

Data Sheet

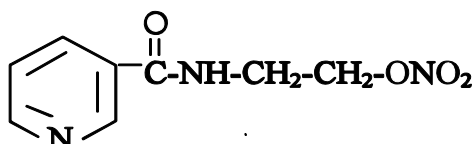
IKOREL[®]

NAME OF THE MEDICINE

Non-proprietary Name

Nicorandil

Chemical Structure



CAS Number

65141-46-0

DESCRIPTION

Nicorandil is N-(2-hydroxyethyl)-nicotinamide nitrate (ester). It is a white crystalline powder or white needles with a faint, characteristic odour. It is freely soluble in acetone, methanol, ethanol and acetonitrile; soluble in ethylacetate and chloroform; sparingly soluble in water; slightly soluble in ether.

C₈H₉N₃O₄. Molecular Weight: 211.18.

Nicorandil tablets also contain maize starch, croscarmellose sodium, stearic acid and mannitol as inactive ingredients.

PHARMACOLOGY

Uses

Pharmacodynamics

Nicorandil, a nicotinamide ester, is a vasodilator agent with a compound and balanced mechanism of action as a potassium channel activator with adjunctive nitrate effects.

Potassium channel opening effects a titratable and sustained dilating action on both arterial and coronary vasculature, including both coronary artery conductance and resistance vessels, to reduce cardiac afterload. The nitrate moiety effect dilates venous capacitance vessels to decrease cardiac preload.

Nicorandil has a marked coronary spasmolytic action, exerting a direct effect on both normal and stenotic segments of coronary arteries without significant effects on myocardial contractility or conductivity, or the development of the so-called "steal phenomenon". Furthermore, the reduction of end-diastolic pressure and wall tension decreases the extravascular component of vascular resistance. This results in an improved oxygen balance in the myocardium and improved blood flow in the post-stenotic areas of the myocardium.

Pharmacokinetics

After oral administration, nicorandil is absorbed rapidly and completely from the gastrointestinal tract. The absolute bioavailability is about 75%. There is no significant hepatic first-pass effect.

Maximum plasma concentrations are reached after about 30-60 minutes. The plasma concentration (and the area under the curve) show a linear proportionality to the dose. The drug disposition processes (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain stable whatever the dose in the therapeutic range.

Nicorandil is only slightly bound to human plasma proteins (free fraction estimated at about 75%). The decrease in plasma concentration reveals two different processes:

1. a rapid elimination phase with a half-life of about 1 hour, which covers about 96% of the plasma concentration
2. a slow elimination phase occurring between the 8th and the 24th hour following the oral dose

Metabolism takes place mainly via denitration of the molecule with the denitrated product then merging into the nicotinamide pathway. Nicorandil and its metabolites are mainly excreted by the kidney. About 21% of the administered dose is eliminated through the urine with about 1% as the unchanged compound and the remainder as mainly the denitrated metabolite (about 7%) and derivatives following denitration (eg. nicotinic acid, nicotinamide, N-methylnicotinamide and nicotinic acid).

Steady state is rapidly achieved during twice daily administration.

No clinically relevant modifications of the nicorandil pharmacokinetic profile is evidenced in populations at risk such as elderly people, or patients with liver disease or chronic renal failure. Moreover, the metabolism of nicorandil does not appear to significantly interact with that of cimetidine, rifampicin, anticoagulants, digoxin or other antianginal treatments.

