Pharmacopoeias. In *Jpn.*

Profile

Niceritrol, an ester of pentaerythritol and nicotinic acid, has general properties similar to those of nicotinic acid (p.1957), to which it is slowly hydrolysed. Niceritrol has been used as a lipid regulating drug in hyperlipidaemias and as a vasodilator in the treatment of peripheral vascular disease.

◊ References.

1. Owada A, *et al.* Antiproteinuric effect of niceritrol, a nicotinic acid derivative, in chronic renal disease with hyperlipidemia: a randomized trial. *Am J Med* 2003; **114:** 347–53.

Nicorandil *(BAN, USAN, rINN)*

Nicorandilum; SG-75. *N*-[2-(Nitroxy)ethyl]-3-pyridinecarboxamide.

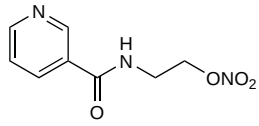
Никорандил

$C_8H_9N_3O_4$ = 211.2.

CAS — 65141-46-0.

ATC — C01DX16.

ATC Vet — QC01DX16.



Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions

Adverse effects reported with nicorandil are headache (which is usually transitory and seen at the start of therapy), cutaneous vasodilatation and flushing, nausea, vomiting, dizziness, and weakness. Rarely reported effects include myalgia, skin rashes, and oral ulceration, and there have been very rare reports of angioedema and hepatic function abnormalities. A reduction in blood pressure and/or an increase in heart rate may occur with high doses.

Nicorandil is contra-indicated in patients with cardiogenic shock, left ventricular failure with low filling pressures, and hypotension. In patients with hypovolaemia, low systolic blood pressure, acute pulmonary oedema, or acute myocardial infarction with acute left ventricular failure and low filling pressures, nicorandil should preferably be avoided but may be used with caution.

Incidence of adverse effects. Postmarketing surveillance for nicorandil was carried out by prescription-event monitoring[1] of 13 620 patients, and showed that adverse reactions occurred in 175. The most frequent was headache, occurring in 58 patients, mainly in the first month of treatment. Unspecified adverse effects occurred in 36 patients. Other effects included dizziness (19), nausea (17), malaise (13), palpitations (8), flushing and vomiting (6 each), and lassitude (4). Rare adverse effects included 3 cases each of angioedema and photosensitivity.

1. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; **8:** 197–205.

Ulceration. Nicorandil has been associated with ulceration of mucosal surfaces. Painful, large aphthous ulcers on the *tongue* and *oral mucosa* have been reported[1-3] in patients receiving nicorandil for angina. The ulcers were usually resistant to treatment but all healed when nicorandil was withdrawn. Colchicine or thalidomide treatment has improved ulcers associated with nicorandil in a few patients, but relapse occurred when the colchicine or thalidomide was stopped.[3] However, a large study[4] casts some doubt on the evidence for a causal link between nicorandil and oral ulceration, although it was suggested that this could be further investigated.

Anal ulceration has been reported[5-7] in patients taking nicorandil. Healing of the ulcers occurred in those patients in whom nicorandil was withdrawn.

Multiple ulcers of the upper and lower *gastrointestinal tract*, in addition to oral and anal ulceration, have been reported[8] in a patient taking nicorandil; all of the ulcers healed when nicorandil was stopped. There have also been several cases of *peristomal* ulceration, which resolved after stopping nicorandil.[9]

Perivulval ulceration has also been reported, and in 1 case was associated with a *cutaneous* ulcer.[10] Another patient[11] developed both perianal and leg ulcers, both of which improved rapidly when nicorandil was stopped.

