ments such as prostaglandins (see Termination of Pregnancy p.2004). Isosorbide dinitrate has been used similarly after missed abortion.[16]

1. DeSimone CA, *et al.* Intravenous nitro-glycerin aids manual extraction of a retained placenta. *Anesthesiology* 1990; **73:** 787.
2. Lowenwirt IP, *et al.* Safety of intravenous glyceryl trinitrate in management of retained placenta. *Aust N Z J Obstet Gynaecol* 1997; **37:** 20–4.
3. Greenspoon JS, Kovacic A. Breech extraction facilitated by glyceryl trinitrate sublingual spray. *Lancet* 1991; **338:** 124–5.
4. Yadava RP. Sublingual glyceryl trinitrate spray facilitates IUD insertion. *Br J Sex Med* 1990; **17:** 217.
5. Lees C, *et al.* Arrest of preterm labour and prolongation of gestation with glyceryl trinitrate, a nitric oxide donor. *Lancet* 1994; **343:** 1325–6.
6. Smith GN, *et al.* Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. *Br J Obstet Gynaecol* 1999; **106:** 736–9.
7. Lees CC, *et al.* Glyceryl trinitrate and ritodrine in tocolysis: an international multicenter randomized study. *Obstet Gynecol* 1999; **94:** 403–8.
8. Bisits A, *et al.* The Randomized Nitric Oxide Tocolysis Trial (RNOTT) for the treatment of preterm labor. *Am J Obstet Gynecol* 2004; **191:** 683–90.
9. El-Sayed YY, *et al.* Randomized comparison of intravenous nitroglycerin and magnesium sulfate for treatment of preterm labor. *Obstet Gynecol* 1999; **93:** 79–83.
10. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 28/11/07).
11. Pittrof R, *et al.* Crossover study of glyceryl trinitrate patches for controlling pain in women with severe dysmenorrhoea. *BMJ* 1996; **312:** 884.
12. The Transdermal Nitroglycerine/Dysmenorrhoea Study Group. Transdermal nitroglycerine in the management of pain associated with primary dysmenorrhoea: a multinational pilot study. *J Int Med Res* 1997; **25:** 41–4.
13. Grunewald C, *et al.* Effects of nitroglycerin on the uterine and umbilical circulation in severe preeclampsia. *Obstet Gynecol* 1995; **86:** 600–4.
14. Thomson AJ, *et al.* Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first-trimester termination of pregnancy. *Lancet* 1998; **352:** 1093–6.
15. Chen FC-K, *et al.* Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. *Eur J Obstet Gynecol Reprod Biol* 2008; **138:** 176–9.
16. Arteaga-Troncoso G, *et al.* Intracervical application of the nitric oxide donor isosorbide dinitrate for induction of cervical ripening: a randomised controlled trial to determine clinical efficacy and safety prior to first trimester surgical evacuation of retained products of conception. *BJOG* 2005; **112:** 1615–19.

Oesophageal motility disorders. Achalasia is obstruction caused by failure of the lower oesophageal sphincter to relax and permit passage of food into the stomach. Nitrates such as isosorbide dinitrate have been reported to produce effective relaxation and to reduce symptoms when given sublingually. They have a role when mechanical dilatation of the sphincter or surgery are not feasible (see Oesophageal Motility Disorders, p.1702).

Nitrates may also be employed in oesophageal disorders such as variceal haemorrhage (see below).

Pain. Nitrates have been tried topically in the management of pain. Beneficial results have been reported with glyceryl trinitrate, applied as patches[1] or as a spray,[2] and isosorbide dinitrate spray,[3] in patients with painful diabetic neuropathy. Glyceryl trinitrate has also been used topically in musculoskeletal disorders[4] (see also Soft-tissue Rheumatism, below), and in surgical pain,[5] and intravenously as an adjunct to regional anaesthesia.[6]

Glyceryl trinitrate is also used topically to relieve pain in patients with anal fissure (above). For reference to its use in biliary colic, see Gallstones, above.

