *et al.* Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; **97** (Issue 8 suppl 1): 89C–94C.
6. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; **370:** 1781–90.

Incidence of adverse effects. By February 1992 the UK CSM had received 738 reports of adverse effects associated with simvastatin,[1] from an estimated 257 000 prescriptions. Abnormal hepatic function and myalgia were 2 of the most frequently reported reactions, with 36 and 48 reports respectively, including 5 reports of hepatitis and 2 of jaundice. Other muscle effects included 3 reports of myositis, 10 of myopathy, and 7 reports of asymptomatic increases in serum creatine kinase concentrations. Gastrointestinal adverse effects accounted for 20% of the reports; skin, neurological and musculoskeletal effects for 15% each; psychiatric effects for 10%; liver effects for 7%; and visual effects for 4%. A systematic review[2] of data from clinical studies confirmed that the risk of liver transaminase elevation was increased by statins but there was no significant increase in the incidence of myalgia (reported in about 15% of patients), creatine kinase elevation (0.9%), or rhabdomyolysis (0.2%), compared with placebo. The incidence of adverse effects may be greater with high-dose therapy.[3,4]

1. Committee on Safety of Medicines. Simvastatin. *Current Problems 33* 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Kashani A, *et al.* Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; **114:** 2788–97.
3. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol* 2007; **49:** 1753–62.
4. Silva M, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; **29:** 253–60.

Carcinogenicity. For discussion of the effects of statins on the risk of cancer, see Malignant Neoplasms under Uses, below.

Effects on the blood. *Thrombocytopenia* has been reported rarely with statin therapy. Serious thrombocytopenic purpura has occurred with simvastatin, with the onset ranging from 1 or 2 days[1,2] to 11 or 12 months[3,4] after starting treatment. Platelet counts improved after stopping simvastatin in each case, although most patients were given corticosteroids, immunoglobulins, or plasma exchange. There has also been a similar report with atorvastatin,[5] which recurred on rechallenge; the patient had previously taken simvastatin without developing thrombocytopenia, suggesting an idiosyncratic reaction.

A case of *haemolytic anaemia* has been reported[6] in a patient taking lovastatin; no adverse effect was seen when the patient was given simvastatin.

Statins have effects on coagulation and fibrinolysis but these are generally beneficial (see Action under Uses, below); there have been rare reports of *ocular haemorrhage*,[7] but the association with statins is not established.

1. McCarthy LJ, *et al.* Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; **352:** 1284–5.
2. Sundram F, *et al.* Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J* 2004; **80:** 551–2.
3. Possamai G, *et al.* Thrombocytopenic purpura during therapy with simvastatin. *Haematologica* 1992; **77:** 357–8.
4. Groneberg DA, *et al.* Simvastatin-induced thrombocytopenia. *Am J Hematol* 2001; **67:** 277.
5. González-Ponte ML, *et al.* Atorvastatin-induced severe thrombocytopenia. *Lancet* 1998; **352:** 1284.
6. Robbins MJ, *et al.* Lovastatin-induced hemolytic anemia: not a class-specific reaction. *Am J Med* 1995; **99:** 328–9.
7. Fraunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004; **20:** 179–82.

Effects on the eyes. Studies in *animals* have suggested that some statins could cause cataracts, but this has not been confirmed in humans. Although a study[1] with lovastatin found lens opacities in 13 of 101 patients after treatment for 18 weeks, no deterioration in visual function was found in 11 of these who continued lovastatin and were followed up for an average of 26 months from the start of treatment. Similarly, no differences were found in the development of lens opacities or in changes in visual acuity between patients treated with lovastatin for 48 weeks and patients taking placebo in a study of 8245 patients.[2] A large case-control study[3] found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin. Further observational studies have suggested that statins may have beneficial effects; in one study[4] there was no effect on the overall incidence of cataract but the risk of developing nuclear cataract appeared to be decreased, while another study[5] reported a reduction in the overall incidence but this was not significant for any specific cataract type.

For mention of ocular haemorrhage in patients taking statins, see above.

1. Hunninghake DB, *et al.* Lovastatin: follow-up ophthalmologic data. *JAMA* 1988; **259:** 354–5.

2. Laties AM, *et al.* The human lens after 48 weeks of treatment with lovastatin. *N Engl J Med* 1990; **323:** 683–4.
3. Schlienger RG, *et al.* Risk of cataract in patients treated with statins. *Arch Intern Med* 2001; **161:** 2021–6.
4. Klein BEK, *et al.* Statin use and incident nuclear cataract. *JAMA* 2006; **295:** 2752–8.
5. Tan JSL, *et al.* Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; **143:** 687–9.

Effects on the hair. Between its introduction in Australia and 1993, 16 cases of alopecia associated with the use of simvastatin had been reported to the Adverse Drug Reactions Advisory Committee.[1] Most cases involved either excessive hair loss or hair thinning, although 2 cases of hair loss in patches and 1 resembling alopecia areata were reported. Onset occurred between 3 days and 15 months after starting therapy. Progressive hair loss has also been reported[2] in a woman within 6 weeks of commencing atorvastatin; the hair regrew when atorvastatin was stopped but alopecia recurred when therapy was restarted 5 months later.

1. Anonymous. Simvastatin and alopecia. *Aust Adverse Drug React Bull* 1993; **12:** 7.
2. Segal AS. Alopecia associated with atorvastatin. *Am J Med* 2002; **113:** 171.

Effects on the kidneys. *Proteinuria* was reported in 10 patients taking simvastatin 40 mg daily.[1] The protein loss was of a pattern typical for increased glomerular permeability. In 2 patients proteinuria disappeared when simvastatin was withdrawn and recurred on its subsequent reintroduction. However, there is also some evidence that statins may improve proteinuria (see Kidney Disorders under Uses, below).

Acute tubulointerstitial *nephritis* developed[2] in a patient receiving high-dose therapy with rosuvastatin. It resolved over 3 weeks when rosuvastatin was stopped, but recurred 2 weeks after rechallenge. A similar reaction was noted with atorvastatin, but improved with dose reduction, and the patient was finally stabilised on simvastatin without a further recurrence.

Renal failure due to rhabdomyolysis has been reported rarely (see under Effects on Skeletal Muscle, below).

1. Deslypere JP, *et al.* Proteinuria as complication of simvastatin treatment. *Lancet* 1990; **336:** 1453.
2. van Zyl-Smit R, *et al.* Renal tubular toxicity of HMG-CoA reductase inhibitors. *Nephrol Dial Transplant* 2004; **19:** 3176–9.

Effects on the liver. Statins cause dose-related increases in liver enzymes but the incidence appears to be low with low to moderate doses[1] and serious hepatic effects appear to be rare.[2] Although monitoring of liver function tests is advised, the value of routine assessment has been questioned.[3] There is some evidence[4] that the incidence of hepatic reactions may be higher with fluvastatin than with other statins, but this is not yet established.

There have also been case reports[5-7] of cholestasis in patients receiving statins.

1. de Denus S, *et al.* Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004; **24:** 584–91.
2. Charles EC, *et al.* Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; **118:** 618–24.
3. Kostner K, Howes LG. Statins and monitoring of liver function tests. *Drug Safety* 2007; **30:** 1–4.
4. Conforti A, *et al.* Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. *Drug Safety* 2006; **29:** 1163–72.
5. Jiménez-Alonso J, *et al.* Atorvastatin-induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. *Arch Intern Med* 1999; **159:** 1811–12.
6. Wierzbicki AS, Crook MA. Cholestatic liver dysfunction. *Lancet* 1999; **354:** 954.
7. Batey RG, Harvey M. Cholestasis associated with the use of pravastatin sodium. *Med J Aust* 2002; **176:** 561.

Effects on the lungs. Interstitial lung disorders, including hypersensitivity pneumonitis, have been reported with a number of statins.[1-4] In some cases the condition improved when the statin was stopped[2] but treatment with corticosteroids and immunosuppressants was required in some patients[1-4] and progressive disease and fatalities have occurred.[4]

1. de Groot REB, *et al.* Interstitial lung disease with pleural effusion caused by simvastin [sic]. *J Intern Med* 1996; **239:** 361–3.
2. Liebhaber MI, *et al.* Polymyalgia, hypersensitivity pneumonitis and other reactions in patients receiving HMG-CoA reductase inhibitors: a report of ten cases. *Chest* 1999; **115:** 886–9.
3. Lantuejoul S, *et al.* Statin-induced fibrotic nonspecific interstitial pneumonia. *Eur Respir J* 2002; **19:** 577–80.
4. Walker T, *et al.* Potential link between HMG-CoA reductase inhibitor (statin) use and interstitial lung disease. *Med J Aust* 2007; **186:** 91–4.

Effects on mental function. There have been conflicting reports of the effects of statins on mental function, and a number of adverse psychiatric reactions have been reported with statins and with other lipid regulating drugs, although the exact association is unclear.

There have been a few case reports of *depressive symptoms* developing in patients treated with pravastatin[1] or simvastatin.[2] The symptoms appeared during the first few weeks or months of treatment. However, randomised studies investigating the effects of lowering cholesterol on mental function have found no effect on mood disorders (with simvastatin[3]) or psychological well-being (with lovastatin[4] or pravastatin[5]), and epidemiological studies have suggested that use of statins may be associated with improved psychological status[6] and a reduction in the risk of depression and suicide.[7]

Impairment of cognitive function has been reported with statins. In the study using lovastatin,[4] reductions in some measures of cognitive function were noted, and similar results were found in a study using simvastatin.[8] New onset cognitive impairment in a patient a week after starting simvastatin resolved when the drug was stopped but recurred on rechallenge with a lower dose,[9] while analyses of reports to adverse drug reaction reporting databases[10,11] have found a number of cases of memory loss in patients receiving statins, some of which were confirmed by rechallenge. However, clinical studies have not found statins to have an adverse effect on cognition, and there is epidemiological evidence that use of statins may reduce the incidence of dementia (see under Uses, below). A study with atorvastatin[12] also found beneficial effects on cognitive function.

