

**Cinepazet Maleate** (BANM, USAN, piNNM)

Cinépazet, Maléate de; Cinepazeti Maleas; Cinepazic Acid Ethyl Ester Maleate; Maleato de cinepazet. Ethyl 4-(3,4,5-trimethoxycinnamoyl)piperazin-1-ylacetate hydrogen maleate.

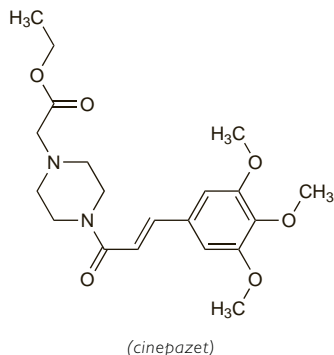
Цинепазета Малеат

$C_{20}H_{28}N_2O_6 \cdot C_4H_4O_4 = 508.5$ .

CAS — 23887-41-4 (cinepazet); 50679-07-7 (cinepazet maleate).

ATC — C01DX14.

ATC Vet — QC01DX14.

**Profile**

Cinepazet maleate is a vasodilator that has been used in angina pectoris.

**Cinepazide Maleate** (BANM, riNNM)

Cinépazide, Maléate de; Cinepazidi Maleas; Maleato de cinepazida; MD-67350. 1-(Pyrrolidin-1-ylcarbonylmethyl)-4-(3,4,5-trimethoxycinnamoyl)piperazine hydrogen maleate.

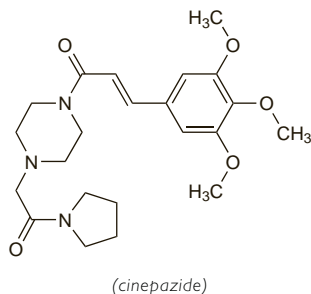
Цинепазида Малеат

$C_{22}H_{31}N_3O_5 \cdot C_4H_4O_4 = 533.6$ .

CAS — 23887-46-9 (cinepazide); 26328-04-1 (cinepazide maleate).

ATC — C04AX27.

ATC Vet — QC04AX27.

**Profile**

Cinepazide maleate is a vasodilator that has been used in peripheral vascular disorders, but has been withdrawn from the market in some countries after reports of agranulocytosis.

**Ciprofibrate** (BAN, USAN, riNN)

Ciprofibrát; Ciprofibrat; Ciprofibratas; Ciprofibrato; Ciprofibratum; Ciprofibratti; Win-35833. 2-[4-(2,2-Dichlorocyclopropyl)phenoxy]-2-methylpropionic acid.

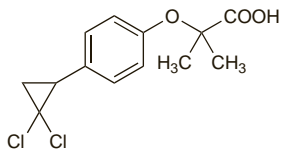
Ципрофибрат

$C_{13}H_{14}Cl_2O_3 = 289.2$ .

CAS — 52214-84-3.

ATC — C10AB08.

ATC Vet — QC10AB08.



**Pharmacopoeias.** In *Eur.* (see p.vii).

**Ph. Eur. 6.2** (Ciprofibrate). A white or slightly yellow, crystal-

line powder. Practically insoluble in water; freely soluble in dehydrated alcohol; soluble in toluene. Store in airtight containers. Protect from light.

**Adverse Effects and Precautions**

As for Bezafibrate, p.1232.

**Interactions**

As for Bezafibrate, p.1232.

**Pharmacokinetics**

Ciprofibrate is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 to 4 hours. Ciprofibrate is highly protein bound. It is excreted in the urine as unchanged drug and as glucuronide conjugates. The elimination half-life varies from about 38 to 86 hours in patients on long-term therapy.

**Uses and Administration**

Ciprofibrate, a fibric acid derivative, is a lipid regulating drug with actions on plasma lipids similar to those of bezafibrate (p.1233).

It is used to reduce total cholesterol and triglycerides in the management of hyperlipidaemias (p.1169), including type IIa, type IIb, type III, and type IV hyperlipoproteinaemias. The usual oral dose is 100 mg daily. The dose should be reduced in renal impairment (see below).

**Administration in renal impairment.** Ciprofibrate is contra-indicated in patients with severe renal impairment. Licensed product information suggests reducing the dose to 100 mg every other day for patients with moderate renal impairment.