1. Rayman G, *et al.* Glyceryl trinitrate patches as an alternative to isosorbide dinitrate spray in the treatment of chronic painful diabetic neuropathy. *Diabetes Care* 2003; **26:** 2697–8.
2. Agrawal RP, *et al.* Glyceryl trinitrate spray in the management of painful diabetic neuropathy: a randomized double blind placebo controlled cross-over study. *Diabetes Res Clin Pract* 2007; **77:** 161–7.
3. Yuen KCJ, *et al.* Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes Care* 2002; **25:** 1699–1703.
4. Paoloni JA, *et al.* Topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow: a randomized, double-blinded, placebo-controlled clinical trial. *Am J Sports Med* 2003; **31:** 915–20.
5. McCabe JE, *et al.* A randomized controlled trial of topical glyceryl trinitrate before transrectal ultrasonography-guided biopsy of the prostate. *BJU Int* 2007; **100:** 536–8.
6. Sen S, *et al.* The analgesic effect of nitroglycerin added to lidocaine on intravenous regional anesthesia. *Anesth Analg* 2006; **102:** 916–20.

Peripheral vascular disease. In peripheral vascular disease (p.1178) nitrates have been tried as vasodilators and smooth muscle relaxants in order to improve resting blood flow. Glyceryl trinitrate has been applied topically in patients with Raynaud's syndrome[1-3] and in distal limb ischaemia[4] resulting in some benefit but this form of therapy is not widely used in these disorders.

1. Franks AG. Topical glyceryl trinitrate as adjunctive treatment in Raynaud's disease. *Lancet* 1982; **i:** 76–7.
2. Coppock JS, *et al.* Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon. *Postgrad Med J* 1986; **62:** 15–18.
3. Teh LS, *et al.* Sustained-release transdermal glyceryl trinitrate patches as a treatment for primary and secondary Raynaud's phenomenon. *Br J Rheumatol* 1995; **34:** 636–41.
4. Fletcher S, *et al.* Locally applied transdermal nitrate patches for the treatment of ischaemic rest pain. *Int J Clin Pract* 1997; **51:** 324–5.

Pulmonary hypertension. Glyceryl trinitrate reduces total pulmonary resistance in most patients with pulmonary arterial hypertension (p.1179),[1,2] including when given by inhalation.[3] However, other vasodilators such as calcium-channel blockers, epoprostenol, or bosentan are generally preferred for long-term treatment.

1. Pearl RG, *et al.* Acute hemodynamic effects of nitroglycerin in pulmonary hypertension. *Ann Intern Med* 1983; **99:** 9–13.
2. Weir EK, *et al.* The acute administration of vasodilators in primary pulmonary hypertension. *Am Rev Respir Dis* 1989; **140:** 1623–30.
3. Goyal P, *et al.* Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease. *Br J Anaesth* 2006; **97:** 208–14.

Quinine oculotoxicity. Intravenous nitrate has been suggested for the management of quinine oculotoxicity (p.613) and its benefit may be due to an increase in retinal vascular bed flow.[1]

1. Moore D, *et al.* Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Soft-tissue rheumatism. There is evidence from animal studies that nitric oxide plays an important role in tendon healing, and randomised studies in patients with tennis elbow (epicondylitis), Achilles tendinosis (tendinitis), and supraspinatus tendinosis showed enhanced subjective and objective recovery when a glyceryl trinitrate patch (releasing 1.25 mg over 24 hours) was applied over the area of tenderness once daily.[1] Glyceryl trinitrate has also been tried in musculoskeletal pain (see Pain, above). For the general management of soft-tissue rheumatism see p.13.

1. Murrell GAC. Using nitric oxide to treat tendinopathy. *Br J Sports Med* 2007; **41:** 227–31.

Variceal haemorrhage. The usual treatment in variceal haemorrhage (p.2346) is injection sclerotherapy or banding ligation which may be performed during the emergency endoscopy procedure. Where endoscopy is unavailable drug therapy may be used; it may also have a role when sclerotherapy fails and some have suggested that initial drug therapy may be preferable to sclerotherapy. Vasoconstrictors that are used include vasopressin and its analogue terlipressin, given with glyceryl trinitrate which counteracts the adverse cardiac effects of vasopressin while potentiating its beneficial effects on portal pressure; somatostatin is also used.

