- 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.

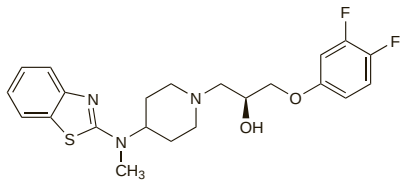
1. Green D, *et al.* Low molecular weight heparin: a critical analysis of clinical trials. *Pharmacol Rev* 1994; **46:** 89–109.
2. Nurmohamed MT, *et al.* Low molecular weight heparin(oid)s: clinical investigations and practical recommendations. *Drugs* 1997; **53:** 736–51.
3. Weitz JI. Low-molecular-weight 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.

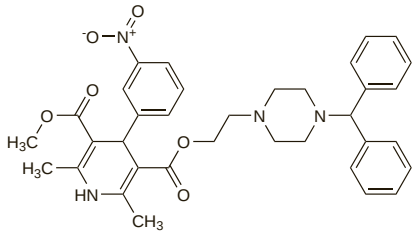
1. Gandolfo C, *et al.* Lubeluzole for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/06/05).

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.

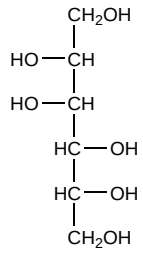
Multi-ingredient: ***Braz.:*** Hipertil; ***Gr.:*** Vivace.

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.

Precautions

Mannitol is contra-indicated in patients with pulmonary congestion or pulmonary oedema, intracranial bleeding (except during craniotomy), heart failure (in patients with diminished cardiac reserve, expansion of the extracellular fluid may lead to fulminating heart failure), and in patients with renal failure unless a test dose has produced a diuretic response (if urine flow is inadequate, expansion of the extracellular fluid may lead to acute water intoxication).

Mannitol should not be given with whole blood.

All patients given mannitol should be carefully observed for signs of fluid and electrolyte imbalance and renal function should be monitored.

Pharmacokinetics

Only small amounts of mannitol are absorbed from the gastrointestinal tract. After intravenous injection mannitol is excreted rapidly by the kidneys before any very significant metabolism can take place in the liver. Mannitol does not cross the blood-brain barrier or penetrate the eye. An elimination half-life of about 100 minutes has been reported.

Uses and Administration

Mannitol is an osmotic agent. Although an isomer of sorbitol, it has little energy value, since it is largely eliminated from the body before any metabolism can take place.

Mannitol is mainly used, with adequate rehydration, to increase urine flow in patients with acute renal failure and to reduce raised intracranial pressure (p.1181) and treat cerebral oedema. It is also used in the short-term management of glaucoma (p.1873), especially to reduce intra-ocular pressure prior to ophthalmic surgery, and to promote the excretion of toxic substances by forced diuresis.

Other indications include bladder irrigation during transurethral resection of the prostate in order to reduce haemolysis and as an oral osmotic laxative for bowel preparation. Mannitol is used as a diluent and excipient in pharmaceutical preparations and as a bulk sweetener. It is under investigation for use in bronchiectasis and cystic fibrosis.

When given parenterally, mannitol raises the osmotic pressure of the plasma thus drawing water out of body tissues and producing an osmotic diuresis. Reduction of CSF and intra-ocular fluid pressure occurs within 15 minutes of the start of a mannitol infusion and lasts for 3 to 8 hours after the infusion is stopped; diuresis occurs after 1 to 3 hours.

When used as an osmotic diuretic, mannitol is given by intravenous infusion. Careful monitoring of fluid balance, electrolytes, renal function, and vital signs is necessary during infusion to prevent fluid and electrolyte imbalance, including circulatory overload and tissue dehydration. Solutions containing more than 15% of mannitol may crystallise during storage, particularly at low temperatures; crystals may be redissolved by warming before use; the giving set should include a filter.

Mannitol may be used to treat patients in the oliguric phase of **renal failure** or those suspected of inadequate renal function after correction of plasma volume, provided a test dose of about 200 mg/kg given by rapid intravenous infusion of a 15 to 25% solution over 3 to 5 minutes produces a diuresis of at least 30 to 50 mL/hour during the next 2 to 3 hours; a second test dose is permitted if the response to the first is inadequate. The usual adult dose of mannitol ranges from 50 to 100 g in a 24 hour period, given by intravenous infusion of a 5 to 25% solution. The rate of infusion is usually adjusted to maintain a urine flow of at least 30 to 50 mL/hour.