Renal clearance of ciprofibrate was reduced and elimination half-life about doubled in patients with severe renal impairment.<sup>1</sup> Mild renal impairment slowed the urinary excretion of ciprofibrate but not its extent. The clearance of ciprofibrate was unaffected by haemodialysis.

1. Ferry N, *et al.* The influence of renal insufficiency and haemodialysis on the kinetics of ciprofibrate. *Br J Clin Pharmacol* 1989; **28**: 675–81.

**Preparations**

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Estaprol; **Belg.:** Hyperlipen; **Braz.:** Lipless; Oroxadin; **Chile:** Estaprol; **Cz.:** Lipanor; **Fr.:** Lipanor; **Gr.:** Savilen; **Hung.:** Lipanor; **Indon.:** Modalim; **Israel:** Lipanor; **Malaysia:** Modalim; **Mex.:** Oroxadin; **Neth.:** Hyperlipen; **Modalim;** **Philipp.:** Modalim; **Pol.:** Lipanor; **Port.:** Fibrinin; **Sin-gapore:** Modalim; **Switz.:** Hyperlipen; **UK:** Modalim; **Venez.:** Hyperlipen.

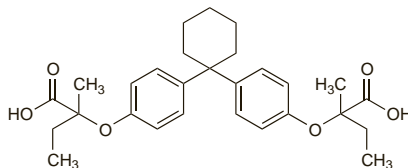
**Clinofibrate** (riNN)

Clinofibrato; Clinofibratum; S-8527. 2,2'-(Cyclohexyldienebis(4-phenyleneoxy))bis[2-methylbutyric acid].

Клинофибрат

$C_{28}H_{36}O_6 = 468.6$ .

CAS — 30299-08-2.



**Pharmacopoeias.** In *Jpn.*

**Profile**

Clinofibrate, a fibric acid derivative (see Bezafibrate, p.1232), is a lipid regulating drug used in the treatment of hyperlipidaemias (p.1169). The usual oral dose is 200 mg three times daily.

**Preparations**

**Proprietary Preparations** (details are given in Part 3)

*Jpn.:* Lipoclin.

**Clofibrate** (BAN, USAN, riNN)

AY-61123; Clofibrato; Clofibratum; Ethyl *p*-Chlorophenoxyisobutyrate; Ethyl Clofibrate; ICI-28257; Klobibraatti; Klobibrát; Klobibrat; Klobibratas; NSC-79389. Ethyl 2-(4-chlorophenoxy)-2-methylpropionate.

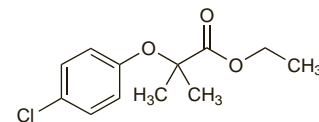
Клофибрат

$C_{12}H_{15}ClO_3 = 242.7$ .

CAS — 637-07-0 (clofibrate); 882-09-7 (clofibric acid).

ATC — C10AB01.

ATC Vet — QC10AB01.



**Pharmacopoeias.** In *Chin.*, *Eur.* (see p.vii), *Jpn.* and *U.S.*

**Ph. Eur. 6.2** (Clofibrate). A clear, almost colourless liquid. Very slightly soluble in water; miscible with alcohol.

**USP 31** (Clofibrate). A colourless to pale yellow liquid with a characteristic odour. Insoluble in water; soluble in alcohol, in acetone, in chloroform, and in benzene. Store in airtight containers. Protect from light.

**Aluminium Clofibrate** (BAN, riNN)

Alufibrate; Aluminii Clofibras; Aluminium, Clofibrate d'; Aluminumklofibratti; Aluminiumklofibrat; Aluminium Clofibrate; Clofibrato de aluminio. Bis[2-(4-chlorophenoxy)-2-methylpropionate]hydroxyaluminium.

Алюминия Клофибрат

$C_{30}H_{21}AlCl_2O_7 = 471.3$ .

CAS — 24818-79-9; 14613-01-5.

ATC — C10AB03.

ATC Vet — QC10AB03.

**Calcium Clofibrate** (riNN)

Calcii Clofibras; Clofibrate de Calcium; Clofibrato de calcio.

Кальция Клофибрат

$C_{20}H_{20}CaCl_2O_6 = 467.4$ .

CAS — 39087-48-4.