Prophylaxis of a first bleed in patients with portal hypertension is controversial since about 70% of patients who have varices will never bleed. It is postulated that a reduction in portal pressure to below 12 mmHg is necessary to reduce the incidence of variceal bleeding and that treatment with beta blockers alone does not achieve this. More effective drugs are being sought and isosorbide mononitrate (as adjunctive therapy with a beta blocker) is under investigation, both for prophylaxis of a first bleed[1,2] and in the prevention of rebleeding.[3] Early emergency treatment (before endoscopy) with terlipressin given intravenously and glyceryl trinitrate transdermally controlled bleeding and lowered mortality rates in patients with gastrointestinal bleeding and a history or clinical signs of cirrhosis.[4] However, use of oral isosorbide mononitrate with somatostatin infusion for acute variceal bleeding was less effective than somatostatin alone and induced more adverse effects.[5]

1. Angelico M, *et al.* Isosorbide-5-mononitrate versus propranolol in the prevention of first bleeding in cirrhosis. *Gastroenterology* 1993; **104:** 1460–5.
2. Merkel C, *et al.* Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. *Lancet* 1996; **348:** 1677–81.
3. Villanueva C, *et al.* Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996; **334:** 1624–9.
4. Levacher S, *et al.* Early administration of terlipressin plus glyceryl trinitrate to control active upper gastrointestinal bleeding in cirrhotic patients. *Lancet* 1995; **346:** 865–8.
5. Junquera F, *et al.* Somatostatin plus isosorbide 5-mononitrate versus somatostatin in the control of acute gastro-oesophageal variceal bleeding: a double blind, randomised, placebo controlled clinical trial. *Gut* 2000; **46:** 127–32.

Venepuncture. Glyceryl trinitrate patches applied to skin adjacent to intravenous infusion sites are used in the prophylactic treatment of phlebitis and extravasation.[1]

Local application of glyceryl trinitrate 1 to 2 mg as ointment was found to be a useful aid to venepuncture in a study of 50 patients undergoing surgery,[2] but conflicting results have been reported in children and neonates.[3,4]

1. Tjon JA, Ansani NT. Transdermal nitroglycerin for the prevention of intravenous infusion failure due to phlebitis and extravasation. *Ann Pharmacother* 2000; **34:** 1189–92.
2. Hecker JF, *et al.* Nitroglycerine ointment as an aid to venepuncture. *Lancet* 1983; **i:** 332–3.
3. Vaksmann G, *et al.* Nitroglycerine ointment as aid to venous cannulation in children. *J Pediatr* 1987; **111:** 89–91.
4. Maynard EC, Oh W. Topical nitroglycerin ointment as an aid to insertion of peripheral venous catheters in neonates. *J Pediatr* 1989; **114:** 474–6.