1. Cribier B, *et al.* Chronic buccal ulceration induced by nicorandil. *Br J Dermatol* 1998; **138:** 372–3.
2. Desruelles F, *et al.* Giant oral aphthous ulcers induced by nicorandil. *Br J Dermatol* 1998; **138:** 712–13.
3. Agbo-Godeau S, *et al.* Association of major aphthous ulcers and nicorandil. *Lancet* 1998; **352:** 1598–9.
4. Dunn N, *et al.* Safety profile of nicorandil—prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Safety* 1999; **8:** 197–205.
5. Watson A, *et al.* Nicorandil associated anal ulceration. *Lancet* 2002; **360:** 546–7.
6. Vella M, Molloy RG. Nicorandil-associated anal ulceration. *Lancet* 2002; **360:** 1979.
7. Passeron T, *et al.* Chronic anal ulceration due to nicorandil. *Br J Dermatol* 2004; **150:** 394–6.
8. Egred M, *et al.* Nicorandil may be associated with gastrointestinal ulceration. *BMJ* 2006; **332:** 889.
9. Ogden S, *et al.* Nicorandil-induced peristomal ulcers: is nicorandil also associated with gastrointestinal fistula formation? *Br J Dermatol* 2007; **156:** 608–9.
10. Claeys A, *et al.* Cutaneous, perivulvar and perianal ulcerations induced by nicorandil. *Br J Dermatol* 2006; **155:** 494–6.
11. McKenna DJ, *et al.* Nicorandil-induced leg ulceration. *Br J Dermatol* 2007; **156:** 394–6.

Interactions

Nicorandil should not be used with phosphodiesterase type-5 inhibitors such as sildenafil as the hypotensive effect of nicorandil may be significantly enhanced.

Pharmacokinetics

Nicorandil is well absorbed from the gastrointestinal tract and maximum plasma concentrations are achieved 30 to 60 minutes after oral doses. Metabolism is mainly by denitration and about 20% of a dose is excreted in the urine mainly as metabolites. The elimination half-life is about 1 hour. Nicorandil is only slightly bound to plasma proteins.

Uses and Administration

Nicorandil is a nitrate derivative of nicotinamide (p.1957) and acts as a vasodilator. It is a potassium-channel opener (p.1155) providing vasodilatation of arterioles and large coronary arteries and its nitrate component produces venous vasodilatation through stimulation of guanylate cyclase. It thus reduces both preload and afterload, and improves coronary blood flow.

Nicorandil is given orally for prevention and long-term treatment of **angina pectoris**, including reduction of the risk of acute coronary events in high-risk patients (p.1157). The usual initial oral dose is 10 mg twice daily (or 5 mg twice daily in patients susceptible to headache), increased as necessary to a maximum of 30 mg twice daily; the usual therapeutic dose is in the range of 10 to 20 mg twice daily.

Nicorandil is also given intravenously in the management of **unstable angina** and **acute heart failure** (p.1165). For unstable angina, a solution containing 100 to 300 micrograms/mL is given by intravenous infusion in a dose of 2 mg/hour, adjusted according to response, to a maximum dose of 6 mg/hour. For acute heart failure, a solution containing 400 to 2500 micrograms/mL is used; the usual dose is 200 micrograms/kg given by intravenous injection over 5 minutes, followed by continuous intravenous infusion at a dose of 200 micrograms/kg per hour. The dosage should be adjusted according to response, within the range of 50 to 200 micrograms/kg per hour.

◊ General references.

1. Markham A, *et al.* Nicorandil: an updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs* 2000; **60:** 955–74.
2. Gomma AH, *et al.* Potassium channel openers in myocardial ischaemia: therapeutic potential of nicorandil. *Drugs* 2001; **12:** 1705–10.
3. Anonymous. Nicorandil for angina – an update. *Drug Ther Bull* 2003; **41:** 86–8.
4. Simpson D, Wellington K. Nicorandil: a review of its use in the management of stable angina pectoris, including high-risk patients. *Drugs* 2004; **64:** 1941–55.

Ischaemic heart disease. A large multicentre double-blind randomised placebo-controlled study[1] suggested that nicorandil, in addition to its anti-anginal effects, may have cardioprotective properties. The incidence of major coronary events, particularly unplanned admission for chest pain, was significantly reduced in patients with stable angina at high risk of future adverse events. Nicorandil may mimic the mechanism of ischaemic pre-conditioning, whereby a brief period of ischaemia makes the myocardium resistant to damage from a further episode,[2] but it is not clear how much this mechanism contributes to its effects. There is some evidence[3-7] that nicorandil improves outcomes when given at the time of percutaneous coronary intervention, although a large study[8] in patients with myocardial infarction failed to confirm a benefit. It has been suggested[5] that an antoxidant effect may be part of the mechanism involved.

