

1. NAME OF THE MEDICINAL PRODUCT

Nitroglycerin Injection U.S.P. 0.5% w/v, 10ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml contains 50mg of Nitroglycerin U.S.P.

3. PHARMACEUTICAL FORM

Clear, colourless or pale yellow sterile solution intended for parenteral administration to human beings after dilution in either Sodium Chloride Injection B.P. or Glucose Injection B.P.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

- a) Control of blood pressure in perioperative hypertension, i.e. hypertension associated with surgical procedures, especially cardiovascular procedures and in the immediate post-surgical period.
- b) Unresponsive congestive cardiac failure secondary to acute myocardial infarction.
- c) Treatment of angina pectoris in patients who have not responded to recommended doses of organic nitrates and/or beta-adrenoceptor blocking agents.
- d) Production of elective hypotension and maintenance of controlled hypotension during surgical procedures.

4.2. Posology and Method of Administration

Route of administration: Intravenous infusion after dilution.

Nitroglycerin Injection is a concentrated potent drug which must be diluted in either Sodium Chloride Injection B.P. or Glucose Injection B.P. prior to its infusion.

Nitroglycerin Injection should not be mixed with other drugs. It is recommended that the drug is diluted to give a final concentration of 400 micrograms/ml or less, according to the dosage requirements of the patient. Most patients respond to doses between 10 - 200 micrograms/minute, although doses up to 400 micrograms/minute may be required during some surgical procedures.

Dosage: The usual recommended dose range is 10 - 200 micrograms/minute. Doses in excess of these have been used and up to 400 micrograms/minute may be required during some surgical procedures. Careful clinical assessment and frequent monitoring of blood pressure and heart rate are essential to maintain the appropriate rate of infusion. Where available, monitoring of pulmonary capillary wedge pressure and cardiac output can be used to titrate dosage to response.

Surgery: For the control of hypertensive episodes, the recommended starting dose is 25 micrograms/minute increasing in steps of 25 micrograms/minute at 5 minute intervals until the desired reduction in blood pressure is achieved. Although most patients respond to doses between 10 to 200 micrograms/minute, doses up to 400 micrograms/minute have been required during some surgical procedures. In the treatment of perioperative myocardial ischaemia, the recommended starting dose is 15 to 20 micrograms/minute increasing in steps of 10 to 15 micrograms/minute until the desired effect is achieved.

Unresponsive congestive cardiac failure secondary to acute myocardial infarction : The recommended starting dose is 20 to 25 micrograms/minute which can be decreased to 10 micrograms/minute or increased in steps of 20 to 25 micrograms/minute at 15 to 30 minute intervals until the desired effect is achieved.

Unstable angina: The recommended starting dose is 10 micrograms/minute increasing in steps of 5 to 10 micrograms/minute at approximately 30 minute intervals.

Children: The safety and effectiveness of nitroglycerin in children have not been established.

Use in the elderly : Special care in dose titration and monitoring is required in elderly patients, as there is an increased risk of a fall in perfusion pressure owing to a higher prevalence of coronary or cerebral artery disease in the elderly.

4.3. Contra-Indications

Known hypersensitivity to organic nitrates. Marked anaemia, raised intracranial pressure (e.g. due to head trauma or cerebral haemorrhage), uncorrected hypovolaemia or severe hypotension. Constrictive pericarditis and pericardiac tamponade.

The hypotensive effects of nitrates are potentiated by sildenafil, and their co-administration is contra-indicated.

4.4. Special Warnings and Special Precautions for Use

Nitroglycerin Injection should be used with caution in patients suffering from severe hepatic or renal disease, hypothyroidism, malnutrition, hypothermia and in those predisposed to closed angle glaucoma.

In order to achieve and maintain the correct dosage, continuous monitoring of physiological parameters must be performed, including blood pressure and heart rate in all patients and other measurements such as capillary wedge pressure as appropriate. The systemic blood pressure and coronary perfusion pressure must be maintained adequately at all times.

Nitroglycerin Injection should be administered by means of a micro-drip set infusion pump or similar device which permits maintenance of a constant infusion rate. The giving set should be composed of glass or rigid polyethylene. Infusion systems composed of PVC may absorb up to 50% of the nitroglycerin from solution, resulting in reduced potency of the infusion (see incompatibilities).

Excessive hypotension, especially for prolonged periods of time, must be avoided because of the possible deleterious effects of poor perfusion on body organs and the consequent risk of ischaemic damage.

Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension.