For children, a dose of 0.25 to 2 g/kg has been used.

The total dosage, the concentration, and the rate of infusion depend on the fluid requirement, the urinary output, and the nature and severity of the condition being treated. Mannitol infusion has also been used to prevent acute renal failure during cardiovascular and other types of surgery, or after trauma.

To reduce **raised intracranial** or **intra-ocular pressure** mannitol may be given by intravenous infusion as a 15 to 25% solution in a dose of 0.25 to 2 g/kg over 30 to 60 minutes. Rebound increases in intracranial or intra-ocular pressure may occur but are less frequent than with urea.

During **transurethral prostatic resection** a 2.5 to 5% solution of mannitol has been used for irrigating the bladder.

Ciguatera poisoning. Ciguatera poisoning occurs throughout the Caribbean and Indopacific as a result of the consumption of certain fish contaminated with ciguatoxin; it is increasingly seen in Europe, in travellers returning from these areas, or as a result of eating imported fish. Symptoms can be severe, including a bizarre reversal of hot and cold sensation. Some neurological symptoms, pruritus, arthralgia, and fatigue, may persist for years.[1] Treatment is usually symptomatic since there is no specific antidote. Dramatic reversal of neuromuscular symptoms with slower resolution of gastrointestinal upset has been reported after giving mannitol 1 g/kg by intravenous infusion over 30 to 45 minutes in the acute phase of the illness.[2-4] Mannitol may also be beneficial up to a week after poisoning.[5] However, a double-blind study[6] found mannitol to be no better than normal saline at relieving symptoms at 24 hours. Amitriptyline has been found on several occasions[7-9] to relieve neurological symptoms (dysaesthesias and paraesthesias) and pruritus. Gabapentin has also been reported to be of benefit.[10]

1. Lehane L. Ciguatera update. *Med J Aust* 2000; **172:** 176–9.
2. Palafox NA, *et al.* Successful treatment of ciguatera fish poisoning with intravenous mannitol. *JAMA* 1988; **259:** 2740–2.
3. Pearn JH, *et al.* Ciguatera and mannitol: experience with a new treatment regimen. *Med J Aust* 1989; **151:** 77–80.
4. Williamson J. Ciguatera and mannitol: a successful treatment. *Med J Aust* 1990; **153:** 306–7.
5. Fenner PJ, *et al.* A Queensland family with ciguatera after eating coral trout. *Med J Aust* 1997; **166:** 473–5.
6. Schnorf H, *et al.* Ciguatera fish poisoning: a double-blind randomized trial of mannitol therapy. *Neurology* 2002; **58:** 873–80.
7. Bowman PB. Amitriptyline and ciguatera. *Med J Aust* 1984; **140:** 802.
8. Davis RT, Villar LA. Symptomatic improvement with amitriptyline in ciguatera fish poisoning. *N Engl J Med* 1986; **315:** 65.
9. Calvert GM, *et al.* Treatment of ciguatera fish poisoning with amitriptyline and nifedipine. *J Toxicol Clin Toxicol* 1987; **25:** 423–8.
10. Perez CM, *et al.* Treatment of ciguatera poisoning with gabapentin. *N Engl J Med* 2001; **344:** 692–3.

Gastrointestinal disorders. ***BOWEL PREPARATION.*** Mannitol, 1000 mL of a 10% solution or 500 mL of 10 or 20% solution, given orally, has been used to prepare the bowel for surgical and diagnostic procedures.[1,2] The potential for formation of explosive gas in the bowel should be borne in mind (see Effects on the Gastrointestinal Tract, above).

1. Palmer KR, Khan AN. Oral mannitol: a simple and effective bowel preparation for barium enema. *BMJ* 1979; **2:** 1038.
2. Newstead GL, Morgan BP. Bowel preparation with mannitol. *Med J Aust* 1979; **2:** 582–3.

DIAGNOSIS AND TESTING. Mannitol has been used with lactulose[1,2] and with cellobiose[3,4] in the detection of abnormal small bowel permeability, particularly that occurring in coeliac disease. For further information on the use of differential sugar absorption tests, see Lactulose, p.1739.

1. Pearson ADJ, *et al.* The gluten challenge—biopsy v permeability. *Arch Dis Child* 1983; **58:** 653.
2. Cooper BT. Intestinal permeability in coeliac disease. *Lancet* 1983; **i:** 658–9.
3. Juby LD, *et al.* Cellobiose/mannitol sugar test—a sensitive tubeless test for coeliac disease: results on 1010 unselected patients. *Gut* 1989; **30:** 476–80.
4. Hodges S, *et al.* Cellobiose: mannitol differential permeability in small bowel disease. *Arch Dis Child* 1989; **64:** 853–5.

