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†.

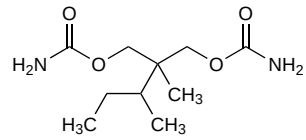
Multi-ingredient: ***Austria:*** Osmofundin 10%; Resectal; ***Chile:*** Gelsolets; ***Denm.:*** Pharmalgen Albumin; ***Fin.:*** Somanol + Ethanol; ***Ger.:*** Flacar; Freka-Drainjet Purisole; Osmosteril 10%; ***Ital.:*** Levoplus; Naturalass; ***Mex.:*** Jarabe de Manzanas; ***Pol.:*** Purisole SM; ***Port.:*** 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

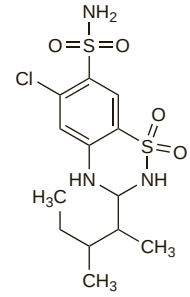
Mebutamate is a carbamate with general properties similar to those of meprobamate (p.1006). It has been given by mouth as an adjunct in the treatment of hypertension.

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

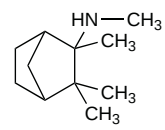
Mebutizide is a thiazide diuretic (see Hydrochlorothiazide, p.1307) that has been used in the treatment of oedema and hypertension.

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.

Pharmacokinetics
Mecamylamine hydrochloride is almost completely absorbed from the gastrointestinal tract. It crosses the placenta and the blood-brain barrier. About 50% of the dose is excreted unchanged in the urine over 24 hours, but the rate is diminished in alkaline urine.

Uses and Administration
Mecamylamine hydrochloride is a ganglion blocker with actions similar to those of trimetaphan (p.1419). It is given orally in the management of hypertension (p.1171), although other antihypertensives with fewer adverse effects are preferred.

The usual initial dosage is 2.5 mg twice daily, gradually increased or decreased, usually in steps of 2.5 mg at intervals of not less than 2 days, until a satisfactory response is obtained. The average maintenance dose is 25 mg daily in three divided doses. Tolerance may develop.

◊ Reviews.

1. Young JM, *et al.* Mecamylamine: new therapeutic uses and toxicity/risk profile. *Clin Ther* 2001; **23:** 532–65.

Smoking cessation. Mecamylamine acts centrally as a nicotinic antagonist and might be of some benefit in assisting withdrawal from smoking. Two studies[1,2] have shown that addition of low-dose oral mecamylamine (2.5 to 5 mg twice daily) appeared to enhance the effectiveness of nicotine skin patches. However, a later controlled study[3] found that a patch containing both mecamylamine and nicotine was not significantly better than transdermal nicotine alone. Smoking cessation is discussed under Nicotine, p.2354.

1. Rose JE, *et al.* Mecamylamine combined with nicotine skin patch facilitates smoking cessation beyond nicotine patch treatment alone. *Clin Pharmacol Ther* 1994; **56:** 86–99.
2. Rose JE, *et al.* Nicotine-mecamylamine treatment for smoking cessation: the role of pre-cessation therapy. *Exp Clin Psychopharmacol* 1998; **6:** 331–43.
3. Glover ED, *et al.* A randomized, controlled trial to assess the efficacy and safety of a transdermal delivery system of nicotine/mecamylamine in cigarette smokers. *Addiction* 2007; **102:** 795–802.

Tourette's syndrome. Mecamylamine has been tried[1-3] in the management of Tourette's syndrome (see under Tics, p.954) although results have been mixed.

1. Sanberg PR, *et al.* Treatment of Tourette's syndrome with mecamylamine. *Lancet* 1998; **352:** 705–6.
2. Silver AA, *et al.* Mecamylamine in Tourette's syndrome: a two-year retrospective case study. *J Child Adolesc Psychopharmacol* 2000; **10:** 59–68.
3. Silver AA, *et al.* Multicenter, double-blind, placebo-controlled study of mecamylamine monotherapy for Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 1103–10.

Preparations
USP 31: Mecamylamine Hydrochloride Tablets.

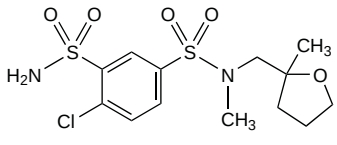
Proprietary Preparations (details are given in Part 3)
USA: Inversine.