Other psychiatric effects that have been noted in reports to another adverse drug reaction reporting database[13] include 5 cases of aggressive reactions, all of which resolved when the statin was stopped.

See also Effects on Sleep Patterns, below.

1. Lechleitner M, *et al.* Depressive symptoms in hypercholesterolaemic patients treated with pravastatin. *Lancet* 1992; **340:** 910.
2. Duits N, Bos FM. Depressive symptoms and cholesterol-lowering drugs. *Lancet* 1993; **341:** 114.
3. Wardle J, *et al.* Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996; **313:** 75–8.
4. Muldoon MF, *et al.* Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000; **108:** 538–47.
5. Stewart RA, *et al.* Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. *Arch Intern Med* 2000; **160:** 3144–52.
6. Young-Xu Y, *et al.* Long-term statin use and psychological well-being. *J Am Coll Cardiol* 2003; **42:** 690–7.
7. Yang C-C, *et al.* Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med* 2003; **163:** 1926–32.
8. Muldoon MF, *et al.* Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* 2004; **117:** 823–9.
9. Padala KP, *et al.* Simvastatin-induced decline in cognition. *Ann Pharmacother* 2006; **40:** 1880–3.
10. Wagstaff LR, *et al.* Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003; **23:** 871–80.
11. Health Canada. Statins and memory loss. *Can Adverse React News* 2005; **15** (4): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n4-eng.pdf (accessed 19/08/08)
12. Parale GP, *et al.* Effects of atorvastatin on higher functions. *Eur J Clin Pharmacol* 2006; **62:** 259–65.
13. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Safety* 2007; **30:** 195–201.

Effects on the nervous system. Treatment with statins may be associated with the development of peripheral neuropathy,[1] although the reaction appears to be rare. Up to 2005, the Australian Adverse Drug Reactions Advisory Committee had received 281 reports[2] of both sensory and sensorimotor peripheral neuropathies associated with statins. Time to onset of symptoms ranged from after the first dose to 4.5 years. Recovery was seen on withdrawal in about half of the cases, including in some diabetics, and there were some reports of positive rechallenge. In 21 cases symptoms persisted at the time of reporting, up to 8 months after the statin was stopped, and in a further 2 reports the symptoms were unresolved after 3 and 5 years respectively. Similar patterns have been noted elsewhere.[3] A case-control study[4] found that the risk of neuropathy was substantially increased in users of statins although the number of cases was small, and the authors concluded that the benefits of therapy generally outweighed the risks.

Upper motor neurone lesions similar to amyotrophic lateral sclerosis have also been reported in patients taking statins,[5] although the association is not yet confirmed.

1. Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother* 2003; **37:** 274–8.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Statins and peripheral neuropathy. *Aust Adverse Drug React Bull* 2005; **24:** 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.pdf (accessed 30/05/08)
3. de Langen JJ, van Puijenbroek EP. HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre. *Neth J Med* 2006; **64:** 334–8.
4. Gaist D, *et al.* Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002; **58:** 1333–7.
5. Edwards IR, *et al.* Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from Vigibase. *Drug Safety* 2007; **30:** 515–25.

Effects on the pancreas. Statins may cause pancreatitis but the incidence appears to be low,[1,2] and a case-control study[3] failed to support a strong association.

1. Singh S, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. *Drug Safety* 2006; **29:** 1123–32.
2. Johnson JL, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. *Pharmacotherapy* 2006; **26:** 414–22.
3. Thisted H, *et al.* Statins and the risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2006; **23:** 185–90.

Effects on sexual function. There have been reports of *erectile dysfunction* in some men receiving statins. Five men receiving simvastatin developed impotence,[1] which resolved when fluvastatin was substituted in 4 of them. In another case,[2] impotence occurred in a patient receiving lovastatin, and recurred when therapy was changed to pravastatin. Up to 1995, the Australian Adverse Drug Reactions Advisory Committee[3] had received 28 reports of impotence associated with simvastatin, which had recurred on rechallenge in 4 cases. A report[4] from the French and Spanish drug monitoring systems, and an observational study[5] in high-risk cardiovascular patients, supported the association between statins and erectile dysfunction, and a systematic review[6] came to similar conclusions. However, it has been pointed out[7] that the increased risk of sexual dysfunction with statins in the Scandinavian Simvastatin Survival Study was not statistically significant, and there has also been a small study[8] suggesting that atorvastatin may improve erectile function in men with hyperlipidaemia as the only risk factor.

Decreased libido has also been reported with statins. Serum-testosterone concentrations were measured in 2 of 8 patients reported to the Netherlands Pharmacovigilance Centre and were found to be low;[9] they rose after the statin was stopped.

Testicular pain has been reported[10] in a 54-year-old patient 7 months after starting lovastatin. The pain resolved when lovastatin was stopped, but recurred with both simvastatin and atorvastatin. The mechanism for the reaction was unclear.

There has also been a report[11] of a *low sperm count* in a patient receiving lovastatin.

Gynaecomastia occurred in a patient 6 months after changing from simvastatin to atorvastatin.[12] Symptoms improved when atorvastatin was stopped and did not recur when treatment with simvastatin was restarted.

1. Jackson G. Simvastatin and impotence. *BMJ* 1997; **315:** 31.
2. Halkin A, *et al.* HMG-CoA reductase inhibitor-induced impotence. *Ann Pharmacother* 1996; **30:** 192.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Simvastatin and adverse endocrine effects in men. *Aust Adverse Drug React Bull* 1995; **14:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/05/08)
4. Carvajal A, *et al.* HMG CoA reductase inhibitors and impotence: two case series from the Spanish and French drug monitoring systems. *Drug Safety* 2006; **29:** 143–9.
5. Solomon H, *et al.* Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract* 2006; **60:** 141–5.
6. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; **19:** 95–8.
7. Pedersen TR, Færgeman O. Simvastatin seems unlikely to cause impotence. *BMJ* 1999; **318:** 192.
8. Saltzman EA, *et al.* Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol (Baltimore)* 2004; **172:** 255–8.
9. de Graaf L, *et al.* Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? *Br J Clin Pharmacol* 2004; **58:** 326–8.
10. Linnebur AS, Hiatt WH. Probable statin-induced testicular pain. *Ann Pharmacother* 2007; **41:** 138–42.
11. Hildebrand RD, Hepperlen TW. Lovastatin and hypospermia. *Ann Intern Med* 1990; **112:** 549–50.
12. Hammons KB, *et al.* Golf-inhibiting gynecomastia associated with atorvastatin therapy. *Pharmacotherapy* 2006; **26:** 1165–8.

Effects on skeletal muscle. The association between muscle disorders and statins is well known.[1-8] Mild *myalgia* is relatively common, but *myositis* and *myopathy*, with elevation of creatine kinase, may also occur. *Rhabdomyolysis*,[9,10] which involves severe muscle damage, substantial elevation of creatine kinase and myoglobulinuria leading to renal impairment, occurs more rarely, but has resulted in fatalities. Muscle toxicity is dose-related and the risk appears to be broadly similar with all of the currently-marketed statins;[5,6,11] the incidence with cerivastatin was found to be considerably higher and this led to its withdrawal worldwide in 2001. Patients with complex medical problems, including renal impairment and possibly endocrine disorders such as hypothyroidism, may be at increased risk of muscle toxicity; drug interactions may also contribute (see below). Myopathy has been reported with other lipid regulating drugs, particularly fibrates, and the risk may be increased in patients with severe hyperlipidaemia who require combination therapy; careful monitoring is required if statins and fibrates are used together.[6,12] The UK CSM[1] and a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute,[6] have both advised that patients treated with statins should consult their doctor if they develop muscle pain, tenderness, or weakness and that treatment should be stopped if muscle toxicity occurs or is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising. If continued therapy is required, the dose may be reduced or another statin or alternative lipid regulating drug may be tried, although the risk of recurrent muscle problems appears quite high.[10] An algorithm for diagnosis and management of statin-associated myalgia has been suggested.[13]

The mechanism by which statins cause muscle toxicity is not clear, but it has been suggested that depletion of ubidecarenone concentrations may be involved.[14] Although positive results have been reported with ubidecarenone supplementation[15] evidence of benefit is limited and it is not generally recommended.[16]

Other muscular disorders that have been reported in patients receiving statins include *dermatomyositis* and *polymyositis*,[17] and *myasthenia gravis*.[18-20]

1. Committee on Safety of Medicines/Medicines Control Agency. HMG CoA reductase inhibitors (statins) and myopathy. *Current Problems* 2002; **28:** 8–9. Also available at:

http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007452&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Fluvastatin and muscle disorders—a class effect. *Aust Adverse Drug React Bull* 1997; **16:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 30/05/08)
3. Ucar M, *et al.* HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety* 2000; **22:** 441–57.
4. Omar MA, *et al.* Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001; **35:** 1096–1107.
5. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002; **36:** 288–95.
6. Pasternak RC, *et al.* ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Circulation* 2002; **106:** 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 30/05/08)
7. Adverse Drug Reactions Advisory Committee (ADRAC). Risk factors for myopathy and rhabdomyolysis with the statins. *Aust Adverse Drug React Bull* 2004; **23:** 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0402.pdf (accessed 30/05/08)
8. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004; **116:** 408–16.
9. Graham DJ, *et al.* Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004; **292:** 2585–90.
10. Antons KA, *et al.* Clinical perspectives of statin-induced rhabdomyolysis. *Am J Med* 2006; **119:** 400–9.
11. Staffa JA, *et al.* Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002; **346:** 539–540.
12. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; **35:** 908–917.
13. Jacobson TA. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc* 2008; **83:** 687–700.
14. Hargreaves IP, *et al.* The effect of HMG-CoA reductase inhibitors on coenzyme Q : possible biochemical/clinical implications. *Drug Safety* 2005; **28:** 659–76.
15. Walravens PA, *et al.* Lovastatin, isoprenes, and myopathy. *Lancet* 1989; **ii:** 1097–8.
16. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q during statin therapy. *Ann Pharmacother* 2006; **40:** 290–4.
17. Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007; **21:** 17–24.
18. Parmar B, *et al.* Statins, fibrates, and ocular myasthenia. *Lancet* 2002; **360:** 717.
19. Cartwright MS, *et al.* Statin-associated exacerbation of myasthenia gravis. *Neurology* 2004; **63:** 2188.
20. Purvin V, *et al.* Statin-associated myasthenia gravis: report of 4 cases and review of the literature *Medicine (Baltimore)* 2006; **85:** 82–5.

