Pharmacopoeias. *Eur.* includes the monohydrate.
Ph. Eur. 6.2 (Spirapril Hydrochloride Monohydrate). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in acetonitrile; practically insoluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile
Spirapril is an ACE inhibitor (p.1193) that is used in the management of hypertension (p.1171). It owes its activity to the diacid spirapriat, to which it is converted after oral doses. It is given orally as the hydrochloride in a usual maintenance dose of 6 mg once daily.

◊ References.

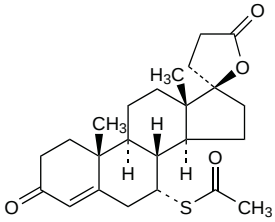
1. Noble S, Sorkin EM. Spirapril: a preliminary review of its pharmacology and therapeutic efficacy in the treatment of hypertension. *Drugs* 1995; **49:** 750–66.
2. Widimský J, *et al.* Czech and Slovak spirapril intervention study (CASSIS): a randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur J Clin Pharmacol* 1995; **49:** 95–102.

Preparations
Proprietary Preparations (details are given in Part 3)
Austria: Quadropril; ***Cz.:*** Renpress; ***Ger.:*** Quadropril; ***Hung.:*** Quadropril; ***Ital.:*** Renormax; Setrilan; ***Neth.:*** Quadropril; ***Rus.:*** Quadropril (Квадроприл); ***Spain:*** Renormax; Renpress; ***Switz.:*** Cardiopril†.

Spironolactone *(BAN, rINN)* ⊗

Espironolactona; SC-9420; Spirolactone; Spironolactonum; Spironolakton; Spironolaktonas; Spironolaktoni. 7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone; (7α,17α)-7-(Acetylthio)-17-hydroxy-3-oxo-pregn-4-ene-21-carboxylic acid γ-lactone.

Спиронолактон
$C_{24}H_{32}O_4S$ = 416.6.
CAS — 52-01-7.
ATC — C03DA01.
ATC Vet — QC03DA01.



NOTE. Compounded preparations of spironolactone may be represented by the following names:
- Co-flumactone (*BAN*)—spironolactone and hydroflumethiazide in equal parts (w/w)
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Spironolactone). A white or yellowish-white powder. Practically insoluble in water; soluble in alcohol. It exhibits polymorphism. Protect from light.
USP 31 (Spironolactone). A light cream-coloured to light tan, crystalline powder with a faint to mild mercaptan-like odour. Practically insoluble in water; soluble in alcohol and in ethyl acetate; freely soluble in chloroform and in benzene; slightly soluble in methyl alcohol and in fixed oils.

Stability. There was no appreciable loss of spironolactone from extemporaneously prepared suspensions of spironolactone, 2.5, 5 and 10 mg/mL, in a cherry syrup after storage for 2 weeks at 5° or 30° or at ambient room temperature under intense fluorescent light.[1] Degradation was less than 5% for samples stored for 4 weeks, but was more noticeable in suspensions with a higher initial concentration. There were no changes in colour or odour. Bacterial and fungal counts were well within acceptable limits after 4 weeks at 30°.

1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm* 1989; **46:** 2040–2.

Adverse Effects
Spironolactone may give rise to headache and drowsiness, and gastrointestinal disturbances, including cramp and diarrhoea. Ataxia, mental confusion, and skin rashes have been reported as adverse effects. Gynaecomastia is not uncommon and in rare cases breast enlargement may persist. Other endocrine disorders include hirsutism, deepening of the voice, menstrual irregularities, and impotence. Transient increases in blood-urea-nitrogen concentrations may occur and mild acidosis has been reported. Spironolactone has been shown to cause tumours in *rats*.

Spironolactone may cause hyponatraemia and hyperkalaemia.

Incidence of adverse effects. A survey found that of 788 patients given spironolactone 164 developed adverse effects.[1] These included hyperkalaemia in 8.6%, dehydration in 3.4%, hyponatraemia in 2.4%, gastrointestinal disorders in 2.3%, neurological disorders in 2%, rash, and gynaecomastia. Hyperkalaemia was associated with renal impairment and the use of potassium supplements: only 2.8% of nonuraemic patients not receiving potassium chloride developed hyperkalaemia, while 42.1% of those with marked uraemia and treated with potassium chloride became hyperkalaemic.

In a study[2] of 54 patients (53 female, 1 male) taking spironolactone 200 mg daily for hirsutism or acne adverse effects were reported in 91%.[2] Menstrual disturbances occurred in 72% of patients, breast tenderness in 39%, dry skin in 39%, and breast enlargement in 24%. Other adverse effects included nausea and vomiting, dizziness, headache, drowsiness, and skin rashes. Two patients developed a chloasma-like pigmentation of the face. The gynaecological effects were reduced in patients taking oral contraceptives.

1. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.
2. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Carcinogenicity. Breast cancer was reported in 5 patients taking spironolactone and hydrochlorothiazide for prolonged periods[1] although it was suggested[2] that the association with spironolactone therapy was unlikely to be causal.

Although the *rat* may not be an appropriate model for determining long-term safety in man,[3,4] evidence of carcinogenicity in this species prompted the UK CSM to limit the product licences of spironolactone-containing products to exclude use in essential hypertension or idiopathic oedema.[5]

1. Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone. *Lancet* 1975; **i:** 1428–9.
2. Jick H, Armstrong B. Breast cancer and spironolactone. *Lancet* 1975; **ii:** 368–9.
3. Lumb G, *et al.* Effects in animals of chronic administration of spironolactone—a review. *J Environ Pathol Toxicol* 1978; **i:** 641–60.
4. Wagner BM. Long-term toxicology studies of spironolactone in animals and comparison with potassium canrenoate. *J Drug Dev* 1987; **1** (suppl 2): 7–11.
5. Committee on Safety of Medicines. Spironolactone. *Current Problems* 1988; 21. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)

Effects on the blood. Agranulocytosis has been reported[1,2] in association with the use of spironolactone.

1. Stricker BHC, Oei TT. Agranulocytosis caused by spironolactone. *BMJ* 1984; **289:** 731.
2. Whitling AM, *et al.* Spironolactone-induced agranulocytosis. *Ann Pharmacother* 1997; **31:** 582–5.

Effects on electrolyte balance. ***CALCIUM.*** A report[1] suggested that spironolactone may have a calcium-sparing effect, in addition to its well known potassium-sparing properties.

1. Puig JG, *et al.* Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. *J Clin Pharmacol* 1991; **31:** 455–61.

POTASSIUM. There have been reports[1-3] of severe hyperkalaemia in patients taking spironolactone, including patients with renal impairment and those with a high potassium intake from either dietary sources or potassium supplements. In the Boston Collaborative Drug Surveillance Program[4] hyperkalaemia was reported in 42.1% of patients with uraemia taking spironolactone and receiving potassium supplements compared with 2.8% of those without uraemia and not receiving potassium supplements. Two deaths were attributed to hyperkalaemia in patients taking spironolactone and potassium chloride. Potassium supplements should be avoided in patients receiving spironolactone, and plasma-potassium concentrations should be carefully monitored in those with renal impairment.

1. Pongpaew C, *et al.* Hyperkalemic cardiac arrhythmia secondary to spironolactone. *Chest* 1973; **63:** 1023–5.
2. Udezue EO, Harrold BP. Hyperkalaemic paralysis due to spironolactone. *Postgrad Med J* 1980; **56:** 254–5.
3. O'Reilly PH, *et al.* Life-threatening hyperkalaemia after bladder decompression for high pressure chronic retention. *Lancet* 1987; **ii:** 859.
4. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; **225:** 40–3.

Effects on endocrine function. Spironolactone has been associated with disturbances of endocrine function. The most prominent in men is gynaecomastia which appears to be related to both dose and duration of treatment. Incidences of 62%[1] and 100%[2] have been reported. Gynaecomastia has also been accompanied by impotence.[3,4] The effects are generally reversible on stopping treatment. Reversal of male-pattern baldness has also been reported.[5]

In women symptoms include breast enlargement and tenderness.[6] The incidence of menstrual abnormalities may be high: unspecified disturbances have been reported in 33 of 53 women,[6] secondary amenorrhoea in 6 of 9,[7] and secondary and primary amenorrhoea in 1 and 2 patients, respectively.[8] The incidence of gynaecological disturbances has been found to be lower in women taking oral contraceptives.[6]

The mechanism of the effects of spironolactone on the endocrine system is unclear. Some workers[9] suggested that although spironolactone affects testosterone synthesis, the more likely explanation was its anti-androgenic action, and reduction in 17-hydroxylase activity. Others[10] found an alteration in the testosterone/oestrogen ratio due to an increase in testosterone clearance and increased peripheral conversion to estradiol. In addition, spironolactone is reported to inhibit binding of dihydrotestosterone to receptors.

1. Huffman DH, *et al.* Gynecomastia induced in normal males by spironolactone. *Clin Pharmacol Ther* 1978; **24:** 465–73.
2. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i:** 626.
3. Greenblatt DJ, Koch-Weser J. Gynecomastia and impotence complications of spironolactone therapy. *JAMA* 1973; **223:** 82.
4. Greenlaw C. Spironolactone induced gynecomastia: a case report. *Drug Intell Clin Pharm* 1977; **11:** 70–3.
5. Thomas PS. Hair: wanted and unwanted. *BMJ* 1986; **293:** 698.
6. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.
7. Levitt JI. Spironolactone therapy and amenorrhea. *JAMA* 1970; **211:** 2014–15.
8. Potter C, *et al.* Primary and secondary amenorrhea associated with spironolactone therapy in chronic liver disease. *J Pediatr* 1992; **121:** 141–3.
9. Loriaux DL, *et al.* Spironolactone and endocrine dysfunction. *Ann Intern Med* 1976; **85:** 630–6.
10. Rose LI, *et al.* Pathophysiology of spironolactone-induced gynecomastia. *Ann Intern Med* 1977; **87:** 398–403.