Preparations

BP 2008: Glyceryl Trinitrate Sublingual Spray; Glyceryl Trinitrate Tablets; Glyceryl Trinitrate Transdermal Patches; ***USP 31:*** Nitroglycerin Injection; Nitroglycerin Ointment; Nitroglycerin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Dauxona; Enetege; Minitran†; Niglinar; Nitradisc†; Nitro-Dur; Nitroderm TTS; Nitrodom; Nitrogray; ***Austral.:*** Anginine; Lycinate; Minitran; Nitro-Dur; Nitrolingual; Rectogesic; Transiderm-Nitro; ***Austria:*** Cordiplast; Deponit; Minitran; Nitro; Nitro Mack; Nitro Pohl; Nitro-Dur; Nitroderm; Nitrolingual; Perlinganit; ***Belg.:*** Deponit; Diafusor; Minitran; Nitro-Dyl†; Nitroderm; Nitrolingual; Nysconitrine; Trinipatch; Willlong; ***Braz.:*** Nitradisc; Nitroderm TTS; Nitronal†; Tridil; ***Canad.:*** Gen-Nitro; Minitran; Nitro-Dur; Nitroject; Nitrol; Nitrolingual; Nitrong†; Nitrostat; Rho-Nitro; Transderm-Nitro; ***Chile:*** Angiolingual; Nitrocor; Nitroderm; Nitronal†; ***Cz.:*** Deponit†; Maycor Nitrospray†; Minitran†; Nit-Ret; Nitrangin†; Nitrilex†; Nitro Mack†; Nitro Pohl; Nitrolingual†; Nitromint; Perlinganit; Rectogesic; ***Denm.:*** Buccard; Discotrine; Glytrin; Nitrolingual; Nitromex; ***Fin.:*** Deponit; Minitran; Nitro; Nitromex; Perlinganit; Transiderm-Nitro; ***Fr.:*** Cordipatch; Diafusor; Discotrine; Epinitril; Lenitral†; Natispray; Nitriderm TTS; Rectogesic; Trinipatch; ***Ger.:*** Aquo-Trinitrosan; Corangin Nitrospray; Coro-Nitro†; Deponit; Gepan†; MinitranS; neos nitro OPT†; Nitrangin; Nitro Mack†; Nitro Solvay; Nitro-Pflaster-ratiopharm TL†; Nitroderm TTS; Nitrokor†; Nitrolingual; Perlinganit; Trinitrosan; ***Gr.:*** Cardiplast; Epinitril; Nitro Mack†; Nitrodyl; Nitrolingual; Nitrong; Nitroretard; Nitrosylon; Pancoran; Rectogesic; Sodemethin†; Supranitrin; Trinipatch; Trinitrine Simple Laleuf†; ***Hong Kong:*** Angised; Deponit; Lenitral†; Nitro Mack; Nitro Pohl†; Nitro-Dur; Nitrocine; Nitroderm TTS; Nitrolingual; Tridil†; ***Hung.:*** Nitro Pohl; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitromint; Perlinganit†; Sustac; ***India:*** Angised; Millisrol; Myonit; Myovin; Nitrocontin; Nitroderm TTS; Nitrogesic; Nitrolingual; ***Indon.:*** Nitrocine; Nitrokaf; ***Irl.:*** Deponit; Epinitril†; Glytrin; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Suscard; Sustac; Transiderm-Nitro; ***Israel:*** Angised†; Deponit; Nitrocine; Nitroderm TTS; Nitrolingual; Nitronal; Trinipatch†; ***Ital.:*** Adesitrin; Deponit; Dermatrans; Epinitril; Keritrina; Minitran; Natispray; Nitraket; Nitro-Dur; Nitrocor; Nitroderm TTS; Nitrosylon; Perganit; Top-Nitro; Triniplas; Trinitrina; Venitrin; ***Jpn:*** Millisrol; ***Malaysia:*** Deponit; Glytrin†; Nitrocine; Nitroderm; ***Mex.:*** Anglix; Cardinit; Minitran; Nitradisc; Nitro-Dur; Nitroder; Nitroderm TTS; ***Neth.:*** Deponit; Glytrin; Lenitral; Minitran; Nitro Pohl; Nitro-Dur; Nitrolingual; Transiderm-Nitro; Trinipatch; ***Norw.:*** Minitran; Nitro-Dur; Nitrolingual; Nitromex; Nitroven; Transiderm-Nitro; ***NZ:*** Anginine†; Glytrin; Lycinate; Minitran; Nitroderm; Nitrolingual; Nitronal; ***Philipp.:*** Deponit; Minitran; Nitrolingual; Nitronal; Nitrostat; Perlinganit; Transderm-Nitro; ***Pol.:*** Nitracor; Nitrocard; Nitroderm; Nitromint; Perlinganit; Sustonit; Trimonit; ***Port.:*** Dermatrans; Diafusor; Discotrine; Epinitril; Glytrin; Nitradisc; Nitro-Dur; Nitroderm TTS; Nitromint; Plastranit; Rectogesic; Trinipatch†; ***Rus.:*** Deponit (Депонит); Nirmin (Нирмин); Nitro (Нитро); Nitrocor (Нитрокор); Nitroject (Нитроджект); Nitromint (Нитроминт); Nitrong (Нитронг); Nitrospray (Нитроспрей); Perlinganit (Перлинганит); Sustac (Сустак); Sustonit (Сустонит); ***S.Afr.:*** Angised; Nitrocine; Nitrolingual; Tridil; ***Singapore:*** Angised; Deponit; Glytrin†; Nitro Mack†; Nitrocine; Rectogesic; ***Spain:*** Cordiplast; Dermatrans; Diafusor; Epinitril; Minitran; Nitradisc; Nitro-Dur; Nitroderm; Nitroplast; Solinitrina; Trinipatch; Trinispray; Vernies; ***Swed.:*** Glytrin; Minitran; Nitrolingual; Nitromex; Perlinganit†; Suscard; Transiderm-Nitro; ***Switz.:*** Deponit; Minitran; Nitro Mack; Nitro-Dur; Nitroderm TTS; Nitrolingual; Nitronal; Perlinganit; Trinitrine; ***Thai.:*** Amitacon†; Angised†; Glytrin; Nitro Mack†; Nitrocine; Nitroderm; Nitroject; ***Turk.:*** Deponit; Nitroderm TTS; Nitrolingual; Perlinganit; ***UAE:*** Cardispray†; ***UK:*** Coro-Nitro; Deponit; Glytrin; Minitran; Nitro-Dur; Nitrocine; Nitrolingual; Nitromin; Nitronal; Percutol; Rectogesic; Suscard; Sustac†; Transiderm-Nitro; Trintek; ***USA:*** Minitran; Nitrek; Nitro-Bid; Nitro-Derm; Nitro-Dur; Nitro-Time; Nitrodisc; Nitrogard; Nitroglyn†; Nitrolingual; NitroMist; Nitrong†; NitroQuick; Nitrostat; NitroTab†; Transderm-Nitro; Transdermal-NTG; Tridil†; ***Venez.:*** Minitran†; Nitro Mack; Nitrocor; Nitroderm; Tridil†.