1. The IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet* 2002; **359:** 1269–75. Correction. *ibid.*; **360:** 806.
2. Lesnefsky EJ. The IONA study: preparing the myocardium for ischaemia? *Lancet* 2002; **359:** 1262–3.
3. Matsuo H, *et al.* Evidence of pharmacologic preconditioning during PTCA by intravenous pretreatment with ATP-sensitive K+ channel opener nicorandil. *Eur Heart J* 2003; **24:** 1296–1303.
4. Ikeda N, *et al.* Nicorandil versus isosorbide dinitrate as adjunctive treatment to direct balloon angioplasty in acute myocardial infarction. *Heart* 2004; **90:** 181–5.
5. Ono H, *et al.* Nicorandil improves cardiac function and clinical outcome in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention: role of inhibitory effect on reactive oxygen species formation. *Am Heart J* 2004; **148:** E15.
6. Ishii H, *et al.* Impact of a single intravenous administration of nicorandil before reperfusion in patients with ST-segment-elevation myocardial infarction. *Circulation* 2005; **112:** 1284–8.
7. Ishii H, *et al.* Effects of intravenous nicorandil before reperfusion for acute myocardial infarction in patients with stress hyperglycemia. *Diabetes Care* 2006; **29:** 202–6.
8. Kitakaze M, *et al.* J-WIND investigators. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. *Lancet* 2007; **370:** 1483–93.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Ikorel; ***Austria:*** Dancor; ***Denm.:*** Angicor; ***Fr.:*** Adancor; Ikorel; ***India:*** Corflo; Zynicor; ***Irl.:*** Ikorel; ***Ital.:*** Andilex†; ***Jpn:*** Sigmart; ***Neth.:*** Dancor; Ikorel; ***NZ:*** Ikorel; ***Port.:*** Dancor; Nikoril; ***Spain:*** Dancor; ***Switz.:*** Dancor; ***UK:*** Ikorel.

Nicotinyl Alcohol *(BAN, USAN)*

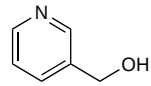
3-Hydroxymethylpyridine; Nicotinic Alcohol; Nicotinílico, alcohol; NSC-526046; NU-2121; 3-Pyridinemethanol; β-Pyridylcarbinol; Ro-1-5155. 3-Pyridylmethanol.

C_6H_7NO = 109.1.

CAS — 100-55-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.



Nicotinyl Alcohol Tartrate *(BANM)*

Alcohol nicotinílico, tartrato de; Nicotinyl Tartrate. 3-Pyridylmethanol hydrogen (2*R*,3*R*)-tartrate.

$C_6H_7NO,C_4H_6O_6$ = 259.2.

CAS — 6164-87-0.

ATC — C04AC02; C10AD05.

ATC Vet — QC04AC02; QC10AD05.

Pharmacopoeias. In *Br.*

BP 2008 (Nicotinyl Alcohol Tartrate). A white or almost white, odourless or almost odourless, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether. A 5% solution in water has a pH of 2.8 to 3.7.

Profile

Nicotinyl alcohol is a vasodilator and lipid regulating drug with general properties similar to those of nicotinic acid (p.1957), to which it is partly hydrolysed.

Nicotinyl alcohol has been given orally, as the tartrate, in the management of peripheral vascular disease, and has also been used in Ménière's disease and in hyperlipidaemias.

Preparations

BP 2008: Nicotinyl Alcohol Tablets.

Proprietary Preparations (details are given in Part 3)
Indon.: Cetacol; ***Pol.:*** Nicotol†.

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

Nifedipine *(BAN, USAN, rINN)*

Bay-a-1040; Nifedipiini; Nifedipin; Nifedipina; Nifedipinas; Nifédipine; Nifedipino; Nifedipinum. Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate.