Effects on lipid metabolism. Unlike thiazide diuretics, spironolactone appeared not to increase serum-cholesterol concentrations in a study of 23 patients.[1]

1. Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. *Arch Intern Med* 1984; **144:** 710–14.

Effects on the liver. Hepatotoxicity characterised by cholestatic lesions has been reported in a patient receiving spironolactone.[1] Only one other published case of spironolactone-associated hepatotoxicity was known to the authors.

1. Renkes P, *et al.* Spironolactone and hepatic toxicity. *JAMA* 1995; **273:** 376–7.

Effects on the skin. Lichen-planus-like skin eruptions developed in a 62-year-old woman who was taking digoxin, propranolol, diazepam, spironolactone, and iron tablets.[1] Flares of the lichen-planus-like eruption seemed to be associated with use of spironolactone and there was evidence of resolution when spironolactone was withdrawn. Cutaneous vasculitis was associated with spironolactone on 3 occasions in an 80-year-old man.[2] A chloasma-like pigmentation of the face was reported in 2 patients receiving spironolactone for hirsutism or acne.[3]

1. Downham TF. Spironolactone-induced lichen planus. *JAMA* 1978; **240:** 1138.
2. Phillips GWL, Williams AJ. Spironolactone induced vasculitis. *BMJ* 1984; **288:** 368.
3. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118:** 687–91.

Hypersensitivity. Eosinophilia and a rash developed in 2 patients with alcoholic cirrhosis while taking spironolactone.[1]

1. Wathen CG, *et al.* Eosinophilia associated with spironolactone. *Lancet* 1986; **i:** 919–20.

Precautions
Spironolactone should not be used in patients with hyperkalaemia or severe renal impairment. It should be used with care in patients who are at increased risk of developing hyperkalaemia; such patients include the elderly, those with diabetes mellitus, and those with some degree of renal or hepatic impairment. It should also be given with care to patients likely to develop acidosis. Serum electrolytes and blood-urea-nitrogen should be measured periodically.

Breast feeding. The concentration of canrenone was measured[1] in the serum and milk of a breast-feeding woman taking 25 mg of spironolactone four times daily. The milk to serum concentration ratios of canrenone at 2 and 14.5 hours after a dose of spironolactone were 0.72 and 0.51 respectively, and it was estimated that the amount of canrenone ingested by the infant would be 0.2% of the mother's daily dose of spironolactone. The serum potassium and sodium levels of the infant were in the normal range. The American Academy of Pediatrics[2] considers that spironolactone is therefore usually compatible with breast feeding.

1. Phelps DL, Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci* 1977; **66:** 1203.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Diabetes mellitus. Severe hyperkalaemia was reported in a type 1 diabetic woman with hyporeninaemic hypoaldosteronism given spironolactone.[1]

1. Large DM, *et al.* Hyperkalaemia in diabetes mellitus—potential hazards of coexisting hyporeninaemic hypoaldosteronism. *Postgrad Med J* 1984; **60:** 370–3.

Interference with laboratory estimations. Spironolactone and canrenoate can interfere with some assays for plasma-digoxin concentrations.[1-3] However, spironolactone may also produce actual changes in digoxin concentrations (see p.1262) and results of assays should be interpreted with caution.

1. Yosselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9:** 67–87.
2. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12:** 82–4.
3. Steimer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354:** 1176–7.

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

Interactions

There is an increased risk of hyperkalaemia if spironolactone is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may occur as well in patients also given ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients given spironolactone with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may reduce the excretion of lithium and increase the risk of lithium toxicity. Hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients given chlorpropamide. Spironolactone may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, spironolactone may enhance the effects of other antihypertensive drugs and may reduce vascular responses to noradrenaline.

ACE inhibitors and angiotensin II receptor antagonists. Severe hyperkalaemia has been reported in patients given spironolactone with ACE inhibitors or angiotensin II receptor antagonists and fatalities have occurred. In a study[1] of 44 patients taking such combinations for heart failure who were admitted to hospital with life-threatening hyperkalaemia, 37 required haemodialysis and 2 developed fatal complications. In another group[2] of 25 patients given spironolactone with ACE inhibitors who were admitted with severe hyperkalaemia, 2 died and 4 others developed severe cardiac arrhythmias. Advanced age, renal impairment or diabetes mellitus were risk factors for hyperkalaemia in both studies. It was suggested that combinations of spironolactone with ACE inhibitors or angiotensin II receptor antagonists should be used with caution in such patients and that they should not be given doses of spironolactone above 25 mg daily.

