- Dalteparin, p.1255
- Enoxaparin, p.1277
- Nadroparin, p.1346
- Parnaparin, p.1366
- Reviparin, p.1388
- Tinzaparin, p.1413

Like heparin (p.1303), these compounds enhance the action of antithrombin III but they are characterised by a higher ratio of anti-factor Xa to anti-factor IIa (antithrombin) activity than heparin. Low-molecular-weight heparins have less effect on platelet aggregation than heparin. They have no significant effect on blood coagulation tests such as activated partial thromboplastin time (APTT). Therapy may be monitored by measurement of plasma-anti-factor-Xa activity but monitoring is less frequently required than with heparin since low-molecular-weight heparins have a more predictable effect.

Low-molecular-weight heparins are used in the management of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p.1189). They are used for prophylaxis, particularly during surgery, and for treatment of established thromboembolism. They are given by subcutaneous injection once or twice daily. They are also used intravenously to prevent coagulation during haemodialysis and other extracorporeal circulatory procedures. They may be given subcutaneously in the management of unstable angina (p.1157) and both intravenously and subcutaneously in acute myocardial infarction (p.1175).

Doses are expressed either in terms of the weight of low-molecular-weight heparin or in terms of units of anti-factor Xa activity. Since low-molecular-weight heparins differ in their relative inhibition of factor Xa and thrombin, doses, even when expressed in terms of anti-factor-Xa activity, cannot be equated. Different preparations of the same low-molecular-weight heparin may appear to have different doses depending on the reference preparation used.

◊ References.

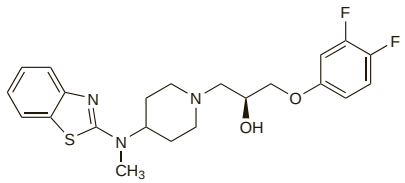
1. Green D, *et al.* Low molecular weight heparin: a critical analysis of clinical trials. *Pharmacol Rev* 1994; **46:** 89–109.
2. Nurmohamed MT, *et al.* Low molecular weight heparin(oid)s: clinical investigations and practical recommendations. *Drugs* 1997; **53:** 736–51.
3. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997; **337:** 688–98. Correction. *ibid.*: 1567.
4. Deitelzweig SB, *et al.* Venous thromboembolism prevention with LMWHs in medical and orthopedic surgery patients. *Ann Pharmacother* 2003; **37:** 402–11.
5. Hirsh J, *et al.* Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; **133** (suppl): 141S–159S.

Lubeluzole *(BAN, USAN, rINN)*

Lubeluzol; Lubéluzole; Lubeluzolum; R-87926. (*S*)-1-{4-[1,3-Benzothiazol-2-yl(methyl)amino]piperidino}-3-(3,4-difluorophenoxy)propan-2-ol.

Лубелузол

$C_{22}H_{25}F_2N_3O_2S$ = 433.5.
CAS — 144665-07-6.



Profile

Lubeluzole is a neuroprotectant that has been investigated for ischaemic stroke, but results have been disappointing.

◊ References.

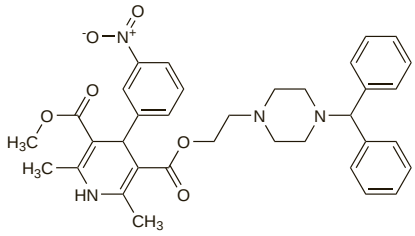
1. Gandolfo C, *et al.* Lubeluzole for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/06/05).

Manidipine Hydrochloride *(rINNM)*

CV-4093; Franidipine Hydrochloride; Hidrocloruro de manidipino; Manidipine, Chlorhydrate de; Manidipini Hydrochloridum. 2-[4-(Diphenylmethyl)-1-piperazinyl]ethyl methyl (±)-1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate dihydrochloride.

Манидипина Гидрохлорид

$C_{35}H_{38}N_4O_6,2HCl$ = 683.6.
CAS — 120092-68-4 (manidipine); 89226-75-5 (manidipine hydrochloride); 126229-12-7 (manidipine hydrochloride).
ATC — C08CA11.
ATC Vet — QC08CA11.



(manidipine)

Profile

Manidipine is a dihydropyridine calcium-channel blocker (see Nifedipine, p.1350). It is given by mouth as the hydrochloride in the management of hypertension (p.1171) in a usual dose of 10 to 20 mg once daily.

◊ Reviews.

1. McKeage K, Scott LJ. Manidipine: a review of its use in the management of hypertension. *Drugs* 2004; **64:** 1923–40.
2. Roca-Cusachs A, Triposkiadis F. Antihypertensive effect of manidipine. *Drugs* 2005; **65** (suppl 2): 11–19.
3. Otero ML. Manidipine-delapril combination in the management of hypertension. *Vasc Health Risk Manag* 2007; **3:** 255–63.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Iperten; ***Braz.:*** Manivasc; ***Fr.:*** Iperten; ***Ger.:*** Manyper; ***Gr.:*** Manyper; ***Ital.:*** Iperten; Vascoman; ***Jpn:*** Calslot; ***Philipp.:*** Caldine; ***Spain:*** Artedil; ***Thai.:*** Madiplot.

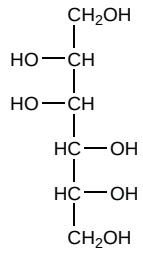
Multi-ingredient: ***Braz.:*** Hipertil; ***Gr.:*** Vivace.

Mannitol ⊗

Cordycepic Acid; E421; Manita; Manitol; Manitolis; Manna Sugar; Mannit; Mannite; Mannitoli; Mannitolum. D-Mannitol.

