PRODUCT INFORMATION
IKOREL®

NAME OF THE MEDICINE
Non-proprietary Name
Nicorandil

Chemical Structure

C8H9N3O4. Molecular Weight: 211.18.

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.

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

PHARMACOLOGY
Pharmacodynamics
Nicorandil, a potassium channel opener with nitrate moiety, is an antianginal agent with a dual mechanism of action:
(i) It opens ATP-dependent potassium (KATP) channels in vascular smooth muscle and hence causes a hyperpolarisation of the smooth muscle cells. This leads to arterial dilatation and afterload reduction.
(ii) Due to its nitrate moiety, nicorandil also relaxes vascular smooth muscle, particularly in the venous vascular system, via an increase in intracellular cyclic GMP. This results in an increase pooling in capacitance vessels with a decrease in preload.

Nicorandil has been shown to exert a direct effect on the coronary arteries, both on normal and stenotic segments, without leading to a steal phenomenon. Furthermore, the reduction of end-diastolic pressure and wall tension decreases the extravascular component of vascular resistance. Ultimately, this results in an improved oxygen balance in the myocardium and improved blood flow in the post-stenotic areas of the myocardium and, thus, reducing infarct size. Nicorandil has no direct effect on myocardial contractility, cardiac conduction and rhythm. Furthermore, nicorandil has demonstrated a powerful spasmolytic activity in both in-vitro and in-vivo studies and reverses coronary spasm induced by methacholine or noradrenaline.

The activation of ATP-dependent K-channels by nicorandil or other potassium channel openers causes relaxation of all types of smooth muscle. In an asthma model, the three known K-channel openers (cromakalim, pinacidil and nicorandil) were compared. Nicorandil was weakest of the
three in terms of bronchodilator activity. Results from clinical trials with nicorandil have not shown any deterioration of airways function during treatment.

Nicorandil has no effect on renal function and electrolytes. Following 1-year therapy of nicorandil, plasma levels of sodium, potassium, creatinine and blood urea nitrogen remained unchanged.

Nicorandil has specificity for the KATP channels in the blood vessels and not for the KATP channels present in the pancreas. At the doses used for its vasodilatory action, nicorandil does not produce hyperpolarisation on the β-cells in the pancreas and therefore does not affect insulin secretion and hence blood glucose. There was no change in plasma glucose levels in patients receiving nicorandil therapy for 1 year. Animal studies show that the vascular effects of potassium channel openers can be inhibited by glibenclamide, however to inhibit the vascular effect of potassium channel openers the sulphonylureas have to be administered at doses 100 to 1000 times higher than the therapeutic dose. There was no change in plasma lipids in patients receiving nicorandil therapy.

The pharmacological data and clinical findings give no indication of a direct interaction between nicorandil and the sympathetic-adrenergic system or neurohumoural mechanism. Indirect activation of the adrenergic system and the renin-angiotensin system may occur as a result of excessive vasodilation or reduction in blood pressure, but only at doses higher than the therapeutic recommended dosage.

Pharmacokinetics

Absorption

After oral administration, nicorandil is absorbed rapidly and maximum plasma concentrations are reached after about 30-60 minutes. The absolute bioavailability of nicorandil is about 75% indicating that nicorandil is well absorbed from the gastrointestinal tract without undergoing significant hepatic first-pass effect. The plasma concentrations (and the area under the curve) show linear proportionality to the dose (5 mg to 40 mg). The drug disposition parameters (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain unchanged within the therapeutic dose range. Following repeated dosing of 10 or 20 mg nicorandil twice daily, higher nicorandil concentrations were observed at Day 10 compared to Day 1. Accumulation ratios (AUCDay 10/AUCDay 1) of 1.7 for 10 mg and 2.0 for 20 mg were observed. Steady-state plasma concentrations of nicorandil usually are reached within approximately 96-120 h after twice daily dosing.

Distribution

The decrease in plasma concentration reveals two distinct phases:

- a rapid elimination phase with a half-life of about 1 hour responsible for approximately 96% of the decline in the plasma concentration;
- a slow elimination phase occurring between the 8th and the 24th hour following oral dosing.

Nicorandil is not extensively bound to human plasma proteins (free fraction estimated to be about 75%).