1. Wrenger E, *et al.* Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. *BMJ* 2003; **327:** 147–9.
2. Schepkens H, *et al.* Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; **110:** 438–41.

Aspirin. Aspirin has been shown to produce substantial reductions in sodium excretion[1] in healthy subjects taking spironolactone and to reduce the excretion of spironolactone's active metabolite, canrenone.[2] However, use of aspirin in hypertensive patients[3] did not alter the effect of spironolactone on blood pressure, serum electrolytes, blood urea nitrogen, or plasma-renin activity.

1. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. *N Engl J Med* 1973; **289:** 198–200.
2. Ramsay LE, *et al.* Influence of acetylsalicylic acid on the renal handling of a spironolactone metabolite in healthy subjects. *Eur J Clin Pharmacol* 1976; **10:** 43–8.
3. Hollifield JW. Failure of aspirin to antagonize the antihypertensive effect of spironolactone in low-renin hypertension. *South Med J* 1976; **69:** 1034–6.

Cardiac glycosides. For discussions of the effects of spironolactone on *digoxin* and *digitoxin*, see p.1262 and p.1259, respectively. See also Interference with Laboratory Estimations, under Precautions, above.

Mitotane. For a report of the inhibition of the action of mitotane by spironolactone, see p.753.

Warfarin. For reference to the interaction between warfarin and spironolactone, see p.1430.

Pharmacokinetics

Spironolactone is well absorbed from the gastrointestinal tract, with a bioavailability of about 90%. It is about 90% bound to plasma proteins.

Spironolactone is metabolised extensively to a number of metabolites including canrenone and 7α-thiomethylspirolactone, both of which are pharmacologically active. The major metabolite may be 7α-thiomethylspirolactone, although it is uncertain to what extent the actions of spironolactone are dependent on the parent compound or its metabolites.

Spironolactone is excreted mainly in the urine and also in the faeces, in the form of metabolites. Spironolactone or its metabolites may cross the placental barrier, and canrenone is distributed into breast milk.

◊ References.

1. Overdiek HWPM, Merkus FWHM. The metabolism and biopharmaceutics of spironolactone in man. *Rev Drug Metab Drug Interact* 1987; **5:** 273–302.
2. Gardiner P, *et al.* Spironolactone metabolism: steady-state serum levels of the sulfur-containing metabolites. *J Clin Pharmacol* 1989; **29:** 342–7.
3. Sungaila I, *et al.* Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. *Gastroenterology* 1992; **102:** 1680–5.

Uses and Administration

Spironolactone, a steroid with a structure resembling that of the natural adrenocortical hormone aldosterone, acts on the distal portion of the renal tubule as a competitive antagonist of aldosterone. It acts as a potassium-sparing diuretic, increasing sodium and water excretion and reducing potassium excretion.

Spironolactone is reported to have a relatively slow onset of action, requiring 2 or 3 days for maximum effect, and a similarly slow diminishment of action over 2 or 3 days on stopping.

Spironolactone is used in the management of heart failure, both to treat refractory oedema and in lower doses as an adjunct to standard therapy (see below). It is also used for refractory oedema associated with cirrhosis of the liver (with or without ascites, p.1159), or the nephrotic syndrome, and in ascites associated with malignancy. It is frequently given with the thiazides, furosemide, or similar diuretics, where it adds to their natriuretic but diminishes their kaliuretic effects, hence conserving potassium in those at risk from hypokalaemia. Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics, is discussed under Effects on the Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p.1308. It has been used in the treatment of essential hypertension (in lower doses than for oedema), but in the UK is no longer recommended for use in either essential hypertension or idiopathic oedema; doubts have been expressed over its safety during long-term administration.

Spironolactone is also used in the diagnosis and treatment of primary hyperaldosteronism (below).

Other conditions in which spironolactone has been tried on the basis of its anti-androgenic properties include hirsutism, particularly in the polycystic ovary syndrome.

In the treatment of **oedema**, spironolactone is usually given in an initial oral dose of 100 mg daily, subsequently adjusted as necessary; some patients may require doses of up to 400 mg daily. In hepatic cirrhosis with ascites and oedema, patients with a urinary sodium/potassium ratio greater than 1 may be given an initial dose of spironolactone 100 mg daily while patients with a ratio of less than 1 may be given initial doses of 200 to 400 mg daily.

Spironolactone is given in doses of 400 mg daily in the presumptive diagnosis of primary **hyperaldosteronism**; in doses of 100 to 400 mg daily for the preoperative management of hyperaldosteronism; and in the lowest effective dosage for long-term maintenance therapy in the absence of surgery.