CLINICAL TRIALS

Clinical studies employing exercise tolerance test as major end point show that nicorandil at doses 10 to 20 mg twice daily is as efficacious as other anti-anginal agents (including diltiazem, nifedipine, isosorbide mononitrate, isosorbide dinitrate, propranolol, metoprolol and atenolol) in treating patients with chronic stable angina. Most of the controlled, comparative studies were of limited duration (= 3 months) and included patients with anginal attacks usually less than five per week. Data on the influence of nicorandil on myocardial infarction and mortality was limited. There is a trend to increased anti-anginal efficacy when nicorandil is added to β -blocker or calcium channel blocker, but this was not statistically significant. Efficacy testings at 2-hour and 12-hour suggest a prolonged anti-anginal effect of nicorandil which is longer than nicorandil's half-life. Some studies did investigate three times daily dosing with nicorandil, but this did not appear to present any advantages over twice daily dosing, although no strictly comparative studies of different dosing frequencies were performed. Long-term uncontrolled studies show that nicorandil maintains its efficacy with no evidence of tolerance developing up to 2 years after commencement of therapy.

The efficacy of nicorandil in preventing coronary artery spasm in patients with vasospastic angina was compared to nifedipine in provocation test using methylergometrine. Nicorandil was shown to be at least as effective as nifedipine. The benefit of nicorandil in unstable angina has not yet been fully established.

Laboratory Safety Monitoring

Abnormal laboratory test results were very infrequent with nicorandil. However, in the short and medium term studies, the testings were performed at the beginning of the study (as a baseline) and at its termination (up to 3 months later). Thus transient laboratory abnormalities could have been missed.

Haemodynamic Safety Monitoring

In hypertensive patients (n = 12), single doses of nicorandil (10, 20 and 30 mg) compared to placebo produced an acute and significant reduction in both systolic and diastolic, supine and upright blood pressure which peaked at 4 to 6 hours. After 24 hours, only the 30 mg dose continued to have a significant effect. Heart rate did not alter significantly. In patients with ischaemic heart disease undergoing routine cardiac catheterisation, a single dose of 40 mg nicorandil caused significant decreases in aortic systolic and diastolic pressure which occurred 30

minutes after dosing and reached maximum at 45 minutes. When nicorandil was administered in doses of 60 mg and, to a lesser extent 40 mg, dizziness and hypotension became relatively common side effects. In normotensive volunteers, a single 10 mg and 20 mg nicorandil dose did not affect blood pressure.

INDICATIONS

Nicorandil is indicated for the symptomatic treatment of stable angina pectoris that is inadequately controlled or have a contraindication or intolerance to first-line anti-anginal therapies.

CONTRAINDICATIONS

- known or idiosyncratic hypersensitivity to nicorandil, nicotinamide, nicotinic acid or any of the excipients in this product
- cardiogenic shock
- in patients with severe hypotension or with a risk of developing severe hypotension including acute myocardial infarction with acute left ventricular failure and low filling pressures and hypovolaemia.
- hypotension
- in patients receiving any soluble guanylate cyclase stimulators (see Interactions).

Due to the risk of severe hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated (see Interactions).

PRECAUTIONS

Nicorandil should be used with caution in patients who present with low systolic blood pressure (eg. below 100 mm Hg). The use of nicorandil in patients with cardiogenic shock, or acute myocardial infarction with acute left ventricular failure and low filling pressures should be avoided.

If mouth ulceration, stomatitis or persistent or severe buccal ulcerations appear, this drug should be discontinued and appropriate measures taken.

Caution is advised for the use of nicorandil in patients with glaucoma.

The hypotensive effect of other vasodilators, tricyclic antidepressants or alcohol can be increased by administration in combination with nicorandil.

Nicorandil may lower the blood pressure of hypertensive patients and therefore should be used with care when prescribed with antihypertensive drugs.

Gastrointestinal, skin, mucosal, corneal and conjunctival ulcerations have been reported with nicorandil (see Adverse Effects). Ulceration may occur at different locations in the same patient. Gastrointestinal haemorrhage secondary to gastrointestinal ulceration has also been reported with nicorandil. Weight loss has been reported in association with gastrointestinal ulcerations. Occurrence of persisting ulcers should lead to drug discontinuation because the ulcers may be refractory to treatment while taking nicorandil. (see Adverse Effects).

If mouth ulceration, stomatitis or persistent or severe buccal ulcerations appear, this drug should be discontinued and appropriate measures taken.

