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.

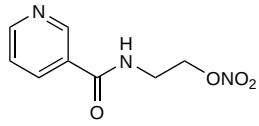
Никорандил

$C_8H_9N_3O_4$ = 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)*

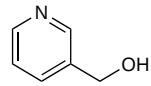
3-Hydroxymethylpyridine; Nicotinic Alcohol; Nicotinílico, alcohol; NSC-526046; NU-2121; 3-Pyridinemethanol; β-Pyridylcarbinol; Ro-1-5155. 3-Pyridylmethanol.

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.