**Magnesium Clofibrate** (riNN)

Clofibrato de magnesio; Clomag; Magnesii Clofibras; Magnésium, Clofibrate de; UR-112.

Магния Клофибрат

$C_{20}H_{20}Cl_2MgO_6 = 451.6$ .

CAS — 14613-30-0.

**Profile**

Clofibrate, a fibric acid derivative, is a lipid regulating drug with similar properties to bezafibrate (p.1233). It is used to reduce triglycerides and possibly total cholesterol in the management of hyperlipidaemias (p.1169), particularly in patients with hypertriglyceridaemia. Because of the incidence of adverse effects during long-term treatment it should not be used for the prophylaxis of ischaemic heart disease (see Adverse Effects, below).

The usual oral dose is 2 g daily in divided doses.

The aluminium, calcium, and magnesium salts of clofibrate have also been used.

**Adverse effects.** Large-scale, long-term studies<sup>1,2</sup> with clofibrate indicated that it was generally well-tolerated but that there was an increased incidence of serious effects, including cholelithiasis, cholecystitis, thromboembolic disorders, and certain cardiac arrhythmias. In one of the studies,<sup>2</sup> an increased mortality rate was unexpectedly found in patients taking clofibrate, producing serious concern over its long-term safety and its use is now generally restricted; the causes of death were spread over a range of malignant and non-malignant disorders.

1. The Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975; **231**: 360–80.
2. Oliver MF, *et al.* A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. *Br Heart J* 1978; **40**: 1069–1118.

**Neonatal jaundice.** Clofibrate has been used in the treatment of jaundice in term infants<sup>1,2</sup> and for prophylaxis in premature infants.<sup>1</sup> In a study<sup>1</sup> involving 93 term infants with jaundice, clofibrate 50 mg/kg as a single oral dose reduced the intensity and duration of jaundice compared with placebo. As a prophylactic measure, clofibrate was shown<sup>1</sup> to reduce the degree of jaundice in premature infants when the plasma concentration of clofibric acid reached 140 micrograms/mL within 24 hours of an oral dose. The dose required to achieve this was estimated to be 100 to 150 mg/kg.

1. Gabilan JC, *et al.* Clofibrate treatment of neonatal jaundice. *Pediatrics* 1990; **86**: 647–8.
2. Mohammadzadeh A, *et al.* Effect of clofibrate in jaundiced term newborns. *Indian J Pediatr* 2005; **72**: 123–6.

**Preparations**

**BP 2008:** Clofibrate Capsules;

**USP 31:** Clofibrate Capsules.

**Proprietary Preparations** (details are given in Part 3)

**Arg.:** Elpi; **Austria:** Arterioflexin; **Hong Kong:** Lipilim; **Port.:** Atromid-S†.

**Multi-ingredient:** **Braz.:** Lipofacton.

## Clonidine (BAN, USAN, rINN)

Clonidina; Clonidinum; Klonidiini; Klonidin; ST-155-BS. 2-(2,6-Dichloroanilino)-2-imidazoline; 2,6-Dichloro-N-(imidazolidin-2-ylidene)aniline.

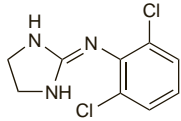
КЛОНИДИН

$C_9H_9Cl_2N_3 = 230.1$ .

CAS — 4205-90-7.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.



### Pharmacopoeias. In US.

**USP 31** (Clonidine). A white to almost white, crystalline powder. Freely soluble in alcohol and in methyl alcohol. Store in airtight containers.

### Clonidine Hydrochloride (BANM, USAN, rINN)

Clonidine, chlorhydrate de; Clonidini hydrochloridum; Hidrocloruro de clonidina; Klonidiinihydroklorid; Klonidin-hidroklorid; Klonidin-hydrochlorid; Klonidinhydroklorid; Klonidino hidrokloridas; Klonidyny chlorowodorek; ST-155.

КЛОНИДИНА Гидрохлорид

$C_9H_9Cl_2N_3.HCl = 266.6$ .

CAS — 4205-91-8.

ATC — C02AC01; N02CX02; S01EA04.

ATC Vet — QC02AC01; QN02CX02; QS01EA04.

### Pharmacopoeias. In Chin., Eur. (see p.vii), Jpn, and US.

**Ph. Eur. 6.2** (Clonidine Hydrochloride). A white or almost white crystalline powder. Soluble in water and in dehydrated alcohol. A 5% solution in water has a pH of 4.0 to 5.0.