Effects on sleep patterns. Changes to sleep patterns have been reported with lipophilic statins such as lovastatin[1-3] and simvastatin,[4] but appear to be less common with pravastatin,[1] possibly because it is hydrophilic and less likely to penetrate the brain. However, a large placebo-controlled study[5] found that simvastatin had no effect on sleep patterns, and smaller studies assessing sleep using questionnaires[6] or polysomnography,[7-9] have found no significant effects with any of the statins, although some patients appeared to have underlying sleep disorders.

Nightmares and sleep disturbances in a patient taking simvastatin and metoprolol resolved when treatment was changed to pravastatin and atenolol.[10] There has been a report of nightmares with atorvastatin, which resolved when the drug was stopped but recurred on rechallenge.[11]

1. Schaefer EJ. HMG-CoA reductase inhibitors for hypercholesterolemia. *N Engl J Med* 1988; **319:** 1222.
2. Rosenson RS, Goranson NL. Lovastatin-associated sleep and mood disturbances. *Am J Med* 1993; **95:** 548–9.
3. Sinzinger H, *et al.* Sleep disturbance and appetite loss after lovastatin. *Lancet* 1994; **343:** 973.
4. Barth JD, *et al.* Inhibitors of hydroxymethylglutaryl coenzyme A reductase for treating hypercholesterolaemia. *BMJ* 1990; **301:** 669.
5. Keech AC, *et al.* Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. *Br J Clin Pharmacol* 1996; **42:** 483–90.
6. Black DM, *et al.* Sleep disturbances and HMG CoA reductase inhibitors. *JAMA* 1990; **264:** 1105.
7. Eckernäs S-Å, *et al.* The effects of simvastatin and pravastatin on objective and subjective measures of nocturnal sleep: a comparison of two structurally different HMG CoA reductase inhibitors in patients with primary moderate hypercholesterolaemia. *Br J Clin Pharmacol* 1993; **35:** 284–9.
8. Kostis JB, *et al.* Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J Clin Pharmacol* 1994; **34:** 989–96.
9. Ehrenberg BL, *et al.* Comparison of the effects of pravastatin and lovastatin on sleep disturbance in hypercholesterolemic subjects. *Sleep* 1999; **22:** 117–21.
10. Boriani G, *et al.* Nightmares and sleep disturbances with simvastatin and metoprolol. *Ann Pharmacother* 2001; **35:** 1292.
11. Gregoor PJHS. Atorvastatin may cause nightmares. *BMJ* 2006; **332:** 950.

Precautions

Statins should not be given to patients with active liver disease. Liver function should be assessed before starting treatment and subsequently when clinically indicated; additional assessment after 3 months and before and after dosage increases has been advised for some statins, particularly when high doses are given. Statins should not be used in patients who already have unexplained persistently raised serum-aminotransferase concentrations and should be stopped if marked or persistent increases in serum-aminotransferase concentrations occur. They should be avoided during pregnancy since there is a possibility that they could interfere with fetal sterol synthesis; there have been a number of reports of congenital abnormalities associated with statins (see Pregnancy, below). Statins may cause myopathy and rhabdomyolysis, especially at higher doses, and they should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking drugs that increase plasma concentrations of the statin (see Interactions, below); the statin should be stopped if creatine phosphokinase increases significantly or if myopathy is diagnosed.

Statins should be used with caution in patients with renal impairment as the risk of myopathy is increased. Dose reduction may be required for statins that are excreted by the kidney and for those with a particularly high risk of myopathy (see Administration in Renal Impairment under Uses of the individual drugs for further details).

Children. For discussion of concerns relating to the use of statins in children, see Administration in Children under Uses, below.

Porphyria. Simvastatin is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Pregnancy. Statins are generally contra-indicated in pregnancy since there is a possibility that they might affect fetal sterol synthesis whereas the risk to the mother from stopping treatment temporarily is usually very low. Evidence that statins have adverse effects on the fetus, however, is limited. Studies based on postmarketing surveillance[1,2] or pregnancy registry data[3] have generally found that the frequency and range of congenital anomalies reported was similar to that expected in the general population. However, reviews of case reports[4,5] found that the incidence of CNS defects and limb anomalies was higher than expected, suggesting a possible adverse effect of statin exposure; 1 of the 5 cases reported as a CNS defect was later found to have cardiac anomalies only.[6]

1. Manson JM, *et al.* Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. *Reprod Toxicol* 1996; **10:** 439–46.
2. Pollack PS, *et al.* Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol* 2005; **73:** 888–96.
3. Ofori B, *et al.* Risk of congenital anomalies in pregnant users of statin drugs. *Br J Clin Pharmacol* 2007; **64:** 496–509.
4. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *N Engl J Med* 2004; **350:** 1579–82.
5. Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *Am J Med Genet* 2004; **131A:** 287–98.
6. Edison RJ, Muenke M. Gestational exposure to lovastatin followed by cardiac malformation misclassified as holoprosencephaly. *N Engl J Med* 2005; **352:** 2759.

Interactions

The most serious consequence of drug interactions with simvastatin and other statins is the development of myopathy or rhabdomyolysis. Drugs that can cause myopathy when given alone increase the risk of myopathy with all statins; these drugs include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by drugs that increase the plasma concentrations of statins, by inhibiting their metabolism or by inhibiting their uptake into the liver. Since the statins have different metabolic pathways, these interactions depend on the individual drug concerned. Simvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4, as are atorvastatin and lovastatin, and interactions may occur with drugs that inhibit this enzyme, including ciclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, danazol, amiodarone, and verapamil; there may also be a similar interaction with grapefruit juice. Such combinations should be used with caution, if at all, and dose reduction may be advised (see Uses and Administration, below); UK licensed product information contra-indicates the use of simvastatin in patients receiving potent CYP3A4 inhibitors. Fluvastatin is metabolised mainly by CYP2C9, while pravastatin and rosuvastatin are not significantly metabolised; interactions specific to these statins are discussed on p.1290, p.1374, and p.1389, respectively.

Statins may also have effects on other drugs. Bleeding and increases in prothrombin time have been reported in patients taking simvastatin or other statins with coumarin anticoagulants.

◊ General reviews.

1. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002; **41:** 343–70.
2. Martin J, Krum H. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant? *Drug Safety* 2003; **26:** 13–21.
3. Committee on Safety of Medicines/Medicines and Healthcare Products Regulatory Agency. Statins and cytochrome P450 interactions. *Current Problems* 2004; **30:** 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
4. Rätz Bravo AE, *et al.* Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Safety* 2005; **28:** 263–75.
5. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006; **97** (suppl 8A): 27C–31C.
6. Neuvonen PJ, *et al.* Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006; **80:** 565–81.

Antiarrhythmics. *Amiodarone* is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations of statins metabolised by this enzyme, increasing the risk of toxicity. There have been reports[1-3] of myopathy and rhabdomyolysis in patients taking amiodarone and simvastatin (in some cases with other CYP3A4 inhibitors), and a pharmacokinetic study[4] found that amiodarone increased plasma-simvastatin concentrations in healthy subjects. High doses of simvastatin are not recommended in patients taking amiodarone (see Uses and Administration, below).

An asymptomatic increase in serum aminotransferases in a patient receiving rosuvastatin and amiodarone may have been the result of an interaction between the drugs.[5]

1. Roten L, *et al.* Rhabdomyolysis in association with simvastatin and amiodarone. *Ann Pharmacother* 2004; **38:** 978–81.
2. Chouhan UM, *et al.* Simvastatin interaction with clarithromycin and amiodarone causing myositis. *Ann Pharmacother* 2005; **39:** 1760–1.
3. Ricaurte B, *et al.* Simvastatin–amiodarone interaction resulting in rhabdomyolysis, azotemia, and possible hepatotoxicity. *Ann Pharmacother* 2006; **40:** 753–7.
4. Becquemont L, *et al.* Amiodarone interacts with simvastatin but not with pravastatin disposition kinetics. *Clin Pharmacol Ther* 2007; **81:** 679–84.
5. Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. *Am J Health-Syst Pharm* 2007; **64:** 1818–21.

