For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

NIKORAN I.V.

(Nicorandil Injection I.V.)

COMPOSITION :

NIKORAN I.V.-2

Each lyophilized vial contains :

Nicorandil I.P. 2 mg

Excipients q.s.

NIKORAN I.V.-48

Each lyophilized vial contains :

Nicorandil I.P. 48 mg

Excipients q.s.

Nicorandil belongs to a novel class of agents for the management of Coronary Heart Disease. It has a dual mode of action being a selective ATP dependent potassium channel opener and nitric oxide donor.

CLINICAL PHARMACOLOGY :

Nicorandil is a new antianginal drug having potent vasodilator and antispasmodic properties, which are relatively selective to the coronary arteries. Nicorandil is a potassium channel opener that also contains a nitrate moiety. Potassium channel opening hyperpolarizes vascular cell membranes, causing voltage operated calcium (Ca^{++}) ion channels to close with a consequent reduction in free intracellular Ca^{++} concentration that results in a reduction in vasomotor tone, particularly in the coronary resistance vessels. Nicorandil also induces vascular smooth muscle relaxation by releasing Nitric oxide (NO) which in turn increases intracellular cyclic guanosine monophosphate (cGMP) levels. Nicorandil markedly increases coronary blood flow in a dose dependent manner and has little effect on cardiac output, arterial pressure and pulse pressure. Nicorandil thus dilates the large coronary arteries to the same extent as nitroglycerine through NO release and reduces the vasomotor tone of the resistant coronary vessels through its potassium channel opener action. In non-ischemic myocardium, Nicorandil at therapeutic doses has neither negative inotropic effect nor any effect on atrioventricular conduction. The overall action improves blood flow to post-stenotic regions and the oxygen balance in the myocardium. Furthermore, increasing clinical evidence suggests that potassium channel activation exerts a direct cytoprotective effect by augmenting normal physiological processes which protects the heart against ischemic events mimicking the action of Adenosine.

Intravenous nicorandil (4-12 mg) has been shown to produce an 8-27% increase in the diameter of the major coronary arteries and 9-53% decrease in coronary vascular resistance in patients with coronary artery disease. The effect of intravenous nicorandil was dose dependent and was greater in the coronary arteries of patients with variant angina pectoris. Intravenous nicorandil was found to produce an increase in coronary sinus blood flow of between 6 and 81 % in contrast to nitroglycerine and isosorbide nitrate, which decreased blood flow. Coronary vascular resistance was reduced by 9 to 53% after a single intravenous dose of Nicorandil. Nicorandil was found to decrease the frequency of chest pain attack rate and complete suppression of chest pain was achieved in 75% of those treated with Nicorandil.

A single intravenous dose of nicorandil 4 to 12 mg was found to produce a significant decrease in mean arterial pressure (5 to 15%), systemic vascular resistance (8 to 27%), pulmonary capillary wedge pressure (15 to 41%) and left ventricular end-diastolic pressure (8 to 18%) in patients with coronary artery disease, myocardial infarction or congestive heart failure as well as in healthy subjects. Cardiac index and stroke index remained unchanged after Nicorandil administration.

A double-blind controlled clinical study in patients with unstable angina demonstrated significant usefulness of Nicorandil injection I.V. Global clinical improvement rates of 68.4 to 75.0% have been reported in clinical studies including double-blind trials with a total of 134 assessable patients with unstable angina.

Nicorandil Injection I.V. when administered by intravenous infusion at a rate of 2, 4 or 6 mg/hour for 6 hours, reached a steady state plasma concentration between 3 and 6 hours after the initial infusion followed by a biphasic elimination with a half-life ($T_{1/2}$ (β) of 1.56, 1.98 and 1.32 hours, respectively. When a single 2 mg intravenous dose of Nicorandil injection I.V. was administered to five healthy volunteers, the half-life ($T_{1/2}$) was 0.11 hour, the area under the plasma concentration time curve (AUC) was 16.2 ng.hour/mL, and the total clearance (Cl_{total})was 126 L /hour.

INDICATIONS :

Nikoran I.V. is indicated in management of unstable angina.