**USP 31** (Clonidine Hydrochloride). pH of a 5% solution in water is between 3.5 and 5.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

### Adverse Effects and Treatment

Drowsiness, dry mouth, dizziness, and headache are common when starting therapy with clonidine. Constipation is also common, and other adverse effects reported include depression, anxiety, fatigue, nausea, anorexia, parotid pain, sleep disturbances, vivid dreams, impotence and loss of libido, urinary retention or incontinence, orthostatic hypotension, and dry, itching, or burning sensations in the eye. Fluid retention may occur and is usually transient, but may be responsible for a reduction in the hypotensive effect during continued treatment. Clonidine can cause rashes and pruritus, and these are more common with transdermal delivery systems. Bradycardia, including sinus bradycardia with AV block, other ECG disturbances, heart failure, hallucinations, cramp, Raynaud's syndrome, gynecomastia, and transient abnormalities in liver function tests have been reported less often. Large doses have been associated with initial increases in blood pressure and transient hyperglycaemia, although these do not persist during continued therapy.

Symptoms of overdosage include transient hypertension or profound hypotension, bradycardia, sedation, miosis, respiratory depression, convulsions, and coma. Treatment consists of general supportive measures. An alpha blocker may be given if necessary for hypertension, and atropine may be required for bradycardia and associated hypotension. Cardiac pacing may be needed rarely.

Sudden withdrawal of clonidine may produce rebound hypertension—see Precautions, below.

**Effects on the gastrointestinal tract.** Constipation is a relatively common adverse effect of clonidine. US licensed product information reporting an incidence of about 10%. Ileus or pseudo-obstruction of the bowel have been reported;<sup>1,3</sup> withdrawal of clonidine was associated with a return of bowel function to normal. Abdominal pain mimicking acute appendicitis occurred in another patient; symptoms recurred on restarting the drug and subsided on withdrawal.<sup>4</sup>

- Davidov M, *et al.* The antihypertensive effects of an imidazoline compound. *Clin Pharmacol Ther* 1967; **8**: 810–16.
- Bear R, Steer K. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1**: 197.

- Bauer GE, Hellestrand KJ. Pseudo-obstruction due to clonidine. *BMJ* 1976; **1**: 769.
- Mjörndal T, Mellbring G. Abdominal pain associated with clonidine. *BMJ* 1986; **292**: 174.

**Effects on the heart.** Clonidine has been associated with impaired atrioventricular conduction in a few patients,<sup>1,2</sup> although some of these may have had underlying conduction defects and had previously received digitalis, which may have contributed to their condition. Other ECG abnormalities may also occur. Sudden death has been reported in 3 children receiving clonidine and methylphenidate,<sup>3,4</sup> although the significance of these reports has been questioned.<sup>5</sup>

- Kibler LE, Gazes PC. Effect of clonidine on atrioventricular conduction. *JAMA* 1977; **238**: 1930–2.
- Abiuso P, Abelow G. Atrioventricular dissociation in a patient receiving clonidine. *JAMA* 1978; **240**: 108–9.
- Maloney MJ, Schwam, JS. Clonidine and sudden death. *Pediatrics* 1995; **96**: 1176–7.
- Fenichel RR. Combining methylphenidate and clonidine: the role of post-marketing surveillance. *J Child Adolesc Psychopharmacol* 1995; **5**: 155–6.
- Blackman JA, *et al.* Clonidine and electrocardiograms. *Pediatrics* 1996; **98**: 1223–4.

**Effects on mental function.** There have been occasional reports of disturbed mental state in patients given clonidine.<sup>1–4</sup>

- Lavin P, Alexander CP. Dementia associated with clonidine therapy. *BMJ* 1975; **1**: 628.
- Enoch MD, Hammad GEM. Acute hallucinosis due to clonidine. *Curr Med Res Opin* 1977; **4**: 670–1.
- Brown MJ, *et al.* Clonidine hallucinations. *Ann Intern Med* 1980; **93**: 456–7.
- Delaney J, *et al.* Clonidine-induced delirium. *Int J Cardiol* 2006; **113**: 276–8.