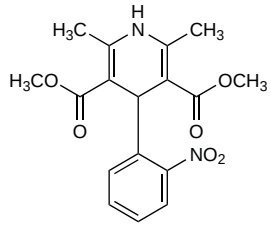
Нифедипин

$C_{17}H_{18}N_2O_6$ = 346.3.

CAS — 21829-25-4.

ATC — C08CA05.

ATC Vet — QC08CA05.



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

Ph. Eur. 6.2 (Nifedipine). A yellow crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Solutions should be prepared in the dark or under light of wavelength greater than 420 nm, immediately before use. Protect from light.

USP 31 (Nifedipine). A yellow powder. Practically insoluble in water; soluble 1 in 10 of acetone. When exposed to daylight or to certain wavelengths of artificial light it is converted to a nitrosophenylpyridine derivative, while exposure to ultraviolet light leads to formation of a nitrophenylpyridine derivative. Store in airtight containers. Protect from light.

Stability. Yellow food colourings such as curcumin have been used[1] to slow photodegradation of nifedipine solutions. An extemporaneously prepared solution of nifedipine in a peppermint-flavoured vehicle was reported[2] to be stable for at least 35 days when stored in amber glass bottles.

1. Thoma K, Klimek R. Photostabilization of drugs in dosage forms without protection from packaging materials. *Int J Pharmaceutics* 1991; **67:** 169–75.
2. Dentinger PJ, *et al.* Stability of nifedipine in an extemporaneously compounded oral solution. *Am J Health-Syst Pharm* 2003; **60:** 1019–22.

Adverse Effects

The most common adverse effects of nifedipine are associated with its vasodilator action and often diminish on continued therapy. They include dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, and palpitations. Nausea and other gastrointestinal disturbances, increased micturition frequency, lethargy, eye pain, visual disturbances, and mental depression have also occurred. A paradoxical increase in ischaemic chest pain may occur at the start of treatment and in a few patients excessive fall in blood pressure has led to cerebral or myocardial ischaemia or transient blindness.

There have been reports of rashes (including erythema multiforme), fever, and abnormalities in liver function, including cholestasis, due to hypersensitivity reactions. Gingival hyperplasia, myalgia, tremor, and impotence have been reported.

Some tablets formulated for once-daily use are covered in a membrane which is not digested and may cause gastrointestinal obstruction; bezoars may rarely occur.

Overdosage may be associated with bradycardia and hypotension; hyperglycaemia, metabolic acidosis, and coma may also occur.

Nifedipine has been reported to be teratogenic in *animals*.

Effects on mortality. Since 1995 there have been reports and reviews that have implicated calcium-channel blockers (particularly short-acting nifedipine and high doses) in increasing cardiovascular[1] and overall mortality.[2] Possible links with cancer, haemorrhage, and depression and suicide are discussed separately (see Cancer Occurrence, Effects on the Blood, and Effects on Mental Function, below, respectively).

In response, the US National Heart, Lung, and Blood Institute issued a statement warning that short-acting nifedipine should be used with great caution (if at all), especially at higher doses, in the treatment of hypertension, angina, and myocardial infarction,[3] and in some countries short-acting nifedipine preparations have been withdrawn. However, there has been much debate and controversy over the reports that questioned the safety of calcium-channel blockers.[4-6]

A review by the WHO/ISH pointed out that much of the evidence for adverse effects comes from observational studies or small randomised studies and concluded that, as there was insufficient evidence to confirm either benefit or harm, recommendations on the management of angina, hypertension, and myocardial infarction should remain unchanged.[7] In addition, many of the studies that led to the negative reports used the older short-acting calcium-channel blockers. The calcium-channel blockers used now are largely modified-release formulations of short half-life blockers or are calcium-channel blockers with long half-lives.