Antibacterials. *Erythromycin* and other *macrolides* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Increased plasma concentrations of simvastatin have been reported with erythromycin,[1] and increased plasma concentrations of atorvastatin have been found with erythromycin[2] and *clarithromycin*,[3] but not with *azithromycin*.[3] There have been reports of myopathy or rhabdomyolysis in patients receiving simvastatin with clarithromycin,[4] and in patients receiving lovastatin with azithromycin,[5] clarithromycin,[5] or erythromycin.[6]

Rifampicin, an inducer of CYP2C9 and CYP3A4, may reduce the bioavailability of fluvastatin, and has also been reported to reduce the plasma concentration of simvastatin[7] and atorvastatin.[8]

There have been reports of rhabdomyolysis in patients receiving atorvastatin[9] or simvastatin[10] with *fusidic acid*.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64:** 177–82.
2. Siedlik PH, *et al.* Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol* 1999; **39:** 501–4.
3. Amsden GW, *et al.* A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002; **42:** 444–9.
4. Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001; **35:** 26–31.
5. Grunden JW, Fisher KA. Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 1997; **31:** 859–63.
6. Ayanian JZ, *et al.* Lovastatin and rhabdomyolysis. *Ann Intern Med* 1988; **109:** 682–3.
7. Kyrklund C, *et al.* Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 2000; **68:** 592–7.
8. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; **78:** 154–67.
9. Wenisch C, *et al.* Acute rhabdomyolysis after atorvastatin and fusidic acid therapy. *Am J Med* 2000; **109:** 78.
10. Yuen SLS, McGarity B. Rhabdomyolysis secondary to interaction of fusidic acid and simvastatin. *Med J Aust* 2003; **179:** 172.

Anticoagulants. For reports of bleeding and increased prothrombin time in patients receiving oral anticoagulants with statins, see Lipid Regulating Drugs, p.1431.

Antidepressants. Myositis and rhabdomyolysis, with raised liver enzyme values, have been reported[1-4] in patients given simvastatin with *nefazodone*; in one case[3] the reaction appeared to be precipitated by the addition of azithromycin. Increased creatine kinase concentrations also occurred in a patient given pravastatin with nefazodone.[5]

A study[6] in healthy subjects found that *St John's wort* reduced the plasma concentration of simvastatin but had no effect on pravastatin.

1. Jacobson RH, *et al.* Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. *JAMA* 1997; **277:** 296.
2. Thompson M, Samuels S. Rhabdomyolysis with simvastatin and nefazodone. *Am J Psychiatry* 2002; **159:** 1607.
3. Skrabal MZ, *et al.* Two cases of rhabdomyolysis associated with high-dose simvastatin. *Am J Health-Syst Pharm* 2003; **60:** 578–81.
4. Karnik NS, Maldonado JR. Antidepressant and statin interactions: a review and case report of simvastatin and nefazodone-induced rhabdomyolysis and transaminitis. *Psychosomatics* 2005; **46:** 565–8.
5. Alderman CP. Possible interaction between nefazodone and pravastatin. *Ann Pharmacother* 1999; **33:** 871.
6. Sugimoto K-i, *et al.* Different effects of St John's Wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001; **70:** 518–24.

Antifungals. *Itraconazole* and *ketoconazole* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Raised plasma concentrations of simvastatin,[1,2] lovastatin,[3,4] and atorvastatin[5] have been reported with itraconazole, whereas the effect on pravastatin,[1] rosuvastatin,[6] or fluvastatin[4] appears to be minimal. Myopathy and rhabdomyolysis have been reported with simvastatin and itraconazole[2,7] or ketoconazole,[8] and with lovastatin and itraconazole.[9] *Fluconazole* inhibits CYP2C9 and has been reported[10] to increase the plasma concentration of fluvastatin. There has also been a report[11] of rhabdomyolysis in a patient taking fluconazole and simvastatin.

1. Neuvonen PJ, *et al.* Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998; **63:** 332–41.
2. Segaert MF, *et al.* Drug-interaction-induced rhabdomyolysis. *Nephrol Dial Transplant* 1996; **11:** 1846–7.
3. Neuvonen PJ, Jalava K-M. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996; **60:** 54–61.
4. Kivistö KT, *et al.* Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998; **46:** 49–53.
5. Kantola T, *et al.* Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998; **64:** 58–65.
6. Cooper KJ, *et al.* Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2003; **73:** 322–9.
7. Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol* 1996; **132:** 1254.
8. Gilad R, Lampl Y. Rhabdomyolysis induced by simvastatin and ketoconazole treatment. *Clin Neuropharmacol* 1999; **22:** 295–7.
9. Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. *N Engl J Med* 1995; **333:** 664–5.
10. Kantola T, *et al.* Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000; **56:** 225–9.
11. Shaukat A, *et al.* Simvastatin–fluconazole causing rhabdomyolysis. *Ann Pharmacother* 2003; **37:** 1032–5.

Antiplatelet drugs. For discussion of a possible interaction between statins and clopidogrel, see p.1250

Antivirals. *HIV-protease inhibitors* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may affect the metabolism of simvastatin and other statins. Studies have shown increased plasma concentrations of both simvastatin and atorvastatin with *nelfinavir*,[1] and with *ritonavir-boosted saquinavir*,[2] whereas the plasma concentration of pravastatin was reduced with ritonavir-boosted saquinavir.[2] Rhabdomyolysis has been reported[3] in a patient taking simvastatin when ritonavir was added to her therapy. Although rosuvastatin is not significantly metabolised, increased plasma concentrations have been reported with *ritonavir-boosted lopinavir*.[4,5]

There has also been a report[6] of rhabdomyolysis in a patient receiving atorvastatin with the non-nucleoside reverse transcriptase inhibitor *delavirdine*.

Efavirenz is an inducer of CYP3A4 and a study in healthy subjects[7] found that it could reduce plasma concentrations of atorvastatin and simvastatin; plasma concentrations of pravastatin were also reduced, although it is not metabolised by CYP3A4.

1. Hsyu P-H, *et al.* Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother* 2001; **45:** 3445–50.
2. Fichtenbaum CJ, *et al.* Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002; **16:** 569–77.
3. Cheng CH, *et al.* Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. *Am J Health-Syst Pharm* 2002; **59:** 728–30.
4. van der Lee M, *et al.* Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. *Antivir Ther* 2007; **12:** 1127–32.
5. Kiser JJ, *et al.* Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2008; **47:** 570–8.
6. Castro JG, Gutierrez L. Rhabdomyolysis with acute renal failure probably related to the interaction of atorvastatin and delavirdine. *Am J Med* 2002; **112:** 505.
7. Gerber JG, *et al.* Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; **39:** 307–12.

Calcium-channel blockers. Calcium-channel blockers may increase plasma concentrations of some statins, probably by inhibition of the cytochrome P450 isoenzyme CYP3A4. Pharmacokinetic studies have reported increased plasma concentrations of simvastatin with *verapamil*,[1] and with *diltiazem*,[2] and of lovastatin with diltiazem;[3] the small increase with simvastatin and *lacidipine* was not considered clinically relevant.[4]

The interaction between statins and diltiazem has also been reported in patients. A retrospective study[5] found that the cholesterol-lowering effect of simvastatin was greater in patients who were also receiving diltiazem, and there have also been reports[6-8] of rhabdomyolysis, associated with hepatitis in 1 case,[6] in patients receiving simvastatin and diltiazem together. Rhabdomyolysis[8,9] and hepatitis[9] have also been reported in patients receiving atorvastatin with diltiazem.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; **64:** 177–82.
2. Mousa O, *et al.* The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000; **67:** 267–74.
3. Azie NE, *et al.* The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther* 1998; **64:** 369–77.
4. Ziviani L, *et al.* The effects of lacidipine on the steady/state plasma concentrations of simvastatin in healthy subjects. *Br J Clin Pharmacol* 2001; **51:** 147–52.
5. Yeo KR, *et al.* Enhanced cholesterol reduction by simvastatin in diltiazem-treated patients. *Br J Clin Pharmacol* 1999; **48:** 610–615.
6. Kanathur N, *et al.* Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. *Tenn Med* 2001; **94:** 339–41.
7. Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron* 2001; **89:** 117–118.
8. Gladding P, *et al.* Potentially fatal interaction between diltiazem and statins. *Ann Intern Med* 2004; **140:** W31. Available at: http://www.annals.org/cgi/reprint/140/8/W-31.pdf (accessed 14/11/07)
9. Lewin JJ, *et al.* Rhabdomyolysis with concurrent atorvastatin and diltiazem. *Ann Pharmacother* 2002; **36:** 1546–9.

Colchicine. For reports of additive muscle toxicity with statins and colchicine, see Cardiovascular Drugs under Interactions of Colchicine, p.556.

Danazol. Rhabdomyolysis has been reported[1] in a patient receiving lovastatin with a number of other drugs; it was considered that an interaction with danazol was the most likely cause. A similar reaction has been reported[2] with simvastatin.

1. Dallaire M, Chamberland M. Rhabdomyolyse sévère chez un patient recevant lovastatine, danazol et doxycycline. *Can Med Assoc J* 1994; **150:** 1991–4.
2. Andreou ER, Ledger S. Potential drug interaction between simvastatin and danazol causing rhabdomyolysis. *Can J Clin Pharmacol* 2003; **10:** 172–4.

Endothelin receptor antagonists. *Bosentan* is an inducer of the cytochrome P450 isoenzyme CYP3A4 and has been reported[1] to reduce plasma-simvastatin concentrations in healthy subjects.

1. Dingemanse J, *et al.* Investigation of the mutual pharmacokinetic interactions between bosentan, a dual endothelin receptor antagonist, and simvastatin. *Clin Pharmacokinet* 2003; **42:** 293–301.