**Effects on the skin.** Skin reactions have been reported in up to 50% of patients using clonidine transdermal patches.<sup>1</sup> Localised erythema and irritation during early treatment are usually mild, but allergic contact dermatitis may develop.<sup>2,4</sup> Skin reactions may become commoner during prolonged treatment; although only mild skin reactions were seen in a study of transdermal clonidine during 8 to 14 weeks of treatment in 15 patients, severe skin reactions occurred after an average of 20 weeks in 4 of 5 patients who continued treatment.<sup>5</sup> Despite a claim that skin reactions were due to a component in the patch and not to clonidine itself,<sup>6</sup> positive patch tests to clonidine have been obtained.<sup>2,4</sup> Subsequent reaction to oral clonidine in patients who develop skin reactions to the transdermal patch is reported to be rare.<sup>7,8</sup>

- Carmichael AJ. Skin sensitivity and transdermal drug delivery: a review of the problem. *Drug Safety* 1994; **10**: 151–9.
- Groth H, *et al.* Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii**: 850–1.
- McMahon FG, Weber MA. Allergic skin reactions to transdermal clonidine. *Lancet* 1983; **ii**: 851.
- Boekhorst JC. Allergic contact dermatitis with transdermal clonidine. *Lancet* 1983; **ii**: 1031–2.
- Dick JBC, *et al.* Skin reactions to long-term transdermal clonidine. *Lancet* 1987; **i**: 516.
- Anonymous. Transdermal clonidine sensitiser identified? *Pharm J* 1984; **233**: 16.
- Bigby M. Transdermal clonidine dermatitis. *JAMA* 1987; **258**: 1819.
- Burris JF. Transdermal clonidine dermatitis. *JAMA* 1987; **258**: 1819–20.

**PEMPHIGOID.** Anogenital cicatricial pemphigoid has been reported<sup>1</sup> in a patient receiving long-term clonidine therapy.

- van Joost T, *et al.* Drug-induced anogenital cicatricial pemphigoid. *Br J Dermatol* 1980; **102**: 715–18.

**Hypersensitivity.** See Effects on the Skin, above.

**Overdosage.** Analysis by the UK National Poisons Information Service<sup>1</sup> of poisoning by clonidine in 133 children and 37 adults between 1976 and 1977 revealed that there were no deaths but clinical features were often severe. Supportive measures were usually adequate but atropine was often needed for severe and persistent bradycardia. Forced diuresis was not advised because hypotension could be enhanced and there was no evidence that excretion of clonidine was increased. More recently, death has been reported<sup>2</sup> in a 23-month old child.

Direct medical evaluation has been recommended<sup>3</sup> for children who have ingested the following amounts: 100 micrograms or more in those aged 4 years and under; more than 200 micrograms in those aged 5 to 8 years; and 400 micrograms or more in older children; 4 hours may be long enough to detect full onset of symptoms. However, others<sup>4</sup> believe that medical evaluation is indicated in any child who has unintentionally ingested more than a weight-appropriate therapeutic dose.

Although naloxone has been suggested as an antidote for clonidine overdose, no reversal of the hypotensive effects of clonidine 300 micrograms was noted in 6 hypertensive subjects given naloxone by intravenous infusion.<sup>5</sup> In a retrospective analysis of 47 children with clonidine poisoning, only 3 of 19 given naloxone showed definite improvement;<sup>6</sup> it was concluded that naloxone is at best an inconsistent antidote for clonidine poisoning.

Severe symptoms of overdosage have also been reported after the ingestion of clonidine transdermal patches,<sup>7</sup> and following probable subcutaneous injection during filling of an epidural pump reservoir.<sup>8</sup>

- Stein B, Volans GN. Dixarit overdose: the problem of attractive tablets. *BMJ* 1978; **2**: 667–8.

- Klein-Schwartz W. Trends and toxic effects from pediatric clonidine exposures. *Arch Pediatr Adolesc Med* 2002; **156**: 392–6.
- Spiller HA, *et al.* Toxic clonidine ingestion in children. *J Pediatr* 2005; **146**: 263–6.
- Langham M, Chan GM. Clonidine exposures, not toxicity. *J Pediatr* 2006; **148**: 565.
- Rogers JF, Cubeddu LX. Naloxone does not antagonise the antihypertensive effect of clonidine in essential hypertension. *Clin Pharmacol Ther* 1983; **34**: 68–73.
- Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; **116**: 654–8.
- Raber JH, *et al.* Clonidine patch ingestion in an adult. *Ann Pharmacother* 1993; **27**: 719–22. Correction. *ibid.*; 1143.
- Frye CB, Vance MA. Hypertensive crisis and myocardial infarction following massive clonidine overdose. *Ann Pharmacother* 2000; **34**: 611–15.