Маннит; Маннитол

$C_6H_{14}O_6$ = 182.2.
CAS — 69-65-8.
ATC — A06AD16; B05BC01; B05CX04.
ATC Vet — QA06AD16; QB05BC01; QB05CX04.



Description. Mannitol is a hexahydric alcohol related to mannose ($C_6H_{12}O_6$ = 180.2). It is isomeric with sorbitol (p.1965).

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Mannitol). A white or almost white crystalline powder or free-flowing granules. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol.

USP 31 (Mannitol). A white odourless crystalline powder or free-flowing granules with a sweet taste. Soluble 1 in 5.5 of water; very slightly soluble in alcohol; practically insoluble in ether; slightly soluble in pyridine; soluble in alkaline solutions.

Incompatibility. Mannitol should never be added to whole blood for transfusion or given through the same set by which blood is being infused. For details of the adverse effects of mannitol on red blood cells, see Effects on the Blood under Adverse Effects, below.

Supersaturated solutions. Supersaturated aqueous solutions are prepared with the aid of heat. Any crystals that form during storage of the injection should be dissolved by warming before use; this may be a particular problem with the 20 and 25% injections which are supersaturated. A 5.07% solution in water is isosmotic with serum.

Adverse Effects

The most common adverse effect associated with mannitol therapy is fluid and electrolyte imbalance including circulatory overload and acidosis at high doses. The expansion of extracellular volume can precipitate pulmonary oedema and patients with diminished cardiac reserve are at special risk. The shift of fluid from the intracellular to extracellular compartment can cause tissue dehydration; dehydration of the brain, particularly in patients with renal failure, may give rise to CNS symptoms.

When given orally, mannitol causes diarrhoea. Intravenous infusion of mannitol has been associated with nausea, vomiting, thirst, headache, dizziness, chills, fever, tachycardia, chest pain, hyponatraemia, dehydration, blurred vision, urticaria, and hypotension or hypertension. Large doses have been associated rarely with acute renal failure. Hypersensitivity reactions have occurred.

Extravasation of the solution may cause oedema and skin necrosis; thrombophlebitis may occur.

Effects on the blood. Agglutination and irreversible crenation of erythrocytes occurred when blood was mixed with varying proportions of a 10% mannitol solution.[1] It was suggested that intravenous infusions should be carefully controlled and given at a slow rate. This observation could have particular relevance to patients with sickle-cell disease.[2,3] Although agglutination and crenation had been observed *in vitro*, dilutional effects would make *in-vivo* interaction with blood cells less likely.[4]

1. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 421–2.
2. Konotey-Ahulu FID. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
3. Roberts BE, Smith PH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 591.
4. Samson JH. Hazards of mannitol infusions. *Lancet* 1966; **ii:** 1191.

Effects on the gastrointestinal tract. Potentially explosive intracolonic concentrations of hydrogen gas have been measured in patients given mannitol before colonoscopy,[1,2] and cases of colonic explosion, including fatalities, have been reported in patients undergoing colonoscopic electrocautery, who had received mannitol bowel preparation. However, the risk of explosion was considered to be small when air or carbon dioxide insufflation and suction were used during the colonoscopy procedure.[2,3]

Colonic perforation and subsequent death has been attributed to the use of mannitol for the treatment of constipation.[4]

1. La Brooy SJ, *et al.* Potentially explosive colonic concentrations of hydrogen after bowel preparation with mannitol. *Lancet* 1981; **i:** 634–6.
2. Avgerinos A, *et al.* Bowel preparation and the risk of explosion during colonoscopic polypectomy. *Gut* 1984; **25:** 361–4.
3. Trotman I, Walt R. Mannitol and explosions. *Lancet* 1981; **i:** 848.
4. Moses FM. Colonic perforation due to oral mannitol. *JAMA* 1988; **260:** 640.

Effects on the kidneys. Focal osmotic nephrosis occurred in a patient given mannitol 20% intravenously.[1]

Acute oliguric renal failure has been associated with the use of large doses of mannitol in patients with previously normal renal function,[2-4] and acute renal failure developed[5] in a patient with diabetes mellitus complicated by nephropathy after he was given 420 g of mannitol intravenously over 4 days.

1. Goodwin WE, Latta H. Focal osmotic nephrosis due to the therapeutic use of mannitol: a case of perirenal hematoma after renal biopsy. *J Urol (Baltimore)* 1970; **103:** 11–14.
2. Whelan TV, *et al.* Acute renal failure associated with mannitol intoxication. *Arch Intern Med* 1984; **144:** 2053–5.
3. Goldwasser P, Fotino S. Acute renal failure following massive mannitol infusion: appropriate response of tubuloglomerular feedback? *Arch Intern Med* 1984; **144:** 2214–16.
4. Rabetoy GM, *et al.* Where the kidney is concerned, how much mannitol is too much? *Ann Pharmacother* 1993; **27:** 25–8.
5. Matsumura M. Mannitol-induced toxicity in a diabetic patient receiving losartan. *Am J Med* 2001; **110:** 331.

Overdosage. Severe mannitol intoxication was reported in 8 patients with renal failure given large, and sometimes enormous, amounts of mannitol intravenously over 1 to 3 days.[1] These patients had CNS involvement out of proportion to uraemia, severe hyponatraemia, a large osmolality gap, and fluid overload. Six patients were treated with haemodialysis and this was considered to be more effective than peritoneal dialysis, which was used in 1 patient.

1. Borges HF, *et al.* Mannitol intoxication in patients with renal failure. *Arch Intern Med* 1982; **142:** 63–6.