Based on available information, the time between starting nicorandil use and the onset of ulceration ranges from shortly after initiating nicorandil treatment to several years after starting nicorandil.

Patients with diverticular disease may be at particular risk of fistula formation or bowel perforation during nicorandil treatment.

Gastrointestinal perforations in the context of concomitant use of nicorandil and corticosteroids have been reported. Caution is advised when concomitant use is considered.

Gastrointestinal ulcerations and haemorrhage in the context of concomitant use of acetylsalicylic acid or Non Steroidal Anti Inflammatory Drugs (NSAIDs) with nicorandil have also been reported. Caution is advised when concomitant use is considered.

Nicorandil should be used with care in combination with other medical products that may increase potassium levels because hyperkalaemia has been reported with nicorandil (see Adverse Effects).

Effects on the Ability to Drive and Operate Machinery

Nicorandil, as with other vasodilators, may cause dizziness and patients should be advised not to drive or operate any machinery, should dizziness occur. This is especially the case in combination with alcohol.

Hepatic Impairment

The pharmacokinetics of nicorandil in cirrhotic patients (n = 8) was compared with age matched controls (n = 8) after a single 10 mg oral tablet and IV dose of 0.1 mg/kg. In cirrhotic patients, the AUC after oral dosing was less and $t_{1/2}$ was longer (1.6 h versus 1.1 h) than those for the control groups. As the changes after oral dosing were minor, it is unlikely that dosage adjustment would be necessary in patients with stabilised liver impairment based solely on pharmacokinetic consideration. However, as nicorandil is primarily metabolised in the liver, the need to reduce the nicorandil dose in patients with severe liver disease cannot be excluded to prevent the potential accumulation following repeated dosing.

Renal Impairment

The pharmacokinetics of nicorandil was investigated in 3 groups of subjects with varying degrees of renal function (GFR > 80 mL/min, n = 6; 20-80 mL/min, n = 8 and < 20 mL/min, n = 7) receiving 20 mg of nicorandil twice daily for 5 days. Renal impairment did not significantly modify the rate and extent of nicorandil absorption. No correlation exists between nicorandil clearance and creatinine clearance. Thus the decrease of glomerular filtration rate does not significantly alter the disposition profile of nicorandil; thus no dosage adjustment is necessary in patients with renal impairment.

Use in Pregnancy

Category B3. Nicorandil has not been studied in pregnant women. Although animal studies have shown that nicorandil is not teratogenic, it has been shown to increase pre-implantation loss at oral doses of 40 mg/kg/day in rats and to increase fetal mortality at doses of 100 mg/kg/day. The significance of these findings is unknown. Nicorandil should not be used during pregnancy unless it is considered essential by the physician.

Use in Lactation

It is not known whether nicorandil is excreted in milk. Animal studies have shown that nicorandil increases perinatal mortality at 50 mg/kg/day. The significance of this finding to human use is unclear. Thus, nicorandil is not recommended for use during breast feeding.

Paediatric Use

Nicorandil is not recommended for use in children as its safety and efficacy in children have not been established.

Use in Elderly

The pharmacokinetics of nicorandil in 12 elderly patients was compared with 12 young adults receiving 10 mg twice daily for 8 days. There were no clinically relevant differences in the nicorandil pharmacokinetic parameters. Results from this study suggest that dosage adjustment for elderly patients may not be necessary. However, as with all medicines, use of the lowest effective dose is recommended.

Carcinogenicity

Mutagenicity and carcinogenicity studies did not reveal any adverse effect of nicorandil under the experimental conditions. Nicorandil has shown no genotoxic potential in a series of assays for gene mutations and chromosomal damage. Nicorandil has shown no carcinogenic potential in two

year old studies in mice (100 mg/kg/day) and rats (20 and 40 mg/kg/day for male and female rats respectively). Nicorandil did not affect the fertility of male and female rats at oral doses up to 100 mg/kg/day.