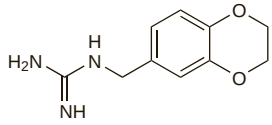
Multi-ingredient: ***Arg.:*** Trinitron; ***Austria:*** Myocardon; Percucor†; Spasmocor; ***Ger.:*** Nitrangin compositum†; ***Pol.:*** Pentaerythritol Compositum; ***Spain:*** Cafinitrina; ***USA:*** Emergent-Ez.

Guabenxan *(rINN)*

Guabenxán; Guabenxane; Guabenxanum. (1,4-Benzodioxan-6-ylmethyl)guanidine.

Гуабенксан

$C_{10}H_{13}N_3O_2$ = 207.2.
CAS — 19889-45-3.



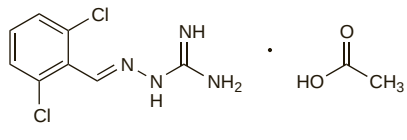
Profile
Guabenxan is an antihypertensive with properties similar to guanethidine (below). It has been given orally as the sulfate.

Guanabenz Acetate *(USAN, rINNM)*

Acetato de guanabenzo; Guanabenz, Acétate de; Guanabenzi Acetas; NSC-68982 (guanabenz); Wy-8678 (guanabenz). (2,6-Dichlorobenzylideneamino)guanidine acetate.

Гуанабенза Ацетат

$C_8H_8Cl_2N_4,C_2H_4O_2$ = 291.1.
CAS — 5051-62-7 (guanabenz); 23256-50-0 (guanabenz acetate).



Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Guanabenz Acetate). A white or almost white powder with not more than a slight odour. Sparingly soluble in water and in 0.1N hydrochloric acid; soluble in alcohol and in propylene glycol. A 0.7% solution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Adverse Effects and Precautions
As for Clonidine Hydrochloride, p.1247.

Overdosage. Overdosage with guanabenz has been reported.[1] The main symptoms were lethargy, drowsiness, bradycardia, and hypotension. A 45-year-old woman who had taken 200 to 240 mg of guanabenz with alcohol recovered after gastric lavage and intravenous fluids; a 3-year-old child who had taken 12 mg of guanabenz responded to atropine and dopamine. Naloxone had little effect in either patient.