Suggested doses of spironolactone for children range from 1 to 3 mg/kg daily, in divided doses.

Potassium supplements should not be given with spironolactone.

◊ References and reviews.

1. Skluth HA, Gums JG. Spironolactone: a re-examination. *DICP Ann Pharmacother* 1990; **24:** 52–9.
2. Doggrell SA, Brown L. The spironolactone renaissance. *Expert Opin Invest Drugs* 2001; **10:** 943–54.
3. Buck ML. Clinical experience with spironolactone in pediatrics. *Ann Pharmacother* 2005; **39:** 823–8.

Acne. Spironolactone has been used for its anti-androgenic properties in some cases of acne (p.1577) where standard therapy is unsuccessful. Beneficial responses to oral therapy have been reported in patients with acne from both open[1] and placebo-controlled[2,3] studies. Topical application has been tried[4,5] but response has been variable. It is possible that the vehicle may affect the response. In women, spironolactone may be useful when treatment with an oestrogen is contra-indicated.

1. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; **112:** 124–5.
2. Goodfellow A, *et al.* Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol* 1984; **111:** 209–14.
3. Muhlemann MF, *et al.* Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol* 1986; **115:** 227–32.
4. Messina M, *et al.* A new therapeutic approach to acne: an antiandrogen percutaneous treatment with spironolactone. *Curr Ther Res* 1983; **34:** 319–24.
5. Walton S, *et al.* Lack of effect of topical spironolactone on sebum excretion. *Br J Dermatol* 1986; **114:** 261–4.

Alopecia. Anti-androgens have a role in the treatment of hirsutism (see below) but have also been used in patients with androgenetic alopecia (p.1577), and there is some evidence that spironolactone may be effective.[1]

1. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; **152:** 466–73.

Bartter's syndrome. Spironolactone may be used to reduce potassium wasting in patients with Bartter's syndrome (p.1670).

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p.1500) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p.1294); results with hydrochlorothiazide or spironolactone have been more ambiguous (p.1310).

Heart failure. Drug therapy of heart failure (p.1165) is based on the use of diuretics, ACE inhibitors, cardiac glycosides, beta blockers, and vasodilators. Spironolactone has been used as a diuretic for refractory oedema, but it also has an additional role as an aldosterone antagonist.[1,2] Although the precise neurohormonal mechanisms leading to the development of heart failure are still not clear, there is evidence that raised levels of aldosterone may contribute to the pathophysiology.[3,4] ACE inhibitor therapy suppresses aldosterone production but this effect is not complete and the use of spironolactone with ACE inhibitors has therefore been studied. In the Randomized Aldactone Evaluation Study (RALES)[5] in patients with severe heart failure, addition of spironolactone in a dose of 25 to 50 mg daily to therapy with ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation,[5] and the use of spironolactone should therefore be considered in such patients.[6-8] A small study[9] has also shown benefit in patients with less severe heart failure. However, use of spironolactone with ACE inhibitors may lead to hyperkalaemia and careful monitoring of potassium concentrations is required[10,11] (see Interactions, above). A retrospective analysis[12] of heart failure patients found that over 10% had to stop spironolactone because of hyperkalaemia, and a further 10% stopped because of worsening renal function. Risk factors were advanced age and higher baseline plasma-potassium concentrations.

1. Tang WHW, *et al.* Aldosterone receptor antagonists in the medical management of chronic heart failure. *Mayo Clin Proc* 2005; **80:** 1623–30.
2. Marcy TR, Ripley TL. Aldosterone antagonists in the treatment of heart failure. *Am J Health-Syst Pharm* 2006; **63:** 49–58.
3. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol* 1999; **47:** 479–82.
4. Rocha R, Williams GH. Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs* 2002; **62:** 723–31.
5. Pitt B, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341:** 709–17.
6. Hunt SA, *et al.* ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Summary article: *J Am Coll Cardiol* 2005; **46:** 1116–43. Also available at: http://circ.ahajournals.org/cgi/reprint/112/12/e154 (accessed 07/05/08)
7. The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). Executive summary: *Eur Heart J* 2005; **26:** 1115–40. Full text: http://www.escardio.org/NR/rdonlyres/8A2848B4-5DEB-41B9-9A0A-5B5A90494B64/0/CHFFullTextehi205FVFW170505.pdf (accessed 07/05/08)
8. Scottish Intercollegiate Guidelines Network. Management of chronic heart failure (February 2007). Available at: http://www.sign.ac.uk/pdf/sign95.pdf (accessed 07/05/08)

9. Macdonald JE, *et al.* Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* 2004; **90:** 765–70.
10. Georges B, *et al.* Spironolactone and congestive heart-failure. *Lancet* 2000; **355:** 1369–70.
11. Juurlink DN, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; **351:** 543–51.
12. Witham MD, *et al.* Tolerability of spironolactone in patients with chronic heart failure—a cautionary message. *Br J Clin Pharmacol* 2004; **58:** 554–7.