Metabolism and Excretion

Metabolism occurs mainly by denitration of the molecule. The denitrated product is then further metabolised via the nicotinamide pathway. Nicorandil and its metabolites are mainly excreted in the urine. Only 1% of the administered dose was excreted in the faeces, whereas more than 60% of the administered dose was eliminated in the urine 24 hours after dosing. Only approximately 1% of nicorandil is excreted unchanged in the urine, and the remaining being mainly the denitrated metabolite (9%) and its derivatives (e.g. nicotinuric acid 6%, nicotinamide 1%, N-methylnicotinamide < 1% and nicotinic acid < 1%).
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 treatment of chronic stable angina pectoris.

CONTRAINDICATIONS
- known or idiosyncratic hypersensitivity to nicorandil, nicotinamide and nicotinic acid
- cardiogenic shock
- hypotension
- acute myocardial infarction with acute left ventricular failure and low filling pressures

Due to the risk of severe hypotension, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors (e.g sildenafile, tadalafil, vardenafil) is contraindicated.
PRECAUTIONS
Nicorandil should be used with caution in patients who may have blood volume depletion or in those who present low systolic blood pressure (e.g. 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.

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

Gastrointestinal ulcerations and skin ulcerations have been reported with nicorandil (see Adverse Reactions). Occurrence of persisting ulcers should lead to drug discontinuation because the ulcers may be refractory to treatment while taking nicorandil.

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 t1/2 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.

Effects on Fertility
Nicorandil did not affect the fertility of male and female rats at oral doses up to 100 mg/kg/day.

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 in human use 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 the 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.

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).

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\text{max}, t\text{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,β}. 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 clinical studies when nicorandil is administered concomitantly with β-blockers, a calcium antagonist, digoxin, a combination of digoxin/frusemide, 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).
Corticosteroids

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

ADVERSE EFFECTS

The following CIOMS frequency rating is used:

- **very common** $\geq 1/10$ (10%)
- **common** $\geq 1/100$ (1%) and $< 1/10$ (10%)
- **uncommon** $\geq 1/1000$ (0.1%) and $< 1/100$ (1%)
- **rare** $\geq 1/10000$ (0.01%) and $< 1/1000$ (0.1%)
- **very rare** $< 1/10000$ (< 0.01%)

**Body as a Whole**
- common: 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: angina pectoris, hypertension, palpitations, vasodilation/flush
- uncommon: postural hypotension, hypotension, tachycardia, arrhythmia, myocardial infarction, syncope, peripheral vascular disorder

A decrease in blood pressure and/or an increase in heart rate may occur, particularly following the administration of nicorandil in high doses.

**Gastrointestinal Disorders**
- common: dyspepsia, nausea, vomiting
- uncommon: anorexia, diarrhoea, constipation, abdominal pain, gastrointestinal disorder
- rare: stomatitis/mouth ulceration, severe cases of painful aphthosis or mouth ulcers, tongue ulcers, gastrointestinal ulcersations, such as small intestine ulcer, large intestine ulcer and anal ulcer. These ulcers, if advanced, may develop into perforation, fistulating disease, or abscess formation (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

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 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.

DOSAGE AND ADMINISTRATION

Adults
The recommended therapeutic dose for nicorandil is 10 to 20 mg twice daily. The usual starting dose is 10 mg twice daily (preferably in the morning and in the evening). A lower starting dose of 5 mg twice daily may be used in patients who are prone to headache or other adverse reactions. Dosage should be titrated to the minimum effective dose.

Elderly
There are no dosage adjustments required for the elderly patients. However, as with all other medications, the lowest effective dose should be used.

Children
Not recommended for use in children as safety and efficacy have not been established.

OVERDOSE

No data are available concerning overdose of nicorandil in humans. However, in case of overdose, 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 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS
10 mg tablets: (off-white, round, scored, plain on one side and IK/10 on the other): 20s#, 60s.
20 mg tablets: (off-white, round, scored, plain on one side and IK/20 on the other): 20s#, 60s.
#This presentation is not marketed

Store below 25ºC. Store in a dry place.

NAME AND ADDRESS OF THE SPONSOR
sanofi-aventis australia pty ltd
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Macquarie Park NSW 2113
POISON SCHEDULE OF THE MEDICINE
Prescription Only Medicine

DATE OF APPROVAL
Date of TGA approval: 7 May 2004
Date of most recent amendment: 22 March 2011