1. Hall AH, *et al*. Guanabenz overdose. *Ann Intern Med* 1985; **102:** 787–8.

Interactions
As for Clonidine Hydrochloride, p.1248.

Pharmacokinetics
About 75% of an oral dose of guanabenz is absorbed and undergoes extensive first-pass metabolism. Peak plasma concentrations occur about 2 to 5 hours after a dose. It is about 90% bound to plasma proteins. Guanabenz is mainly excreted in urine, almost entirely as metabolites, with less than 1% as unchanged drug; about 10 to 30% is excreted in faeces. The average elimination half-life is reported to range from 4 to 14 hours.

Uses and Administration
Guanabenz is an alpha$_2$-adrenoceptor agonist with actions and uses similar to those of clonidine (p.1248). It is used in the management of hypertension (p.1171), either alone or with other antihypertensives, particularly thiazide diuretics.

Guanabenz is given orally as the acetate, but doses are usually expressed in terms of the base. Guanabenz acetate 5 mg is equivalent to about 4 mg of guanabenz.

In hypertension, the usual dose is 4 mg twice daily initially; the daily dose may be increased by amounts of 4 to 8 mg every 1 to 2 weeks according to response. Doses of up to 32 mg twice daily have been used.

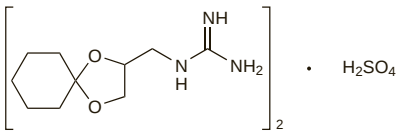
Preparations
USP 31: Guanabenz Acetate Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Lisapres; ***USA:*** Wytensin.

Guanadrel Sulfate *(USAN, rINNM)*

CL-1388R; Guanadrel, Sulfate de; Guanadrel Sulphate; Guanadreli Sulfas; Sulfato de guanadrel; U-28288D. 1-(Cyclohexane-spiro-2′-[1′,3′]dioxolan-4′-ylmethyl)guanidine sulfate; 1-(1,4-Dioxaspiro[4.5]dec-2-ylmethyl)guanidine sulfate.

Гуанадрела Сульфат
$(C_{10}H_{19}N_3O_2)_2,H_2SO_4$ = 524.6.
CAS — 40580-59-4 (guanadrel); 22195-34-2 (guanadrel sulfate).



Pharmacopoeias. In *US*.
USP 31 (Guanadrel Sulfate). A white to off-white crystalline powder. Soluble in water; slightly soluble in alcohol and in acetone; sparingly soluble in methyl alcohol.

Adverse Effects, Treatment, and Precautions
As for Guanethidine Monosulfate, below. Guanadrel has been reported to cause less diarrhoea, and less orthostatic hypotension on rising in the morning, than guanethidine, but orthostatic symptoms seem to occur with a similar frequency to guanethidine during the day.

Interactions
As for Guanethidine Monosulfate, below.

Pharmacokinetics
Guanadrel is rapidly and almost completely absorbed from the gastrointestinal tract, with a bioavailability of about 85%. It is widely distributed throughout the body and about 20% is bound to plasma proteins. It is reported not to cross the blood-brain barrier. Plasma concentrations decline in a biphasic manner: the half-life varies widely between individuals, in the initial phase from 1 to 4 hours, and in the terminal phase from 5 to 45 hours, with a mean of about 10 hours. Guanadrel is metabolised in the liver and about 85% is excreted in the urine over 24 hours as the unchanged drug and its metabolites. About 40 to 50% of the drug is excreted unchanged.

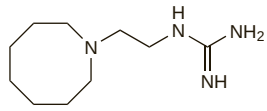
Uses and Administration
Guanadrel is an antihypertensive with actions and uses similar to those of guanethidine (below). After oral administration, guanadrel acts within 2 hours with the maximum effect after 4 to 6 hours. The hypotensive effect is reported to last for 4 to 14 hours following a single dose. It has been given orally as the sulfate in the management of hypertension, although it has largely been superseded by other drugs less likely to cause orthostatic hypotension.