High-altitude disorders. Acetazolamide is generally the drug of choice for prophylaxis of high-altitude disorders (p.1168). Anecdotal reports[1-4] and a small-scale double-blind study[5] suggested that spironolactone could be useful in preventing acute mountain sickness, although a deterioration in pulmonary function despite spironolactone prophylaxis has been noted in a patient.[6]

1. Currie TT, *et al.* Spironolactone and acute mountain sickness. *Med J Aust* 1976; **2:** 168–70.
2. Snell JA, Cordner EP. Spironolactone and acute mountain sickness. *Med J Aust* 1977; **1:** 828.
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4. Rutter LD. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; **281:** 618.
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Hirsutism. Hirsutism (p.2089) is frequently treated with antiandrogens, usually cyproterone or spironolactone. Spironolactone in doses of 50 to 200 mg daily has produced both subjective and objective improvement in hirsutism in patients with idiopathic hirsutism or polycystic ovary syndrome,[1-4] and its use has been reviewed.[5] It is preferably used with oral contraceptives,[6,7] to improve efficacy and menstrual irregularity and to avoid the risk of feminisation to a male fetus. Most studies have involved premenopausal women and it has been suggested[4,8] that spironolactone would be useful in women in whom cyproterone is contra-indicated or not tolerated. A randomised study (not placebo-controlled) found spironolactone 100 mg daily and cyproterone 100 mg daily to be equally effective,[9] while a systematic review[10] of the use of spironolactone in hirsutism concluded that it was significantly more effective than both cyproterone and finasteride for up to 12 months after treatment.

For reference to the use of spironolactone in alopecia, see above.

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3. Evans DJ, Burke CW. Spironolactone in the treatment of idiopathic hirsutism and the polycystic ovary syndrome. *J R Soc Med* 1986; **79:** 451–3.
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9. O'Brien RC, *et al.* Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *J Clin Endocrinol Metab* 1991; **72:** 1008–13.
10. Farquhar C, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/06/05).

Hyperaldosteronism. Hyperaldosteronism (aldosteronism) is a disorder characterised by mineralocorticoid excess due to high circulating levels of aldosterone.[1-4] Mineralocorticoid excess due to other mineralocorticoids is rare. Primary hyperaldosteronism is usually caused by an aldosterone-producing adenoma (Conn's syndrome) or primary adrenal hyperplasia. Other causes include aldosterone-producing adrenal carcinoma, and glucocorticoid-suppressible hyperaldosteronism.

Secondary hyperaldosteronism is more common and results from conditions in which there is activation of the renin-angiotensin-aldosterone system, including diuretic therapy, and oedematous conditions such as heart failure, hepatic cirrhosis, and nephrotic syndrome. Bartter's syndrome (p.1670) also results in hyperaldosteronism.

Most patients with primary hyperaldosteronism are asymptomatic, although they may present with signs or symptoms of mineralocorticoid excess (p.1490). Diagnosis often follows the incidental discovery of hypokalaemia. Symptomatic hypokalaemia (p.1669) may develop in some patients, particularly those taking diuretics.

Diagnosis is confirmed by the presence of raised plasma and urinary aldosterone concentrations. However, the concentrations may be affected by serum-potassium concentration, posture, and time of day, and interpretation may be difficult. The plasma aldosterone:renin ratio may also be measured. In primary hyperaldosteronism the aldosterone concentration is raised but renin is suppressed, although this does not necessarily prove the diagnosis; in secondary hyperaldosteronism both are raised. Radiological and nuclear imaging are useful for further differentiating between adenoma and hyperplasia.

Hyperaldosteronism due to an aldosterone-producing adenoma is usually treated surgically. The aldosterone antagonist spironolactone may be given pre-operatively to lower the blood pressure and normalise the serum potassium. In patients who are not suitable for surgery, long-term medical management involves spironolactone, initially in high doses but reduced to the lowest dose for maintenance. If spironolactone is not tolerated, amiloride may be used as an alternative, but high doses are required. There has also been a report[5] of the successful use of eplerenone, another aldosterone antagonist; gynaecomastia had developed with spironolactone but resolved when treatment was changed to eplerenone. Trilostane, an adrenal suppressant, has been used to inhibit aldosterone synthesis.

In primary adrenal hyperplasia surgery is not usually effective and medical management with spironolactone or amiloride is required. Additional antihypertensive therapy may also be needed. Glucocorticoid-suppressible hyperaldosteronism, also known as familial hyperaldosteronism type I (FH-I), is a rare autosomal dominant form and may be treated with dexamethasone. However, this may not control the blood pressure and spironolactone or amiloride may be required in addition.