Studies completed after the WHO/ISH review have generally failed to show any increase in mortality with calcium-channel blockers, although their effects on cardiovascular outcomes remain less clear. A placebo-controlled study (SYST-EUR) reported[8] a reduction in incidence of stroke and cardiovascular events in 4695 elderly patients treated with nitrendipine (and enalapril and hydrochlorothiazide in addition if necessary) for isolated systolic hypertension, while a retrospective cohort study[9] in post-myocardial infarction patients failed to show any increase in mortality after one year in those receiving calcium-channel blockers. Another cohort study[10] in patients with hypertension also found no overall increase in mortality with calcium-channel blockers, although there was a trend towards a higher rate with short-acting formulations. A meta-analysis[11] of randomised studies comparing calcium-channel blockers with other antihypertensives in patients with hypertension suggested that calcium-channel blockers were associated with an increased risk of major cardiovascular events (except stroke) although all-cause mortality was not increased. However, large, long-term studies have found no difference in cardiovascular outcomes or overall mortality in patients randomised to amlodipine or chlortalidone,[12] while a lower incidence of cardiovascular events was reported for amlodipine compared with atenolol.[13] A long-term study[14] of nifedipine added to standard therapy in patients with stable angina also found no increased mortality, and there was a reduced need for coronary interventions.

1. Psaty BM, *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274:** 620–5.
2. Furberg CD, *et al.* Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; **92:** 1326–31.
3. McCarthy M. US NIH issues warning on nifedipine. *Lancet* 1995; **346:** 689–90.
4. Opie LH, Messerli FH. Nifedipine and mortality: grave defects in the dossier. *Circulation* 1995; **92:** 1068–72.
5. Grossman E, Messerli FH. Calcium antagonists in cardiovascular disease: a necessary controversy but an unnecessary panic. *Am J Med* 1997; **102:** 147–9.
6. Stanton AV. Calcium channel blockers. *BMJ* 1998; **316:** 1471–3.
7. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
8. Staessen JA, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350:** 757–64. Correction. *ibid.*; 1636.
9. Jollis JG, *et al.* Calcium channel blockers and mortality in elderly patients with myocardial infarction. *Arch Intern Med* 1999; **159:** 2341–8.
10. Abascal VM, *et al.* Calcium antagonists and mortality risk in men and women with hypertension in the Framingham Heart Study. *Arch Intern Med* 1998; **158:** 1882–6.
11. Pahor M, *et al.* Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomised controlled trials. *Lancet* 2000; **356:** 1949–54.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.
13. Dahlöf B, *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366:** 895–906.
14. Poole-Wilson PA, *et al* on behalf of the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system) investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004; **364:** 849–57.

Carcinogenicity. An observational study carried out between 1988 and 1992 suggested that calcium-channel blockers were associated with an increased risk of cancer.[1] Subsequent studies have failed to support this finding.[2-7] A review by the WHO/ISH concluded that there is no good evidence that calcium-channel blockers increase cancer risk,[8] and the biological basis for an effect of calcium-channel blockers on cancer risk has also been questioned.[9] The large, long-term, randomised Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT)[10] found no increase in the incidence of cancer in patients receiving a calcium-channel blocker (amlodipine) compared with those receiving a diuretic (chlortalidone).

1. Pahor M, *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348:** 493–7.
2. Jick H, *et al.* Calcium-channel blockers and risk of cancer. *Lancet* 1997; **349:** 525–8.
3. Rosenberg L, *et al.* Calcium channel blockers and the risk of cancer. *JAMA* 1998; **279:** 1000–4.
4. Braun S, *et al.* Calcium channel blocking agents and risk of cancer in patients with coronary heart disease. *J Am Coll Cardiol* 1998; **31:** 804–8.
5. Sajadieh A, *et al.* Verapamil and risk of cancer in patients with coronary artery disease. *Am J Cardiol* 1999; **83:** 1419–22.
6. Meier CR, *et al.* Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. *Arch Intern Med* 2000; **160:** 349–53.
7. Cohen HJ, *et al.* Calcium channel blockers and cancer. *Am J Med* 2000; **108:** 210–15.
8. Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hypertens* 1997; **15:** 105–15.
9. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? *J Am Coll Cardiol* 1999; **34:** 1857–66.
10. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:** 2981–97. Correction. *ibid.*; **289:** 178.