CONTRAINDICATIONS :

Nikoran I.V. is contraindicated in patients with serious hepatic or renal dysfunction, cerebral dysfunction, serious hypotension or cardiogenic shock. It is also contraindicated in patients with Eisenmenger's syndrome or primary pulmonary hypertension and in patients with right ventricular infarction. Nicorandil is not recommended in patients with symptoms of dehydration, neurocirculatory asthenia, with closed angle glaucoma and with a history of hypersensitivity to potassium channel openers, nitrates and nitrite derivatives and any excipients of this product.

USE IN PREGNANCY, LACTATION & CHILDREN :

Safety of Nicorandil has not been studied in pregnant women. Therefore, it is advisable not to administer nicorandil to pregnant women or women having possibilities of being pregnant.

As it is not known whether nicorandil is excreted in human milk, breast feeding should be avoided by nursing mothers who require therapy.

Safety of nicorandil in children has not been established (no clinical experience).

PRECAUTIONS :

While administering Nicorandil injection I.V., blood pressure and hemodynamics should be monitored frequently. Dose adjustment should be done gradually according to patient's hemodynamic status and symptoms.

In patients showing hypotension, correction can be made by dose reduction or discontinuation of nicorandil injection I.V. or by administration of a pressor agent.

DRUG INTERACTIONS :

No pharmacological or pharmacokinetic interactions of nicorandil have been observed in humans or animals with betablockers, digoxin, rifampicin, cimetidine, nicoumalone, calcium antagonist or a combination of digoxin and frusemide. Nevertheless, there is the possibility that nicorandil may potentiate the blood pressure lowering effect of other vasodilators, tricyclic antidepressants or alcohol.

ADVERSE REACTIONS :

Following adverse reactions have been reported infrequently with Nicorandil injection I.V.

1. Cardiovascular

Decrease in blood pressure, Increase in heart rate.

2. Psychoneurologic

Headache, light-headed feeling, numbness of limbs.

3. Gastrointestinal

Nausea, vomiting, upper abdominal discomfort.

4. Hepatic

Elevation of SGOT, SGPT and total bilirubin.

5. Hematologic

Anemia

OVERDOSAGE :

Acute overdosage is likely to be associated with peripheral vasodilation, hypotension and reflex tachycardia. Cardiac function should be monitored and general supportive measures should be employed. If necessary, circulating plasma volume should be increased by infusion of plasma expanders . In life threatening situations administration of vasopressors should be considered.

DOSAGE & ADMINISTRATION :

For intravenous infusion only (Sterile & Nonpyrogenic)

Do not use the vial if the reconstituted solution is not clear or shows any particulate matter

The usual adult starting dosage for intravenous drip infusion is 2 mg of nicorandil per hour. The dose may be adjusted depending on the symptoms and must not exceed 6mg per hour. The contents of Nicorandil injection vial are to be dissolved in physiological saline or 5% glucose solution for injection to yield a 0.01-0.03% solution and should be used within 24 hours of preparation. Nikoran I.V. should not be simultenously administerd through same line with other I.V. solutions

Instructions for dilutions

VIAL STRENGTH	NO OF VIALS	VOLUME OF DILUENT (NS OR 5% DEXTROSE) TO BE ADDED IN VIAL FOR RECONSTITUTION	FINAL VOLUME TO BE MADE WITH DILUENT (NS OR 5% DEXTROSE	% SOLUTION PREPARED	MIN SPEED OF ADMN	MAX. SPEED OF ADMN.
2 mg	1	10 ml	10 ml	0.02% 0.2 mg/ml	10 ml/hr	10 ml/ 20 min
48 mg	1	20 ml	250 ml	0.019% 0.19 mg/ml	250 ml/ 24 hr	250 ml/ 8 hr
48 mg	2	20 ml	500 ml	0.019% 0.19 mg/ml	500 ml/ 24 hr	500 ml/ 8 hr

Use in Elderly

The elderly are often physiologically hypofunctional, which may increase the risk of an adverse event. Therefore, the drug should be administered with caution. Blood pressure and hemodynamics of the elderly patient should be monitored frequently and the dose of the drug should start at 2 mg/hour by intravenous drip infusion. The dose should be adjusted gradually according to the patient's hemodynamic status and symptoms.

CAUTION : To be used under medical supervision only

EXPIRY DATE : Do not use later than date of expiry.

STORAGE : Store in a refrigerator

PRESENTATION :

Nikoran I.V.-2 : Boxes of 14 vials Nikoran I.V.-48 : Boxes of 12 vials

MARKETED BY

torrent PHARMA

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