Mefruside *(BAN, USAN, rINN)* ⊗

Bay-1500; FBA-1500; Mefrusid; Mefrusida; Méfruside; Mefrusidi; Mefrusidum. 4-Chloro-*N*^{1}-methyl-*N*^{1}-(tetrahydro-2-methylfurfuryl)benzene-1,3-disulphonamide.

Мефрузид

$C_{13}H_{19}ClN_2O_5S_2$ = 382.9.
CAS — 7195-27-9.
ATC — C03BA05.
ATC Vet — QC03BA05.



Pharmacopoeias. In *Jpn.*

Profile
Mefruside is a diuretic with properties similar to those of the thiazide diuretics (see Hydrochlorothiazide, p.1307) even though it does not contain a thiazide ring system. It is given orally for oedema, including that associated with heart failure (p.1165), and for hypertension (p.1171).

Diuresis begins about 2 to 4 hours after an oral dose and reaches a maximum between 6 and 12 hours.

In the treatment of oedema the usual dose is 25 to 50 mg daily, increasing if necessary to 75 to 100 mg. For long-term therapy a dose of 25 to 50 mg every second or third day is preferable.

In the treatment of hypertension the usual dose is 25 mg daily, either alone, or with other antihypertensives; initial doses of 25 to 50 mg daily have been recommended; alternate-day maintenance dosage may be used.

Preparations
Proprietary Preparations (details are given in Part 3)
Neth.: Baycaron†.

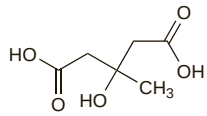
Multi-ingredient: ***Ger.:*** Bendigon N†; duranifin Sali†; Sali-Adalat; Sali-Prent.

Meglutol *(USAN, rINN)*

CB-337; Méglutol; Meglutolum. 3-Hydroxy-3-methylglutaric acid.

Мелутол

$C_6H_{10}O_5$ = 162.1.
CAS — 503-49-1.
ATC — C10AX05.
ATC Vet — QC10AX05.



Profile
Meglutol is a lipid regulating drug that has been used in the treatment of hyperlipidaemias.

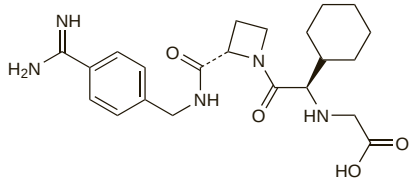
Preparations
Proprietary Preparations (details are given in Part 3)
Ital.: Mevalon†.

Melagatran *(rINN)*

H-319/68; Mélagatran; Melagatrán; Melagatranum. *N*-[(*R*)-({(2*S*)-2-[(*p*-Amidinobenzyl)carbamoyl]-1-azetidinyl}carbonyl)cyclohexylmethyl]glycine.

Мелагатран

$C_{22}H_{31}N_5O_4$ = 429.5.
CAS — 159776-70-2.
ATC — B01AE04.
ATC Vet — QB01AE04.



Ximelagatran *(USAN, rINN)*

H-376/95; Ximélagatran; Ximelagatrán; Ximelagatranum. Ethyl *N*-{(*R*)-cyclohexyl[((2*S*)-2-{[4-(hydroxycarbamimidoyl)benzyl]carbamoyl}-1-azetidinyl)carbonyl]methyl}glycinate.

Ксимелагатран

$C_{24}H_{35}N_5O_5$ = 473.6.
CAS — 192939-46-1.
ATC — B01AE05.
ATC Vet — QB01AE05.

Profile
Melagatran is a direct thrombin inhibitor with actions similar to lepirudin, p.1323, that was used as an anticoagulant in the prevention of postoperative venous thromboembolism in patients undergoing hip or knee replacement surgery. It is the active metabolite of ximelagatran and was given subcutaneously; ximelagatran was given orally. It was withdrawn worldwide because of reported liver toxicity.

◊ References.