### Precautions

Clonidine should be used with caution in patients with cerebrovascular disease, ischaemic heart disease including myocardial infarction, renal impairment, occlusive peripheral vascular disorders such as Raynaud's disease, or those with a history of depression.

Clonidine causes drowsiness and patients should not drive or operate machinery where loss of attention could be dangerous.

Systemic effects also occur after epidural use and patients should be closely monitored, particularly during the first few days of therapy.

Intravenous injections of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already taking other antihypertensives such as guanethidine or reserpine.

**Withdrawal of clonidine therapy** should be gradual as stopping suddenly may cause rebound hypertension, sometimes severe. Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may also occur. Beta blockers can exacerbate the rebound hypertension and if both are being used, clonidine should not be stopped until several days after the withdrawal of the beta blocker. Patients should be warned of the risk of missing a dose or stopping the drug without consulting their doctor and should carry a reserve supply.

Although hypotension may occur during anaesthesia in clonidine-treated patients clonidine should not be withdrawn; indeed, if necessary it should be given intravenously during the operation to avoid the risk of rebound hypertension.

**Abuse.** Despite its central effects and ability to cause a form of physical dependence, WHO rated the likelihood of abuse as very low.<sup>1</sup> However, clonidine may potentiate the psychoactive effects of morphine and abuse has been reported.<sup>2</sup>

- WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser* 775 1989. Available at: [http://libdoc.who.int/trs/WHO\\_TRS\\_775.pdf](http://libdoc.who.int/trs/WHO_TRS_775.pdf) (accessed 19/08/08)
- Sullivan JT, *et al.* Does clonidine alter the abuse potential of morphine? *Clin Pharmacol Ther* 1995; **57**: 163.

**Diabetes mellitus.** The effects of clonidine on carbohydrate metabolism appear to be variable. Some studies suggest that it does not affect carbohydrate metabolism in diabetic<sup>1</sup> or non-diabetic hypertensive patients,<sup>2</sup> although there has been a report of a diabetic patient in whom clonidine was associated with elevated fasting blood-glucose values,<sup>3</sup> and increased insulin requirements were noted in a diabetic child treated with clonidine for tics.<sup>4</sup> Conversely, clonidine was associated with severe hypoglycaemia in children when used as a provocative test for growth hormone deficiency (see Growth Retardation, below). However, a study in 10 diabetic hypertensive patients found that although clonidine impaired response to an acute glucose load, it did not significantly affect diabetic control over a 10-week period.<sup>5</sup> Problems may arise when clonidine is given to diabetics with autonomic neuropathy: both severe orthostatic hypotension<sup>6</sup> and paradoxical hypertension<sup>7</sup> have been reported.

For discussion of the use of clonidine in diabetic diarrhoea see below.

- Nilsson-Ehle P, *et al.* Lipoproteins and metabolic control in hypertensive type II diabetics treated with clonidine. *Acta Med Scand* 1988; **224**: 131–4.
- Molitch ME, *et al.* Effects of antihypertensive medications on carbohydrate metabolism. *Curr Ther Res* 1986; **39**: 398–407.
- Okada S, *et al.* Effect of clonidine on insulin secretion: a case report. *J Int Med Res* 1986; **14**: 299–302.
- Mimouni-Bloch A, Mimouni M. Clonidine-induced hyperglycaemia in a young diabetic girl. *Ann Pharmacother* 1993; **27**: 980.
- Guthrie GP, *et al.* Clonidine in patients with diabetes and mild hypertension. *Clin Pharmacol Ther* 1983; **34**: 713–17.
- Moffat B. Postural hypotension induced by clonidine in insulin dependent diabetes. *BMJ* 1985; **290**: 822.
- Young E, *et al.* Paradoxical hypertension from clonidine. *Ann Intern Med* 1984; **101**: 282–3.