Respiratory disorders. Inhalation of dry powder mannitol improves mucus clearance and small studies have suggested it may be of benefit in bronchiectasis,[1] although further studies are needed to confirm this.

1. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 07/05/08).

Preparations

BP 2008: Mannitol Intravenous Infusion;
USP 31: Mannitol in Sodium Chloride Injection; Mannitol Injection.

Proprietary Preparations (details are given in Part 3)
Austral.: Mede-Prep; Osmitrol; ***Canad.:*** Osmitrol; ***Cz.:*** Ardeaosmosol MA; Mannisol; Osmofundin 15% N†; ***Ger.:*** Deltamannit; Mannit-Losung; Osmofundin 15% N; Osmosteril 20%; Thomaemannit†; ***Hung.:*** Mannisol; ***Ital.:*** Isotol; Mannistol†; ***Mex.:*** Osmorol; ***Neth.:*** Osmosteril; ***NZ:*** Mede-Prep†; ***Port.:*** Osmofundina; ***Spain:*** Osmofundina Concentrada; ***Switz.:*** Mannite; ***Thai.:*** Maniton†; ***Turk.:*** Resectisol; Rezosel; ***USA:*** Osmitrol; Resectisol†.

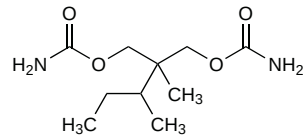
Multi-ingredient: ***Austria:*** Osmofundin 10%; Resectal; ***Chile:*** Gelsolets; ***Denm.:*** Pharmalgen Albumin; ***Fin.:*** Somanol + Ethanol; ***Ger.:*** Flacar; Freka-Drainjet Purisole; Osmosteril 10%; ***Ital.:*** Levoplus; Naturalass; ***Mex.:*** Jarabe de Manzanas; ***Pol.:*** Purisole SM; ***Port.:*** Purisole; Xarope de Macas Reinetas; ***Rus.:*** Rheogluman (Реоглюман); ***Spain:*** Salcemetic†; Salmagne; ***Switz.:*** Cital†.

Mebutamate *(BAN, USAN, rINN)*

Mébutamate; Mebutamato; Mebutamatum; W-583. 2-sec-Butyl-2-methyltrimethylene dicarbamate.

Мебутамат

$C_{10}H_{20}N_2O_4$ = 232.3.
CAS — 64-55-1.
ATC — N05BC04.
ATC Vet — QN05BC04.



Profile

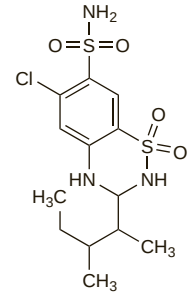
Mebutamate is a carbamate with general properties similar to those of meprobamate (p.1006). It has been given by mouth as an adjunct in the treatment of hypertension.

Mebutizide *(rINN)* ⊗

Mebutizida; Mébutizide; Mebutizidum. 6-Chloro-3-(1,2-dimethylbutyl)-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

Мебутизид

$C_{13}H_{20}ClN_3O_4S_2$ = 381.9.
CAS — 3568-00-1.
ATC — C03AA13.
ATC Vet — QC03AA13.



Profile

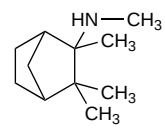
Mebutizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used in the treatment of oedema and hypertension.

Mecamylamine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mecamilamina; Mecamine Hydrochloride; Mécamylamine, Chlorhydrate de; Mecamylamini Hydrochloridum. *N*-Methyl-2,3,3-trimethylbicyclo[2.2.1]hept-2-ylamine hydrochloride.

Мекамиламина Гидрохлорид

$C_{11}H_{21}N,HCl$ = 203.8.
CAS — 60-40-2 (mecamylamine); 826-39-1 (mecamylamine hydrochloride).
ATC — C02BB01.
ATC Vet — QC02BB01.



(mecamylamine)

Pharmacopoeias. In *US*.
USP 31 (Mecamylamine Hydrochloride). Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for Trimetaphan Camsilate, p.1419. Mecamylamine may also cause tremor, convulsions, choreiform movements, insomnia, sedation, dysarthria, and mental aberrations.