Interactions with Food

Although food has been shown to delay the absorption of nicorandil (16%), it does not affect the extent of absorption. Thus nicorandil tablets can be taken with meals.

Interactions with other Medicines

Smoking

The effect of smoking on the pharmacokinetics of nicorandil has not been studied.

Cimetidine

The effects of cimetidine (400 mg twice daily for 7 days) on the pharmacokinetics of nicorandil (20 mg twice daily given for 7 days alone and then another 7 days with cimetidine) were assessed in 12 healthy volunteers. The co-administration of cimetidine with nicorandil did not significantly modify the rate of absorption of nicorandil or other pharmacokinetic parameters (such as C_{max} , t_{max} and urinary excretion parameters). Thus, cimetidine does not significantly inhibit the liver enzymes involved in the metabolism of nicorandil. A dose adjustment of nicorandil in patients treated concomitantly with cimetidine, a drug known to be an inhibitor of liver drug metabolising enzymes, may not be necessary.

Rifampicin

The influence of rifampicin (600 mg/day) on nicorandil (20 mg twice daily) pharmacokinetics was assessed in 16 male volunteers. Rifampicin did not modify significantly the pharmacokinetics of nicorandil, except for a slight decrease of $t_{1/2\beta}$. Therefore, rifampicin does not modify significantly the extent of nicorandil metabolism or its disposition pattern. As a consequence, a dose adjustment of nicorandil in patients treated concomitantly with rifampicin, a drug known to be a potent inducer of liver drug-metabolising enzymes, may not be necessary.

Combination with Nitrate

Although clinical experience to-date suggests that long-acting nitrate administered concomitantly with nicorandil does not appear to alter nicorandil's clinical acceptability, however, as nicorandil contains a nitrate moiety, caution should be taken for the likelihood of additive hypotensive effects.

Other Medicines

Co-administration of nicorandil does not affect the anticoagulation effect of warfarin. No pharmacological and/or pharmacokinetic interaction has been observed in animal and human studies when nicorandil is administered concomitantly with beta-blockers, calcium antagonists, digoxin, a combination of digoxin/furosemide, acenocoumarol, rifampicin, and cimetidine. However, the possibility that nicorandil may potentiate the effect of tricyclic antidepressants, antihypertensive drugs or other vasodilators, particularly alcohol, can not be excluded.

Phosphodiesterase 5 inhibitors

As hypotensive effects of nitrates or nitric oxide donors are potentiated by phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) the concomitant use of nicorandil and phosphodiesterase 5 inhibitors is contraindicated (see Contraindications). Combination use can lead to a serious fall in blood pressure.

Soluble Guanylate Cyclase Stimulators

Nicorandil is contraindicated in the concomitant use of soluble guanylate cyclase stimulators such as riociguat, since it can lead to a serious fall in blood pressure (see Contraindications).

Corticosteroids

Gastrointestinal perforations in the context of concomitant use of nicorandil and corticosteroids or acetylsalicylic acid have been reported. Caution is advised when concomitant use is considered.

ADVERSE EFFECTS

The following CIOMS frequency rating is used:

very common	≥ 1/10 (10%)
common	≥ 1/100 (1%) and < 1/10 (10%)
uncommon	≥ 1/1000 (0.1%) and < 1/100 (1%)
rare	≥ 1/10000 (0.01%) and < 1/1000 (0.1%)
very rare	< 1/10000 (< 0.01%)

Body as a Whole

common: abdominal pain, lethargy, back pain, chest pain, infection, feeling of weakness

uncommon: malaise, face oedema, fever, leg pain, neck pain, pain, pain in the arm

Cardiovascular System

common: increase in heart rate particularly following the administration of nicorandil in high doses, angina pectoris, hypertension, palpitations, vasodilation/flush

uncommon: decrease in blood pressure particularly following the administration of nicorandil in high doses, postural hypotension, hypotension, tachycardia, arrhythmia, myocardial infarction, syncope, peripheral vascular disorder

Gastrointestinal Disorders

common: dyspepsia, nausea, vomiting

uncommon: anorexia, diarrhoea, constipation, gastrointestinal disorder

rare: gastrointestinal ulcerations, such as stomatitis/mouth ulceration, tongue ulcers, small intestine ulcer, large intestine ulcer and anal ulcer. These ulcers, if advanced, may develop into perforation, fistulating disease, or abscess formation or may lead to gastrointestinal haemorrhage or weight loss (see Precautions).