In secondary hyperaldosteronism the underlying condition should be treated, but spironolactone may be of benefit as part of the therapy.

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4. Fraser R, *et al.* Cautions over idiopathic aldosteronism. *Lancet* 2001; **358:** 332.
5. Karagiannis A, *et al.* Eplerenone relieves spironolactone-induced painful gynaecomastia in a patient with primary aldosteronism. *Nephrol Dial Transplant* 2007; **22:** 293.

Precocious puberty. Spironolactone (as an anti-androgen) and testolactone were given to boys with familial precocious puberty (p.2081) for periods of up to 18 months. Rates of growth and bone maturation were restored to normal during combination therapy but not with either drug given alone.[1] However, after further treatment for 2 to 4.2 years there was a diminishing response manifested by the recurrence of clinical features of puberty and an increase in the bone maturation rate.[2] Addition of deslorelin appeared to restore the control of puberty,[2] and in a long-term study[3] growth rate remained normal for 6 years.

1. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; **320:** 496–502.
2. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; **76:** 151–5.
3. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; **84:** 175–8.

Premenstrual syndrome. Spironolactone has been used for its diuretic and anti-androgenic properties in premenstrual syndrome (p.2099).

Preparations

BP 2008: Spironolactone Tablets;
USP 31: Spironolactone and Hydrochlorothiazide Tablets; Spironolactone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Aldactone; Drimux A; Espimax; Expal; Lanx; Modulactone; Normital; Osiren†; Rediun-E; ***Austral.:*** Aldactone; Spiractin; ***Austria:*** Aldactone; Spirobene; Spirohexal; Spirono; ***Belg.:*** Aldactone; Docspirono; Spirotop; ***Braz.:*** Aldactone; Aldosterin†; Espirolona; Spirоctan; ***Canad.:*** Aldactone; Novo-Spiroton; ***Chile:*** Alizar; Cardactona; ***Cz.:*** Spirolone†; Uractone†; Verospiron; Xenalon†; ***Denm.:*** Hexalacton; Spirix; Spiron; ***Fin.:*** Aldactone; Spiresis; Spirix; ***Fr.:*** Aldactone; Flumach; Practon; Spirоctan; Spironone; ***Ger.:*** Aldactone; Aquareduct†; duraspiron†; Jenaspiron; Osyrol; Spiro; Spirobeta; Spirogamma; Spirono; Verospiron; ***Gr.:*** Aldactone; Uridactone†; ***Hong Kong:*** Aldactone; ***Hung.:*** Huma-Spiroton; Spirolone†; Spiron; Verospiron; ***India:*** Aldactone; ***Indon.:*** Aldactone; Carpiaton; Letonal; Spirola; ***Irl.:*** Aldactone; ***Israel:*** Aldactone; Aldospirone; Spironol; ***Ital.:*** Aldactone; Spiroderm†; Spirolang; Uractone; ***Mex.:*** Aldactone; Biolactona; Quimolactona†; Vivitar; ***Neth.:*** Aldactone; ***Norw.:*** Aldactone; Spirix; ***NZ:*** Aldactone†; Spirotone; ***Philipp.:*** Aldactone; ***Pol.:*** Spironol; Verospiron; ***Port.:*** Aldactone; Aldonar; Nefrolactona†; ***Rus.:*** Aldactone (Альдактон)†; Verospiron (Верошпирон); ***S.Afr.:*** Aldactone; Spiractin; ***Singapore:*** Aldactone; Uractonum; ***Spain:*** Aldactone; ***Swed.:*** Aldactone; Spirix; Spiroscand†; ***Switz.:*** Aldactone; Primacton; Xenalon; ***Thai.:*** Aldactone; Altone; Berlactone†; Hyles; Pondactone; Spironex†; ***Turk.:*** Aldacton; ***UK:*** Aldactone; Spirospare†; ***USA:*** Aldactone; ***Venez.:*** Aldactone; Spirоctan†.