Preparations
USP 31: Guanadrel Sulfate Tablets.

Guanethidine Monosulfate *(USAN, rINNM)*

Guanéthidine, monosulfate de; Guanethidine Monosulphate *(BANM)*; Guanethidini Monosufas; Guanethidini monosulfas; Guanethidini Sulfas; Guanethidin-monosulfát; Guanetidiinimonosulfaatti; Guanetidinmonosulfat; Guanetidin-monoszulfát; Guanetidino monosulfatas; Monosulfato de guanetidina; NSC-29863 (guanethidine hemisulfate); Su-5864 (guanethidine hemisulfate). 1-[2-(Perhydroazocin-1-yl)ethyl]guanidine monosulfate.

Гуанетидина Моносульфат
$C_{10}H_{22}N_4,H_2SO_4$ = 296.4.
CAS — 55-65-2 (guanethidine); 60-02-6 (guanethidine hemisulfate); 645-43-2 (guanethidine monosulfate).
ATC — C02CC02; S01EX01.
ATC Vet — QC02CC02; QS01EX01.



(guanethidine)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
Chin. includes the hemisulfate.
Ph. Eur. 6.2 (Guanethidine Monosulphate). A colourless crystalline powder. Freely soluble in water; practically insoluble in alcohol. A 2% solution in water has a pH of 4.7 to 5.5. Protect from light.
USP 31 (Guanethidine Monosulfate). A white to off-white crystalline powder. Very soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform. A 2% solution in water has a pH of 4.7 to 5.7.

Adverse Effects
The commonest adverse effects of guanethidine are severe postural and exertional hypotension and diarrhoea which may be particularly troublesome during the initial stages of therapy and during dose adjustment. Dizziness, syncope, muscle weakness, and lassitude are liable to occur, especially on rising from sitting or lying. Orthostatic hypotension may be severe enough to provoke angina, renal impairment, and transient cerebral ischaemia. Other frequent adverse effects are bradycardia, failure of ejaculation, fatigue, headache, and salt and water retention and oedema, which may be accompanied by breathlessness and may occasionally precipitate overt heart failure.

Nausea, vomiting, dry mouth, nasal congestion, parotid tenderness, blurring of vision, depression, myalgia, muscle tremor, paraesthesias, hair loss, dermatitis, disturbed micturition, priapism, aggravation or precipitation of asthma, and exacerbation of peptic ulcer disease have also been reported. Guanethidine may possibly cause anaemia, leucopenia, and thrombocytopenia.

When guanethidine is used as eye drops, common adverse effects are conjunctival hyperaemia and miosis. Burning sensations and ptosis have also occurred. Superficial punctate keratitis has been reported particularly after prolonged use of high doses.

Treatment of Adverse Effects
Withdrawal of guanethidine or dose reduction reverses many adverse effects. Diarrhoea may also be controlled by giving codeine phosphate or antimuscarinics. If overdosage occurs the benefit of gastric decontamination is uncertain, but activated charcoal may be given if the patient presents within 1 hour. Hypotension may respond to placing the patient in the supine position with the feet raised. If hypotension is severe it may be necessary to give intravenous fluid replacement and small doses of vasopressors may be given cautiously. The patient must be monitored for several days.

Precautions
Guanethidine should not be given to patients with phaeochromocytoma, as it may cause a hypertensive crisis, or to patients with heart failure not caused by hypertension.

It should be used with caution in patients with renal impairment, cerebrovascular disorders, or ischaemic heart disease, or with a history of peptic ulcer disease or asthma. Exercise and heat may increase the hypotensive effect of guanethidine, and dosage requirements may be reduced in patients who develop fever.

There may be an increased risk of cardiovascular collapse or cardiac arrest in patients undergoing surgery while taking guanethidine, but authorities have differed as to whether the drug should be stopped before elective surgery. Former US licensed product information recommended stopping up to 2 or 3 weeks beforehand. In patients undergoing emergency procedures or where treatment has not been interrupted large doses of atropine should be given before induction of anaesthesia.

Patients undergoing treatment with eye drops containing guanethidine should be examined regularly for signs of conjunctival damage.