Fruit juices. *Grapefruit juice* inhibits the cytochrome P450 isoenzyme CYP3A4 and studies using concentrated grapefruit juice have reported increased plasma concentrations of simvastatin,[1] lovastatin,[2] and atorvastatin.[3] A study[4] using less concentrated grapefruit juice found only minimal effect on the activity of lovastatin, but the conclusions of this study have been criticised;[5] studies using normal strength grapefruit juice have found considerable increases in plasma concentrations of atorvastatin[6] and simvastatin.[7] There is also a case report[8] of a woman receiving simvastatin who developed symptoms of rhabdomyolysis 4 days after she started eating one grapefruit each day. Statins that are not significantly metabolised by CYP3A4, such as pitavastatin[6] and pravastatin,[3,9] do not appear to be affected.

Rhabdomyolysis has also been reported[10] in a patient taking rosuvastatin and ezetimibe when he started drinking *pomegranate juice* regularly.

1. Lilja JJ, *et al.* Grapefruit juice–simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998; **64:** 477–83.
2. Kantola T, *et al.* Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1998; **63:** 397–402.
3. Lilja JJ, *et al.* Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999; **66:** 118–27.
4. Rogers JD, *et al.* Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Clin Pharmacol Ther* 1999; **66:** 358–66.
5. Bailey DG, Dresser GK. Grapefruit juice–lovastatin interaction. *Clin Pharmacol Ther* 2000; **67:** 690.
6. Ando H, *et al.* Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *Br J Clin Pharmacol* 2005; **60:** 494–7.
7. Lilja JJ, *et al.* Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. *Br J Clin Pharmacol* 2004; **58:** 56–60.
8. Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. *Neurology* 2004; **62:** 670.
9. Fukazawa I, *et al.* Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br J Clin Pharmacol* 2004; **57:** 448–55.
10. Sorokin AV, *et al.* Rhabdomyolysis associated with pomegranate juice consumption. *Am J Cardiol* 2006; **98:** 705–6.

Immunosuppressants. Myopathy and rhabdomyolysis have been reported in patients receiving atorvastatin,[1] lovastatin,[2-4] or simvastatin[5-7] with immunosuppressant regimens including *ciclosporin*. The mechanism of the interaction may be additive toxicity, since both statins and ciclosporin are known to cause myopathy, but effects on plasma concentrations may also be involved. Pharmacokinetic studies have shown that ciclosporin increases the plasma concentrations of atorvastatin,[8,9] fluvastatin,[10,11] lovastatin,[12] pravastatin,[12,13] rosuvastatin,[14] and simvastatin.[15] For the effects of statins on plasma-ciclosporin concentrations, see p.1827.

1. Maltz HC, *et al.* Rhabdomyolysis associated with concomitant use of atorvastatin and cyclosporine. *Ann Pharmacother* 1999; **33:** 1176–9.
2. Norman DJ, *et al.* Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med* 1988; **318:** 46–7.
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7. Gumprecht J, *et al.* Simvastatin-induced rhabdomyolysis in a CsA-treated renal transplant recipient. *Med Sci Monit* 2003; **9:** CS89–CS91.
8. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; **1:** 382–6.
9. Hermann M, *et al.* Substantially elevated levels of atorvastatin and metabolites in cyclosporine-treated renal transplant recipients. *Clin Pharmacol Ther* 2004; **76:** 388–91.
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11. Park J-W, *et al.* Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. *J Cardiovasc Pharmacol Ther* 2001; **6:** 351–61.
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14. Simonson SG, *et al.* Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004; **76:** 167–77.
15. Arnadottir M, *et al.* Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron* 1993; **65:** 410–13.

Levothyroxine. For reference to the effect of lovastatin and simvastatin in patients receiving levothyroxine, see Lipid Regulating Drugs, p.2173.

Lipid regulating drugs. Myopathy and myositis are recognised adverse effects of both statins and fibric acid derivatives, including *fibrates* and *gemfibrozil*, and the risk is increased if they are given together. There has also been a report[1] of both hepatotoxicity and rhabdomyolysis in a patient given a statin and gemfibrozil together. The interaction between gemfibrozil and statins may also have a pharmacokinetic basis; studies have shown increased plasma concentrations of atorvastatin,[2] lovastatin,[3] pravastatin,[4] rosuvastatin,[5] and simvastatin[6] when given with gemfibrozil.

Myopathy has also been reported[7,8] in patients given statins with *nicotinic acid*, although a study[9] of adverse effects reported to the FDA found no increase in reports for lovastatin given with nicotinic acid compared with either drug alone.

For reports of increased hepatotoxicity when statins were given with *ezetimibe* see Effects on the Liver, p.1284.

1. Akoglu H, *et al.* Combined organ failure with combination antihyperlipidemic treatment: a case of hepatic injury and acute renal failure. *Ann Pharmacother* 2007; **41:** 143–7.
2. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; **78:** 154–67.
3. Kyrklund C, *et al.* Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001; **69:** 340–5.
4. Kyrklund C, *et al.* Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003; **73:** 538–44.
5. Schneck DW, *et al.* The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004; **75:** 455–63.
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7. Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med* 1988; **109:** 597–8.

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Proton pump inhibitors. There is a report[1] of rhabdomyolysis causing AV block in a patient receiving atorvastatin when *esomeprazole* and clarithromycin were added to her treatment. As symptoms started before the introduction of clarithromycin, it was thought that a possible contributory mechanism for the interaction was a reduction in the first-pass metabolism of atorvastatin due to the inhibition of p-glycoprotein by esomeprazole.

1. Sipe BE, *et al.* Rhabdomyolysis causing AV blockade due to possible atorvastatin, esomeprazole, and clarithromycin interaction. *Ann Pharmacother* 2003; **37:** 808–11.

Ranolazine. A study[1] in healthy subjects showed that ranolazine moderately increased plasma concentrations of simvastatin but it was not thought that the interaction would be clinically significant.

1. Jerling M, *et al.* Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects. *J Clin Pharmacol* 2005; **45:** 422–33.

Pharmacokinetics

Simvastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Other active metabolites have been detected and a number of inactive metabolites are also formed. Simvastatin 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 the oral dose has been reported to reach the circulation as active metabolites. Both simvastatin and its β-hydroxyacid metabolite are about 95% bound to plasma proteins. Simvastatin is mainly excreted in the faeces via the bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms. The half-life of the active β-hydroxyacid metabolite is 1.9 hours.

◊ General reviews.

1. Mauro VF. Clinical pharmacokinetics and practical applications of simvastatin. *Clin Pharmacokinet* 1993; **24:** 195–202.
2. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; **31:** 348–71.
3. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; **32:** 403–25.

Genetic variation. The pharmacokinetics of statins are influenced not only by metabolising enzymes but also by their affinity for organ-specific transporter proteins responsible for their uptake and efflux from cells, in particular in the intestine and liver.[1,2] Statins differ not only in their affinity for cytochrome P450 isoenzymes, but also in their affinity for transporter proteins such as organic anion transporting polypeptides (OATPs) and P-glycoprotein (multi-drug resistance 1; MDR1). Both metabolising enzymes and transporter proteins may be subject to ethnic and genetic variation, and it has been suggested that this may explain some of the variability in the efficacy and the risk of adverse effects in different populations.

1. Kim RB. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and genetic variability (single nucleotide polymorphisms) in a hepatic drug uptake transporter: what's it all about? *Clin Pharmacol Ther* 2004; **75:** 381–5.
2. Tirona RG. Ethnic differences in statin disposition. *Clin Pharmacol Ther* 2005; **78:** 311–16.

Uses and Administration

Simvastatin is a lipid regulating drug; it is a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-determining enzyme for cholesterol synthesis. Inhibition of HMG-CoA reductase leads to reduced cholesterol synthesis in the liver and lower intracellular cholesterol concentrations; this stimulates an increase in low-density-lipoprotein (LDL)-cholesterol receptors on hepatocyte membranes, thereby increasing the clearance of LDL from the circulation. HMG-CoA reductase inhibitors (also called statins) reduce total cholesterol, LDL-cholesterol, and very-low-density lipoprotein (VLDL)-cholesterol concentrations in plasma. They also tend to reduce triglycerides and to increase high-density lipoprotein (HDL)-cholesterol concentrations.

Simvastatin is used to reduce LDL-cholesterol, apolipoprotein B, and triglycerides, and to increase HDL-cholesterol in the treatment of hyperlipidaemias (p.1169). It is used in hypercholesterolaemias, combined (mixed) hyperlipidaemia (type IIa or IIb hyperlipoproteinaemias), hypertriglyceridaemia (type IV), and primary dysbetalipoproteinaemia (type III), and may also be used as adjunct therapy in patients with homozygous familial hypercholesterolaemia who have some LDL-receptor function. Simvastatin is also used for cardiovascular risk reduction (p.1164).

Simvastatin is given orally and doses range from 5 to 80 mg daily. For the treatment of **hyperlipidaemias**, the usual initial dose is 10 to 20 mg in the evening; an initial dose of 40 mg may be used in patients who require a large reduction in cholesterol or who are at high cardiovascular risk. The dose may be adjusted at intervals of not less than 4 weeks up to a maximum of 80 mg once daily in the evening. Patients with homozygous familial hypercholesterolaemia may be treated with 40 mg once daily in the evening, or 80 mg daily in 3 divided doses of 20 mg, 20 mg, and an evening dose of 40 mg.