1. Wallentin L, *et al.* Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet* 2003; **362:** 789–97.
2. Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; **362:** 1691–8.
3. Evans HC, *et al.* Ximelagatran/Melagatran: a review of its use in the prevention of venous thromboembolism in orthopaedic surgery. *Drugs* 2004; **64:** 649–78.
4. SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA* 2005; **293:** 690–8.

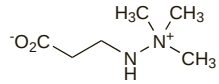
Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Exanta†; ***Austria:*** Exanta†; ***Denm.:*** Exanta†; ***Fin.:*** Exanta†; ***Fr.:*** Exanta†; ***Ger.:*** Exanta†; ***Neth.:*** Exanta†; ***Norw.:*** Exanta†; ***Swed.:*** Exarta†.

Meldonium *(rINN)*

Meldonio; MET-88; 3-(2,2,2-Trimethylhydrazinium)propionate. 3-(2,2,2-Trimethyldiazaniumyl)propanoate.

Мельдоний

$C_6H_{14}N_2O_2$ = 146.2.
CAS — 76144-81-5 (meldonium); 86426-17-7 (meldonium dihydrate).



Profile
Meldonium is an inhibitor of carnitine synthesis and is reported to have cardioprotective and anti-ischaemic effects. It has been used in a variety of disorders. In the management of ischaemic heart disease and ischaemic cerebrovascular disturbances oral doses have ranged from 500 mg to 1 g daily. A course of 500 mg given four times daily for 7 to 10 days has been used in alcohol abstinence syndrome. Meldonium has also been given intravenously in doses similar to those used orally.

◊ References.

1. Dambrova M, *et al.* Mildronate: cardioprotective action through carnitine-lowering effect. *Trends Cardiovasc Med* 2002; **12:** 275–9.
2. Sjakste N, *et al.* Mildronate: an antiischemic drug for neurological indications. *CNS Drug Rev* 2005; **11:** 151–68.

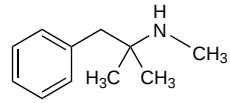
Preparations
Proprietary Preparations (details are given in Part 3)
Rus.: Mildronate (Милдронат); Mildroxyn (Милдроксин).

Mephentermine Sulfate *(rINNM)* ⊗

Méphentermine, Sulfate de; Mephentermine Sulphate *(BANM)*; Mephentermini Sulfas; Mephetedrine Sulphate; Sulfato de mefentermina. *N*,α,α-Trimethylphenethylamine sulphate dihydrate.

Мефентермина Сульфат

$(C_{11}H_{17}N)_2.H_2SO_4.2H_2O$ = 460.6.
CAS — 100-92-5 (mephentermine); 1212-72-2 (anhydrous mephentermine sulfate); 6190-60-9 (mephentermine sulfate dihydrate).
ATC — C01CA11.
ATC Vet — QC01CA11.



(mephentermine)

Adverse Effects, Treatment, and Precautions
As for Sympathomimetics, p.1407; adverse effects may be related to alpha- or beta-adrenergic stimulation. Mephentermine may produce CNS stimulation, especially in overdosage; anxiety, drowsiness, incoherence, hallucinations, and convulsions have been reported.

Interactions
As for Sympathomimetics, p.1407.

Pharmacokinetics
Mephentermine acts in about 5 to 15 minutes after intramuscular injection and has a duration of action of up to about 4 hours; it acts almost immediately after intravenous injection with a duration of action of up to about 30 minutes. It is rapidly metabolised in the body by demethylation; hydroxylation may follow. It is excreted as unchanged drug and metabolites in the urine; excretion is more rapid in acidic urine.

Uses and Administration
Mephentermine is a sympathomimetic (p.1408) with mainly indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity, and a slight stimulating effect on the CNS. It has an inotropic effect on the heart.

Mephentermine has been used to maintain blood pressure in hypotensive states, for example after spinal anaesthesia. It is given as the sulfate but doses are expressed in terms of the base; 21 mg of sulfate is equivalent to about 15 mg of base. Typical doses are up to 45 mg by slow intravenous injection, or 15 to 30 mg intramuscularly.

Preparations
Proprietary Preparations (details are given in Part 3)
India: Mephentine; ***USA:*** Wyamine†.

Multi-ingredient: ***USA:*** Emergent-Ez.