Effects on the blood. Treatment with nifedipine significantly reduces platelet aggregation *in vitro*[1] and results indicating inhibition of platelet function in healthy subjects receiving oral (but not intravenous) nifedipine have been reported.[2,3] Thus, concern has been expressed[4] that calcium-channel blockers may have the potential to produce haemorrhagic complications in surgical patients (specifically, those undergoing coronary bypass surgery). Major surgical bleeding was associated with nimodipine in patients undergoing cardiac valve replacement,[5] although it has been used in other situations apparently without an increased risk of bleeding.[6]

Conflicting results have been reported with regard to the risk of gastrointestinal bleeding. A prospective cohort study in 1636 elderly hypertensive patients,[7] and a subsequent case-control study,[8] reported that calcium-channel blockers were associated with an increased risk of gastrointestinal haemorrhage compared with beta blockers. However, it was suggested[9] that this may have been due to a protective effect of beta blockers rather than an adverse effect of calcium-channel blockers, and another study[10] also suggested that the risk of gastrointestinal bleeding was not materially increased by calcium-channel blockers.

Calcium-channel blockers have also been associated with a number of blood dyscrasias; there have been case reports of aplastic anaemia with nifedipine,[11] and of thrombocytopenia with amlodipine[12] and with diltiazem.[13,14]

1. Ośmiałwska Z, *et al.* Effect of nifedipine monotherapy on platelet aggregation in patients with untreated essential hypertension. *Eur J Clin Pharmacol* 1990; **39:** 403–4.
2. Winther K, *et al.* Dose-dependent effects of verapamil and nifedipine on in vivo platelet function in normal volunteers. *Eur J Clin Pharmacol* 1990; **39:** 291–3.
3. Walley TJ, *et al.* The effects of intravenous and oral nifedipine on ex vivo platelet function. *Eur J Clin Pharmacol* 1989; **37:** 449–52.
4. Becker RC, Alpert JS. The impact of medical therapy on hemorrhagic complications following coronary artery bypass grafting. *Arch Intern Med* 1990; **150:** 2016–21.
5. Wagenknecht LE, *et al.* Surgical bleeding: unexpected effect of a calcium antagonist. *BMJ* 1995; **310:** 776–7.
6. Öhman J and others. Surgical bleeding and calcium antagonists. *BMJ* 1995; **311:** 388–9. [Several letters.]
7. Pahor M, *et al.* Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347:** 1061–5.
8. Kaplan RC, *et al.* Use of calcium channel blockers and risk of hospitalized gastrointestinal tract bleeding. *Arch Intern Med* 2000; **160:** 1849–55.
9. Suissa S, *et al.* Antihypertensive drugs and the risk of gastrointestinal bleeding. *Am J Med* 1998; **105:** 230–5.
10. Kelly JP, *et al.* Major upper gastrointestinal bleeding and the use of calcium channel blockers. *Lancet* 1999; **353:** 559.
11. Laporte J-R, *et al.* Fatal aplastic anaemia associated with nifedipine. *Lancet* 1998; **352:** 619–20.
12. Usalan C, *et al.* Severe thrombocytopenia associated with amlodipine treatment. *Ann Pharmacother* 1999; **33:** 1126–7.
13. Lahav M, Arav R. Diltiazem and thrombocytopenia. *Ann Intern Med* 1989; **110:** 327.
14. Michalets EL, Jackson DV. Diltiazem-associated thrombocytopenia. *Pharmacotherapy* 1997; **17:** 1345–8.

Effects on the brain. Cerebral ischaemia[1,2] has been reported in small numbers of patients given nifedipine.

1. Nobile-Orazio E, Sterzi R. Cerebral ischaemia after nifedipine treatment. *BMJ* 1981; **283:** 948.
2. Schwartz M, *et al.* Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose. *Arch Intern Med* 1990; **150:** 686–7.

Effects on carbohydrate metabolism. There are reports of deterioration of diabetes,[1] reduction in glucose tolerance,[2] and development of diabetes[1,3] in patients given nifedipine. Nifedipine has also been reported to increase plasma-glucose concentrations.[3,4] However, other reports and studies have found no