For **cardiovascular risk reduction** in high-risk patients, such as those with atherosclerotic cardiovascular disease or diabetes mellitus, the usual dose is 20 to 40 mg once daily. Patients who are at moderate risk may be given a dose of 10 mg once daily.

The dose of simvastatin should be reduced in patients at risk of myopathy, including patients with severe renal impairment (see below). For patients taking drugs that interact with simvastatin, dose reduction is also advised, as follows:

- patients taking *ciclosporin* or *danazol*, initial dose 5 mg once daily and maximum dose 10 mg once daily
- patients taking *gemfibrozil* or other *fibrates*, or *nicotinic acid*, maximum dose 10 mg once daily
- patients taking *amiodarone* or *verapamil*, maximum dose 20 mg once daily
- patients taking *diltiazem*, maximum dose 40 mg once daily

For the use of simvastatin in children, see below.

◊ General reviews.

1. Mauro VF, MacDonald JL. Simvastatin: a review of its pharmacology and clinical use. *DICP Ann Pharmacother* 1991; **25:** 257–64.
2. Plosker GL, McTavish D. Simvastatin: a reappraisal of its pharmacology and therapeutic efficacy in hypercholesterolaemia. *Drugs* 1995; **50:** 334–63.
3. Schectman G, Hiatt J. Dose–response characteristics of cholesterol-lowering drug therapies: implications for treatment. *Ann Intern Med* 1996; **125:** 990–1000.
4. White CM. Pharmacological effects of HMG CoA reductase inhibitors other than lipoprotein modulation. *J Clin Pharmacol* 1999; **39:** 111–18.
5. Mata P, *et al.* Benefits and risks of simvastatin in patients with familial hypercholesterolaemia. *Drug Safety* 2003; **26:** 769–86.

Action. The effects of statins on *plasma lipids* are well established.[1-4] Their primary action is to inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis. Cholesterol is an important precursor for synthesis of a number of substances by the liver, and reduced intracellular concentrations stimulate an increase in the expression of low-density lipoprotein (LDL) receptors in the liver. This leads to increased uptake of LDL-cholesterol from the plasma into liver cells, with a subsequent reduction in both LDL and total cholesterol. Triglycerides are also decreased, due to decreased synthesis of very-low-density lipoprotein (VLDL), while high-density lipoprotein (HDL)-cholesterol is either modestly increased or unchanged, leading to an improvement in the LDL:HDL ratio. An effect on LDL-cholesterol may also occur independent of the effect on receptors; some statins have been shown to lower LDL-cholesterol in patients with homozygous familial hypercholesterolaemia, despite their lack of functional LDL receptors. Statins generally provide a greater reduction in LDL-cholesterol than other classes of lipid regulating drugs, but where large reductions are required combination therapy may be necessary. Statins have been used with bile-acid binding resins and with ezetimibe; they have also been given with fibrates or nicotinic acid, although the increased risk of adverse effects needs to be considered. Cholesterol synthesis in the liver peaks during the early morning (midnight to 3 a.m.) and there is some evidence that statins with short half-lives, such as simvastatin, should be taken in the evening.[5]

Statins have a number of additional (pleiotropic) actions,[1-4,6,7] although whether these contribute to their cardiovascular effects is controversial.[8]

In *atherosclerosis* they have beneficial effects on endothelial function, which may be partly independent of their effect on lipids, and also appear to stabilise atherosclerotic plaques. A number of studies[9,10] have also shown that statins reduce concentrations of C-reactive protein (CRP), a marker of inflammation that is raised in atherosclerosis, and there is some evidence that the reduction in CRP is independently associated with a reduction in cardiovascular events[11] and regression of atherosclerotic lesions,[12] although results have been mixed in a related condition, calcific aortic stenosis.[13] Statins have a number of actions that may be beneficial in *heart failure*,[14] but detrimental effects are also possible and their role specifically for heart failure is unclear.[15] Evidence from cohort studies[16-18] suggests statins may improve mortality in heart failure, and analyses of cardiovascular risk reduction studies[19,20] also suggest benefit. However, a randomised study[21] of rosuvastatin in patients with heart failure of ischaemic origin failed to show an effect on mortality, although there were fewer hospitalisations in patients given the active drug. Statins may also have *antihypertensive*[22] and *antiarrhythmic* effects; they reduce the incidence of atrial fibrillation,[23] and have also been associated with a reduced risk of ventricular arrhythmias,[24,25] although this requires confirmation. Beneficial effects have also been reported on some measures of *haemostasis*,[26] and a reduced incidence of venous thromboembolism has been noted in some studies.[27]

Statins also appear to have anti-inflammatory and immunomodulatory actions and these may contribute to their beneficial effects. There is evidence from epidemiological studies that they reduce the risk of bacterial infections, although this has been attributed to a 'healthy-user' effect,[28,29] and they may also reduce mortality in patients with sepsis.[29] Benefit has also been reported in *rheumatoid arthritis* and other inflammatory arthropathies.[30-33] In patients with *organ transplantation*, both cardiovascular and immunomodulatory actions may be of benefit (see below). However, the use of statins in these diseases remains to be confirmed.

For discussion of the use of statins in other non-cardiovascular disorders, including dementia, kidney disorders, malignant neoplasms, and osteoporosis, see below.

1. Maron DJ, *et al.* Current perspectives on statins. *Circulation* 2000; **101:** 207–13.
2. Shepherd J. The statin era: in search of the ideal lipid regulating agent. *Heart* 2001; **85:** 259–64.
3. Chong PH, *et al.* Clinically relevant differences between the statins: implications for therapeutic selection. *Am J Med* 2001; **111:** 390–400.
4. Igel M, *et al.* Pharmacology of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), including rosuvastatin and pitavastatin. *J Clin Pharmacol* 2002; **42:** 835–45.
5. Plakogiannis R, Cohen H. Optimal low-density lipoprotein cholesterol lowering—morning versus evening statin administration. *Ann Pharmacother* 2007; **41:** 106–10.
6. Sotiriou CG, Cheng JWM. Beneficial effects of statins in coronary artery disease—beyond lowering cholesterol. *Ann Pharmacother* 2000; **34:** 1432–9.
7. Balk EM, *et al.* Effects of statins on nonlipid serum markers associated with cardiovascular disease: a systematic review. *Ann Intern Med* 2003; **139:** 670–82.
8. Robinson JG, *et al.* Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005; **46:** 1855–62.
9. Ridker PM, *et al.* Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; **344:** 1959–65.
10. Albert MA, *et al.* Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; **286:** 64–70.
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13. Chua D, Kalb K. Statins and progression of calcified aortic stenosis. *Ann Pharmacother* 2006; **40:** 2195–9.
14. Laufs U, *et al.* HMG-CoA reductase inhibitors in chronic heart failure: potential mechanisms of benefit and risk. *Drugs* 2006; **66:** 145–54.
15. van der Harst P, *et al.* Statins in the treatment of chronic heart failure: a systematic review. *PLoS Med* 2006; **3:** e333.
16. Horwich TB, *et al.* Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. *J Am Coll Cardiol* 2004; **43:** 642–8.
17. Foody JM, *et al.* Statins and mortality among elderly patients hospitalized with heart failure. *Circulation* 2006; **113:** 1086–92.
18. Go AS, *et al.* Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006; **296:** 2105–11.
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20. Khush KK, *et al.* Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. *Circulation* 2007; **115:** 576–83.
21. Kjekshus J, *et al.* CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; **357:** 2248–61.
22. Strazzullo P, *et al.* Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. *Hypertension* 2007; **49:** 792–8.
23. Patel AA, *et al.* The relationship between statin use and atrial fibrillation. *Curr Med Res Opin* 2007; **23:** 1177–85.

24. Mitchell LB, *et al.* Are lipid-lowering drugs also antiarrhythmic drugs? An analysis of the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Am Coll Cardiol* 2003; **42:** 81–7.
25. Vyas AK, *et al.* Reduction in ventricular tachyarrhythmias with statins in the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006; **47:** 769–73.
26. Krysiak R, *et al.* Effects of HMG-CoA reductase inhibitors on coagulation and fibrinolysis processes. *Drugs* 2003; **63:** 1821–54.
27. Ray JG, *et al.* Use of statins and the subsequent development of deep vein thrombosis. *Arch Intern Med* 2001; **161:** 1405–10.
28. Majumdar SR, *et al.* Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. *BMJ* 2006; **333:** 999–1001.
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30. Kanda H, *et al.* Antiinflammatory effect of simvastatin in patients with rheumatoid arthritis. *J Rheumatol* 2002; **29:** 2024–6.
31. McCarey DW, *et al.* Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *Lancet* 2004; **363:** 2015–21.
32. ten Cate R, *et al.* Therapy-refractory systemic juvenile idiopathic arthritis successfully treated with statins. *Rheumatology (Oxford)* 2004; **43:** 934–5.
33. van Denderen JC, *et al.* Statin therapy might be beneficial for patients with ankylosing spondylitis. *Ann Rheum Dis* 2006; **65:** 695–6.