Multi-ingredient: ***Arg.:*** Aldactone-D; Aldazida; Lasilacton; ***Austria:*** Aldactone Saltucin; Buti-Spirobene; Deverol mit Thiazid; Digi-Aldopur; Furo-Aldopur; Furo-Spirobene; Furolacton; Lasilacton; Sali-Aldopur; Spirono comp; Supracid; ***Belg.:*** Aldactazine; Docspirochlor; ***Braz.:*** Aldazida; Lasilactona; ***Canad.:*** Aldactazide; Novo-Spirozine; ***Cz.:*** Spiro Compositum†; ***Fr.:*** Aldactazine; Aldalix; Practazin; Spirоctazine; ***Ger.:*** Aldactone Saltucin†; duraspiron-comp†; Furo-Aldopur; Furorese Comp; Osyrol Lasix; Risicordin†; Sali-Aldopur†; Spiro comp; Spiro-D; Spironolacton Plus†; Spironothiazid; Spirostada comp†; ***India:*** Lasilactone; Spiromide; ***Indon.:*** Aldazide; ***Irl.:*** Aldactide; ***Ital.:*** Aldactazide; Lasitone; Spiridazide; Spirofur; ***Mex.:*** Aldazida; Lasilacton; ***Philipp.:*** Aldazide; ***Port.:*** Aldactazine; Ondolen; ***S.Afr.:*** Aldazide; ***Spain:*** Aldactacine; Aldoleo; Miscidon†; Spirometon; ***Switz.:*** Aldozone; Furocombin; Furospir; Lasilactone; ***Turk.:*** Aldactazide; ***UK:*** Aldactide; Lasilactone; ***USA:*** Aldactazide; ***Venez.:*** Aldactazida; Teradal†.

Staphylokinase

Estafiloquinasa.

Profile

Staphylokinase is a thrombolytic derived from *Staphylococcus aureus*. Recombinant and modified forms are under investigation for the treatment of thromboembolic disorders, including acute myocardial infarction.

◊ References.

1. Vanderschueren S, *et al.* Thrombolytic therapy of peripheral arterial occlusion with recombinant staphylokinase. *Circulation* 1995; **92:** 2050–57.
2. Vanderschueren S, *et al.* Randomized coronary patency trial of double-bolus recombinant staphylokinase versus front-loaded alteplase in acute myocardial infarction. *Am Heart J* 1997; **134:** 213–19.
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Streptokinase *(BAN, rINN)*

Estreptoquinasa; Plasminokinase; Sterptokinasum; Streptokinaasi; Streptokinas; Streptokinasum; Sztreptokináz.

Стрептокиназа

CAS — 9002-01-1.
ATC — B01AD01.
ATC Vet — QB01AD01.

Pharmacopoeias. *Eur.* (see p.vii) includes a concentrated solution.
Ph. Eur. 6.2 (Streptokinase Concentrated Solution; Streptokinasi Solutio Concentrata). A preparation of a protein obtained from culture filtrates of certain strains of haemolytic *Streptococcus* group C. It has the property of combining with human plasminogen to form plasminogen activator. The potency is not less than 510 international units per microgram of nitrogen. A clear, colourless liquid. pH 6.8 to 7.5. Store in airtight containers at a temperature of –20°. Protect from light.

Stability. The incorporation of albumin in commercial preparations of streptokinase has reduced the incidence of flocculation with streptokinase solutions. However, flocculation has occurred with small volumes prepared with sodium chloride 0.9% in sterilised glass containers apparently because of residual acid buffers that remain in empty evacuated containers after sterilisation.[1]

1. Thibault L. Streptokinase flocculation in evacuated glass bottles. *Am J Hosp Pharm* 1985; **42:** 278.

Units

The potency of streptokinase is expressed in international units and preparations are assayed using the second International Standard (1989).

The Christensen unit is the quantity of streptokinase that will lyse a standard blood clot completely in 10 minutes and is equivalent to the international unit.

Adverse Effects

In common with other thrombolytics streptokinase may cause haemorrhage, particularly from puncture sites; severe internal bleeding has occurred and may be difficult to control. Streptokinase is antigenic, and allergic reactions ranging from rashes to rarer anaphylactoid and serum-sickness-like symptoms have occurred. Fever, sometimes high, and associated symptoms such as chills and back or abdominal pain are quite frequent. Nausea and vomiting may occur. There have been a few reports of Guillain-Barré syndrome.

Streptokinase infusion may be associated with hypotension, both direct or as a result of reperfusion; bradycardia and arrhythmias may also occur due to reperfusion. The break-up of existing clots may occasionally produce emboli elsewhere; pulmonary embolism and acute renal failure due to cholesterol embolisation have been reported.

Back pain. Streptokinase infusion has been associated with the development of very severe low back pain, which resolves within a few minutes of stopping the infusion, and may be severe enough to warrant opioid analgesia.[1-4] The back pain may represent a hypersensitivity reaction. Providing that the pain is controlled and that dissecting aortic aneurysm is not suspected, it may still be possible to complete the streptokinase infusion.[4,5] Alternatively, immediate substitution with a different thrombolytic has been suggested.[6]

There have also been a few reports of low back pain associated with anistreplase infusion.[7,8]

1. Shah M, Taylor RT. Low back pain associated with streptokinase. *BMJ* 1990; **301:** 1219.
2. Dickinson RJ, Rosser A. Low back pain associated with streptokinase. *BMJ* 1991; **302:** 111–12.