Musculoskeletal and Connective Tissue Disorders

common: myalgia

Nervous System

Very common: headache, usually transient in nature, especially when treatment is initiated.

common: dizziness, vertigo

uncommon: insomnia, sleep disorder, nervousness, paraesthesia, somnolence, depression

Headache is the most commonly reported adverse event (up to 36.4%). It is dose-related, and usually occurs during the first week of treatment and tends to diminish with time. Occasionally, headache may be severe and prolonged. In clinical trials, 5.3% of patients discontinued nicorandil treatment due to headache. Careful dose titration, using low starting dose (5 mg twice daily) for even two days, has significantly reduced the incidence of headache and number of patients discontinuing treatment due to headache.

Respiratory System

common: bronchitis, dyspnoea, respiratory disorder

uncommon: epistaxis, increased cough

Metabolic Disorder

uncommon: peripheral oedema, oedema

rare: hepatic function abnormalities

very rare: liver disorders such as hepatitis, cholestasis, or jaundice

Skin and Subcutaneous Tissue Disorders

uncommon: pruritus, different types of rash, sweating

very rare: angioedema

Eye Disorder

Very rare: conjunctivitis, conjunctival ulcer and corneal ulcer

Special Senses

uncommon: vestibular disorder

rare: tinnitus

The following additional adverse reactions have been reported during postmarketing experience; they are derived from spontaneous reports and therefore, the frequency of these adverse reactions is not known:

Skin and Subcutaneous Tissue Disorders

Skin and mucosal ulcerations (mainly peri-anal ulcerations, genital ulcerations and para-stomal ulcerations)

Eye Disorders

Diplopia

Blood and Lymphatic System Disorders

Thrombocytopenia has been rarely reported in association with nicorandil treatment

Metabolism and Nutrition Disorders

Hyperkalaemia (see Precautions)

DOSAGE AND ADMINISTRATION

The usual therapeutic range is 10 to 20 mg twice daily.

The usual starting dose is 10mg twice daily, in the morning and in the evening preferably, and should be titrated upwards in accordance with patients' needs, response and tolerance up to 40mg twice daily, if necessary. An even lower starting dose of 5mg twice daily may be used in patients particularly prone to headache.

Elderly

There are no special dosage requirements for elderly patients, but as with all medicines the lowest effective dose should be used. Nicorandil should be administered with care, using low starting dosages, in the elderly.

Children

Not recommended.

Diabetes, Renal or Hepatic Dysfunction

Nicorandil should be used with caution in patients with serious hepatic dysfunction.

OVERDOSAGE

No data are available concerning overdosage of nicorandil in humans. However, in the case of overdosage, peripheral vasodilation with a fall in blood pressure and reflex tachycardia can be expected. In such an event, monitoring of cardiac function and general supportive measures should be used. If not successful, circulating plasma volume should be increased by substitution of fluid. In life-threatening situations, administration of vasopressors should be considered.

Contact the Poisons Information Centre on 0800 POISON or 0800 764 766 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

10 mg tablets: Off-white round, scored, plain on one side, and IK10 on the other. 60s

20 mg tablets: Off-white round, scored, plain on one side, and IK20 on the other. 60s

Store below 25°C. Store in a dry place.

NAME AND ADDRESS

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MEDICINE CLASSIFICATION

Prescription Medicine

DATE OF PREPARATION

25 November 2016