Administration in children. The management of hyperlipidaemias in children and adolescents is controversial and is usually reserved for those with familial hyperlipidaemias who have a high risk of premature cardiovascular disease. Dietary measures and bile-acid binding resins have traditionally been first-line therapy in children, but may be poorly tolerated or inadequate. Studies with statins in children aged 8 to 18 years with familial hypercholesterolaemia have shown[1,2] that they effectively lower total cholesterol and low-density lipoprotein (LDL)-cholesterol and they are now increasingly preferred where drug therapy is indicated.[3,4] However, there have been concerns about the potential adverse effects of statins on growth and sexual development, since these patients require life-long treatment. Although this does not appear to be a problem, most studies have been relatively short-term, and longer follow-up is needed to confirm statin safety.[3,4] Preliminary evidence suggests that statins may also be effective in children with hyperlipidaemia related to nephrotic syndrome[5] or organ transplantation.[3,4]

US licensed product information for simvastatin allows its use in children aged 10 to 17 years with familial heterozygous hypercholesterolaemia in an initial oral dose of 10 mg at night, increased at intervals of 4 weeks as required to a maximum dose of 40 mg daily. A placebo-controlled study[6] in 173 such children found that simvastatin given orally in a dose of up to 40 mg daily for 48 weeks effectively reduced LDL-cholesterol and was well tolerated, with no effect on growth or sexual development.

The *BNFC* recommends the following doses for children with hyperlipidaemia:

- age 5 to 10 years: initial dose 5 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 20 mg at night
- age 10 to 18 years: initial dose 10 mg at night, increased if necessary at intervals of at least 4 weeks to a maximum dose of 40 mg at night

Doses should be reduced in children who are taking drugs that may interact with simvastatin (see Interactions, above).

1. Shafiq N, *et al.* A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia. *Int J Clin Pharmacol Ther* 2007; **45:** 548–55.
2. Avis HJ, *et al.* A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 2007; **27:** 1803–10.
3. McCrindle BW, *et al.* Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation* 2007; **115:** 1948–67.
Available at: http://circ.ahajournals.org/cgi/reprint/115/14/1948.pdf (accessed 30/05/08)
4. Belay B, *et al.* The use of statins in pediatrics: knowledge base, limitations, and future directions. *Pediatrics* 2007; **119:** 370–80.
5. Prescott WA, *et al.* The potential role of HMG-CoA reductase inhibitors in pediatric nephrotic syndrome. *Ann Pharmacother* 2004; **38:** 2105–14.
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Administration in renal impairment. Statins appear to be safe and effective in patients with dyslipidaemia and renal impairment, and there is some evidence that they may have beneficial effects on renal function (see Kidney Disorders, below). However, patients with severe renal impairment may be at increased risk of developing myopathy or rhabdomyolysis and lower doses may be appropriate in such patients. Dose reduction may also be needed for statins that are excreted by the kidneys.

Simvastatin does not undergo significant renal excretion and no dose modification is required in patients with mild or moderate renal impairment. However, in patients with severe renal impairment the recommended initial dose is 5 mg once daily and doses above 10 mg once daily should be used with caution.

Cardiovascular risk reduction. Lipid regulating drugs have an important role in cardiovascular risk reduction (p.1164), and statins are widely used for both primary and secondary prevention. The rationale for their use has been the established link between hypercholesterolaemia and atherosclerosis, but they may have additional actions that contribute to their effect (see Action, above). The efficacy of statins in reducing cardiovascular events has been established in a wide range of patient groups and is generally believed to be a class effect, although outcome studies have not been performed for all the statins in every case.

In patients with established ischaemic heart disease, statins reduce the risk of further cardiovascular events, and also reduce both cardiovascular and overall mortality.[1] Statins shown to be effective for secondary prevention in large, randomised studies include simvastatin,[2] pravastatin,[3,4] and fluvastatin.[5,6] For primary prevention in patients at high risk but without prior cardiovascular events, statins similarly reduce the risk of cardiovascular events, although an effect on mortality has not been shown.[7] Benefit has been established in studies using pravastatin,[8,9] lovastatin,[10] simvastatin,[11] and atorvastatin;[12] the negative results of the ALLHAT-LLT study[13] with pravastatin were attributed to the substantial use of statins in the control group.

Although the main benefit of statins is to reduce mortality and major coronary events, there may also be a reduction in the incidence[14-17] and severity[18] of stroke (although there may be an increase in haemorrhagic stroke[16]), and the incidence of peripheral vascular disease;[19] some studies have also shown a reduction in coronary[19,20] and peripheral[19,21] ischaemic symptoms. Observational studies have suggested that statins may also reduce postoperative mortality in patients with high cardiovascular risk undergoing surgery, although this remains to be confirmed,[22] and there is some evidence that statins may reduce the risk of myocardial damage in patients undergoing percutaneous interventions,[23] although they have not been shown to affect restenosis.[24,25] Early use of statins may also have a role in patients with acute coronary syndromes; one meta-analysis[26] found no evidence of benefit at 1 or 4 months after the initial event, but another[27] reported a reduction in cardiovascular events with statin therapy for 6 months or longer, and some studies[28] have suggested earlier benefit with high-dose regimens.

The main effect of statins appears to relate to their action on lipid concentrations, and increased benefit has been reported[29] with the use of intensive lipid lowering regimens, including a reduction in mortality in patients with acute coronary syndromes.[30] However, studies have shown that statins improve outcomes in patients with both raised[8,26] and average[3,4,10,12] cholesterol concentrations, and meta-analyses[31,32] have concluded that the absolute benefit of statin treatment depends on both the initial cardiovascular risk and the degree of cholesterol reduction achieved. Most benefit has been reported in patients at the highest risk; subgroups in whom particular benefit has been reported include patients with metabolic syndrome compared with those without,[33] and diabetics compared with non-diabetics,[34] although a study[35] with atorvastatin in diabetics undergoing haemodialysis found no benefit. Early studies included mainly middle-aged men, but later studies[11] and meta-analyses[9,31] have confirmed that statins also improve outcomes in women and in the elderly. Observational studies[36,37] have confirmed that these benefits extend to the clinical situation.

Statins differ in potency,[38-40] but evidence that they differ in efficacy for cardiovascular risk reduction when given at comparable lipid-lowering doses is limited.[41] Patients who do not achieve target lipid concentrations or who experience adverse effects with one statin may find an alternative statin effective and tolerable, although recurrence of myalgia is not uncommon.[42]

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Dementia. There is conflicting evidence on the link between statin use and dementia. Epidemiological studies have reported[1,2] that the prevalence of dementia (p.362) is lower in patients taking statins, although it has been suggested that this

may be due to bias in prescribing.[3] (Prevalence may also be reduced in patients taking fibrates.[2]) Some longitudinal studies have reported[4,5] that statins also reduce the incidence of dementia, but others have found no evidence of a reduction in risk,[6-8] and it has been suggested[6] that inappropriate analysis may explain the positive results. Prospective, randomised trials are therefore needed to determine their role, if any, in the prevention of dementia.[3]

There is also some evidence that statins[9-11] and other lipid regulating drugs[11] may reduce the progression of cognitive decline in patients with dementia, although the effect has generally been small. However, negative effects on mental function have been reported with some statins (see under Adverse Effects, above) and their use in the management of dementia is not established.

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Kidney disorders. Although proteinuria has been reported with statins (see Effects on the Kidney under Adverse Effects, above) there is also some evidence that statins modestly reduce the progression of proteinuria and loss of renal function.[1-4] However, further studies are required to confirm these effects.

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Malignant neoplasms. Although studies in *animals* suggest[1] that statins could be carcinogenic, evidence for a detrimental effect in humans is limited, and some studies have suggested that statins may be protective. Low plasma-cholesterol concentrations have been associated with cancer, and an increased incidence of cancer was reported in a randomised study of pravastatin for cardiovascular risk reduction in elderly patients,[2] although this was attributed to chance. Conversely, several observational studies have reported[3-7] that statins reduce the incidence of cancer, although the effect has generally been small. A number of meta-analyses have been performed and have generally found no association between the use of statins and the incidence of cancer. Analyses including only randomised studies[8,9] have found no significant effect on overall risk, although follow-up may not have been long enough in most studies to be conclusive; there is also little evidence of a protective effect for specific cancers.[10-12] However, another large cohort study[13] in elderly patients found no evidence that statins either increased or reduced the risk, and longer follow-up in a randomised study[14] using simvastatin also found no significant effect.

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Organ and tissue transplantation. Cardiovascular disease is an important cause of morbidity and mortality after organ transplantation and statins are useful for cardiovascular risk reduction in these patients. They may also have immunomodulatory effects and have reduced the risk of rejection in some studies.[1] A meta-analysis of patients who had undergone heart transplantation (p.1812) considered that treatment with a statin within 3 months of transplantation reduced allograft rejection with haemodynamic compromise and reduced 1-year mortality;[2] it was calculated that one life was saved for every 8.5 treated heart transplant patients. There is some tentative evidence that statin therapy may also reduce acute rejection and the development of obliterative bronchiolitis in patients who have undergone lung transplantation (p.1815),[3] although prospective controlled studies are lacking.

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Osteoporosis. Statins appear to have effects on bone metabolism and preliminary studies[1,2] have suggested that some statins may increase bone mineral density. However, the clinical relevance of any effect is unclear.[3] Several case-control studies[4-6] have also suggested that use of statins may protect against fractures, but another case-control study[7] and an observational study[8] failed to support such an association. A review[9] of 4 further observational studies found that the risk of fracture was lower in women taking statins, but analysis of data from randomised studies of statins for cardiovascular disease[10,11] failed to confirm any effect, and controlled studies are needed[3,12] to confirm the role of statins in the management of osteoporosis (p.1084).