Interactions
Patients taking guanethidine may show increased sensitivity to the action of adrenaline, amfetamine, and other sympathomimetics, resulting in exaggerated pressor effects. The hypotensive effects may also be antagonised by tricyclic antidepressants, MAOIs, and phenothiazine derivatives and related antipsychotics (although phenothiazines may also exacerbate orthostatic hypotension, which may be more relevant clinically). In the UK licensed product information suggests that MAOIs should be stopped at least 14 days before beginning guanethidine, although in the USA a minimum of a week has been recommended as adequate. It has been reported that oral contraceptives may reduce the hypotensive action of guanethidine. Use of digoxin or other digitalis derivatives with guanethidine may cause excessive bradycardia.

The hypotensive effects of guanethidine may be enhanced by thiazide diuretics, other antihypertensives, and levodopa. Alcohol may cause orthostatic hypotension in patients taking guanethidine.

Pharmacokinetics
Guanethidine is variably and incompletely absorbed from the gastrointestinal tract with less than 50% of the dose reaching the systemic circulation. It is actively taken up into adrenergic neurones by the mechanism responsible for noradrenaline reuptake. A plasma concentration of 8 nanograms/mL is reported to be necessary for adrenergic blockade, but the dose required to achieve this varies between individuals due to differences in absorption and metabolism. Guanethidine is partially metabolised in the liver, and is excreted in the urine as metabolites and unchanged guanethidine. It has a terminal half-life of about 5 days. Guanethidine does not penetrate the blood-brain barrier significantly.

Uses and Administration
Guanethidine is an antihypertensive that acts by selectively inhibiting transmission in postganglionic adrenergic nerves. It is believed to act mainly by preventing the release of noradrenaline at nerve endings. Guanethidine causes the depletion of noradrenaline stores in peripheral sympathetic nerve terminals but does not prevent the secretion of catecholamines by the adrenal medulla.

When given orally its maximal effects may take 1 to 3 weeks to appear on continued dosing and persist for 1 to 3 weeks after treatment has been stopped. It causes an initial reduction in cardiac output but its main hypotensive effect is to cause peripheral vasodilatation; it reduces the vasoconstriction which normally results from standing up and which is the result of reflex sympathetic nervous activity. In the majority of patients it reduces standing blood pressure but has a lesser effect on supine blood pressure. When applied topically to the eye guanethidine reduces the production of aqueous humour.

Guanethidine is used in the management of hypertension (p.1171). Eye drops of guanethidine have been used for open-angle glaucoma (p.1873) and for lid retraction associated with hyperthyroidism. Guanethidine has also been used in the management of neuropathic pain syndromes (see below).

Guanethidine is used in the treatment of hypertension when other drugs have proved inadequate, but it has largely been superseded by other drugs less likely to cause orthostatic hypotension. Tolerance to guanethidine has occurred in some patients; this may be countered by concomitant diuretic therapy.

In **hypertension**, the usual initial oral dose of guanethidine monosulfate has been 10 mg daily. This is increased by increments of 10 to 12.5 mg, not more often than every 5 to 7 days, according to response. The usual maintenance dose has been 25 to 50 mg once daily.

Children have been given 200 micrograms/kg daily with increments of 200 micrograms/kg every 7 to 10 days until a satisfactory response is achieved.

Guanethidine monosulfate has been given intramuscularly in the treatment of hypertensive crises, including severe pre-eclampsia, but more suitable drugs are available. An intramuscular dose of 10 to 20 mg is reported to produce a fall in blood pressure within 30 minutes.

Eye drops containing guanethidine monosulfate have been used in the treatment of open-angle **glaucoma** (usually combined with adrenaline), and for the lid retraction that may accompany hyperthyroidism.

Pain syndromes. Sympathetic nerve blocks may be used in the management of acute or chronic pain associated with a well-defined anatomical site. Guanethidine is one of a number of drugs that have been used for intravenous regional sympathetic block in the management of neuropathic pain (see Complex Regional Pain Syndrome, p.6), to reduce pain and to maintain blood flow.