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Preparations

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

Proprietary Preparations (details are given in Part 3)
Arg.: Coledis†; Colesterminol; Dosavastatin; Gemistatin; Klonastin; Labistatin; Lipimibe; Lisac; Nivelipol; Nosterol; Redusterol; Sevacol; Several; Tanavat; Vasotenal; Zocor; ***Austral.:*** Lipex; Ransim†; Simvabell; Simvahexal; Simvar; Zimstat; Zocor; ***Austria:*** Gerosim; Nyzoc; SimcorHexal†; Simstin†; Simvarcana; Simvastad; Simvatin; Zocord; ***Belg.:*** Cholemed; Docsimvasta; Simvafour; Simvastamed; Zocor; ***Braz.:*** Androlip†; Clinfar; Cordiron†; Lipotex; Liptrat; Lovacor†; Menocol; Mivalen; Revastin; Sinvalip; Sinvascor; Sinvastacor†; Sinvastamed; Sinvastin†; Sinvatrox; Sinvax; Sinvaz†; Sivastin†; Vaslip; Vastatil; Zocor; ***Canad.:*** Zocor; ***Chile:*** Arterosan†; Nimicor; Simvass; Vasomed; Vasotenal; Zocor; ***Cz.:*** Apo-Simva; Corsim; Egilipid; Sim; Simbela; Simgal; Simirex; Simva; Simvacard; Simvax; Simvor; Vasilip; Zocor; ***Denm.:*** Perichol; Zocolip; Zocor; ***Fin.:*** Corolin†; Lipcut; Zocor; ***Fr.:*** Lodales; Zocor; ***Ger.:*** BeL; Denan†; Simva; SimvaAPS; Simvabeta; Simvacard; Simvacor; Simvadoc; Simvadura; Simvagamma; Simvalip; Zemox†; Zocor; ***Gr.:*** Antichol; Arstatin; Avatratin; Bevostatin; Christatin; Doctiverine; Extrastatin; Glipal; Goldastatin; Iamastatin; Ipramid; Kymazol; Lepur; Lip-Down; Lipomin; Lipopress; Liporex; Lipozid; Lowcholid; Lusimva; Medistatin; Nitastin; Normotherin; Placol; Prelon; Priacin; Prizelip; Raptor; Ravostan; Redusterol; Simplaqor; Simvachol†; Simvacor; Simvalark; Simvalid; Simvaprol; Simvatin; Sivinar; Sotovastin; Starezin; Stasiva; Statinal; Statinum; Stativer; Statosan; Stazor; Sterylip; Vassor; Vastatin; Velkastatin; Zocor; Zurocid; ***Hong Kong:*** Avastinee; Corstat; Covastin; Qualicor; Simcard; Simtin; Vasilip; Vidastat; Zocor; ***Hung.:*** Awestatin; Sicor; Simvacol; Simvagamma; Simvep; Simvor; Vasilip; Zocor; ***India:*** Biosim†; Simcard; Simchol; Simlo; Simvotin; ***Indon.:*** Cholestat; Detrovel; Esvat; Ethicol; Lipinorm; Mersivas; Normofat; Pontizoc; Rechol; Rendapid; Simbado; Simchol; Simcor; Sinova; Valemia; Vazim; Vidastat; Zocor; Zovast; ***Irl.:*** Ritechol; Simator; Simtan; Simzor; Sivatin; Zocor; ***Israel:*** Simovil; Simvacor; Simvaxon; ***Ital.:*** Liponorm; Medipo; Sinvacor; Sivastin; Zocor; ***Malaysia:*** Covastin; Simcard; Simtin; Simvacor; Simvor; Stavid; Vascor; Zocor; ***Mex.:*** Apomastina; Colesken; Fansia; Imbistad; Josken†; Pulsar-AT Dual; Simplaqor; Tulip; Zeid; Zocor; Zorced; ***Neth.:*** Altercor†; Simva†; Zocor; ***Norw.:*** Zocor; ***NZ:*** Lipex; Sim-Statin; ***Philipp.:*** Cholestad; Eurocor; Euvasten; Forcad; Ivast; Lipivas; Normastin; Orovas; Simtin; Simvahex; Uni-Per; Vastilan; Vidastat; Wilsim; Zivas; Zocor; Zolvastin; Zovast; ***Pol.:*** Cardin; Simgal; Simratio; Simredin; Simvacard; Simvachol; Simvacor; Simvahexal; Simvasterol; Vasilip; Vastan; Ximve; Zocor; ***Port.:*** Colvastina; Dislipina; Jabastatina; Lipaz; Simvacol; Simvasim; Sinpor; Sintar; Sinvastil; Sumaclina†; Tavitan; Vascorim; Zera; Zocor; ***Rus.:*** Actalipid (Акталипид); Aterostat (Атеростат); Simgal (Симгал); Simlo (Симло); Simvacard (Симвакард); Simvahexal (Симвагексал); Simvalimit (Симвалимит); Simvastol (Симвастол); Simvor (Симвор); Vasilip (Вазилип); Zocor (Зокор); Zorstat (Зорстат); Zovatin (Зоватин); ***S.Afr.:*** Lipidex; Simaspen; Simcard; Simvacor; Simvotin; Zocor; ***Singapore:*** Covastin; Ifistatin; Simtin; Simvacor; Simvor; Vascor†; Zocor; ***Spain:*** Arudel; Belmalip; Colemin; Glutasey; Histop; Lipociden; Pantok; Simvasten†; Simvastur†; Teylor; Zocor; ***Swed.:*** Zocord; ***Switz.:*** Adipur; Simcora; Simvasine; Simvast; Simvastin; Zocor; ***Thai.:*** Bestatin; Eucor; Lochol; Simvor; Torio; Vascor; Zimmex; Zocor; ***Turk.:*** Lipovas; Simvakol; Zocor; Zovatin; ***UAE:*** Simvast; ***UK:*** Simvador; Zocor; ***USA:*** Zocor; ***Venez.:*** Cynt; Hisplenil†; Kavelor; Rowestin†; Simplaqor; Sinvaz; Tavor; Tinasin; Vasotenal; Vastan; Zocor.

Multi-ingredient: ***Arg.:*** Alipas Duo; Labistatin Duo; Redusterol Duo; Vasotenal EZ; Vytorin; ***Austral.:*** Vytorin; ***Austria:*** Inegy; Vytorin; ***Braz.:*** Diocomb Sl; Prevencor; Vytorin; Zetsim; ***Chile:*** Adacai; Vytorin; Zintrepid; ***Cz.:*** Inegy; ***Fr.:*** Inegy; ***Ger.:*** Inegy; ***Gr.:*** Inegy; Vytorin; ***Hong Kong:*** Vytorin; ***Hung.:*** Inegy; ***Indon.:*** Vytorin; ***Irl.:*** Inegy; ***Ital.:*** Inegy; Vytorin; ***Malaysia:*** Vytorin; ***Mex.:*** Amlidual; Vytorin; Zintrepid; ***Neth.:*** Inegy; Vytorin; ***Norw.:*** Inegy; ***NZ:*** Vytorin; ***Philipp.:*** Vytorin; ***Port.:*** Inegy; ***Singapore:*** Vytorin; ***Swed.:*** Zocord/ASA†; ***UK:*** Inegy; ***USA:*** Simcor; Vytorin; ***Venez.:*** Adacai; Vytorin; Zintrepid.

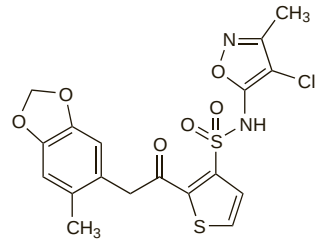
Sitaxentan Sodium *(rINNM)*

Natrii Sitaxentanum; Sitaxentán sódico; Sitaxentan Sodique; Sitaxsentan Sodium; TBC-11251 (sitaxentan or sitaxentan sodium). *N*-(4-Chloro-3-methyl-5-isoxazolyl)-2-{[4,5-(methylenedioxy)-*o*-tolyl]acetyl}-3-thiophenesulfonamide sodium.

Натрий Ситаксентан

$C_{18}H_{14}ClN_2NaO_6S_2$ = 476.9.

CAS — 184036-34-8 (sitaxentan); 210421-74-2 (sitaxentan sodium).



(sitaxentan)

Adverse Effects

As for Bosentan, p.1235. Increases in INR and prolongation of the prothrombin time have also been reported.

Sitaxentan is teratogenic in *rats.*

Precautions

As for Bosentan, p.1235. Sitaxentan is contra-indicated in patients with mild to severe hepatic impairment (Child-Pugh Class A to C).

Although, like bosentan, sitaxentan is teratogenic in *rats* and similar precautions apply, its effects on combined oral contraceptives may differ (see Interactions below).

Interactions

Sitaxentan is both an inhibitor of and a substrate for the cytochrome P450 isoenzyme CYP2C9 and interactions may therefore occur with other drugs that are either metabolised by, or inhibit, this isoenzyme. Plasma concentrations of oral anticoagulants such as warfarin may be increased.

Use with ciclosporin is contra-indicated as plasma concentrations of sitaxentan are greatly increased (see below).

Sitaxentan has increased exposure to ethinylestradiol and norethisterone in those taking oral contraceptives and may possibly increase the associated risk of thromboembolism.

Ciclosporin. Licensed product information for sitaxentan states that its concentration was increased sixfold when given with ciclosporin 3.5 mg/kg twice daily. Although the mechanism of action is unknown it has been postulated that sitaxentan sodium is a substrate for the organic anion transporting polypeptide (OATP) transporter protein and should therefore be used with caution with other, more potent, OATP inhibitors.

Pharmacokinetics

Sitaxentan sodium is absorbed after oral doses with peak plasma concentrations being achieved within 1 to 4 hours. Its absolute bioavailability is 70 to 100%. A high-fat meal delays the rate of absorption but does not affect the extent. Sitaxentan is more than 99% bound to plasma proteins, mainly albumin.