Patients with normal or low left ventricular filling pressure or pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of intravenous nitroglycerin and may respond fully to doses as small as 5 micrograms/minute. Where pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension. Therefore, pulmonary capillary wedge pressure is a useful guide to titration of the drug in these circumstances.

Nitroglycerin Injection contains both alcohol and propylene glycol. Safety for intracoronary injection has not been shown.

Propylene glycol can lead to lactic acidosis and it is recommended that the duration of therapy with this product be restricted to no more than three successive days.

There are no long-term studies to evaluate the carcinogenic potential of nitroglycerin

4.5. Interaction with other Medicinal Products and other Forms of Interaction

Nitroglycerin may potentiate the hypotensive effect of other anti-hypertensive agents. The hypotensive effects of nitrates are potentiated by sildenafil (see Contra-indications).

4.6. Pregnancy and Lactation

There is inadequate evidence of the safety of nitroglycerin in pregnancy and lactation. Nitroglycerin Injection should not be used during pregnancy or lactation unless considered essential by the physician.

4.7. Effects on Ability to Drive and Use Machines

The indications for Nitroglycerin Injection limit its use to situations in which there would not be an opportunity to drive or to operate machinery.

4.8. Undesirable Effects

Adverse reactions to nitroglycerin may include hypotension, tachycardia, headache, nausea, vomiting, restlessness, dizziness, muscle twitching, palpitation, paradoxical bradycardia, retrosternal discomfort and abdominal pain.

4.9. Overdose

Accidental overdosage may result in severe hypotension and reflex tachycardia which can be managed by elevating the lower limbs and decreasing or temporarily withdrawing the infusion until the condition is stabilised. In extreme states of hypotension, intravenous administration of an alpha adrenergic agonist such as methoxamine hydrochloride or phenylephrine hydrochloride should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Nitroglycerin is an organic nitrate. Relaxation of vascular smooth muscle is the principal pharmacological action of nitroglycerin. Nitroglycerin causes dilatation of both venous and arterial smooth muscle in a dose-related manner. Venodilatation predominates at lower infusion rates and, as the infusion rate increases, nitroglycerin dilates both arterial and venous systems. Pulmonary vascular resistance, systemic vascular resistance and arterial pressure are all reduced by administration of intravenous nitroglycerin.

Dilatation of the post-capillary vessels promotes peripheral pooling of blood and decreases venous return, reducing left ventricular end-diastolic pressure (pre-load).

Relaxation of arterioles reduces systemic vascular resistance and arterial pressure (after-load).

Myocardial oxygen consumption (as measured by the rate-pressure product and tension-time index) is decreased by both the venous and arterial effects of nitroglycerin, and a more favourable supply-demand ratio can be achieved. Although the predominant clinical

benefits result from the peripheral vasodilating effects and the resultant decrease in myocardial oxygen demand, some effect on oxygen supply may occur by direct coronary vasodilatation. Redistribution of blood from normal to ischaemic areas of the myocardium has been demonstrated.

5.2. Pharmacokinetic Properties

Pharmacokinetic data for intravenous nitroglycerin are difficult to interpret due to factors such as the variation in sensitivity of assay procedures for calculating plasma concentrations of the drug, intersubject variation in plasma concentrations and adsorption of nitroglycerin by some types of giving sets. There appears to be no close correlation between the infusion rates of intravenous nitroglycerin and the blood concentrations achieved.

Nitroglycerin is extensively distributed and is rapidly metabolised in the liver and erythrocytes by the enzyme glutathione - organic nitrate reductase. The enzyme converts nitroglycerin to dinitrates, mononitrates and inorganic nitrites, which have about one tenth of the vasodilating activity of nitroglycerin and which are excreted in the urine within 24 hours after a single dose. The elimination half-life of nitroglycerin ranges from less than one minute to three minutes. Impaired hepatic function may impair the clearance of the drug.

5.3. Pre-clinical Safety Data

No further relevant information other than that which is contained in the other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Propylene Glycol B.P.

Ethanol B.P.

Water for Injections B.P.

6.2. Incompatibilities

Nitroglycerin Injection is compatible with glass infusion bottles. It has been shown to be compatible with certain rigid infusion packs made of polyethylene, such as the polyfusor from Kendall or bottlepak and flatpak from Braun, Dublin. The injection can be administered as an infusion using one of these recommended infusion bottles/packs.

Nitroglycerin Injection is not compatible with infusion bags made from polyvinyl chloride (PVC) and over 40% of the nitroglycerin activity can be lost if contact with PVC is prolonged. Therefore, it is recommended that contact with PVC bags is avoided. Some loss of activity can also occur through the infusion sets but the clinical response should be used to determine the rate of infusion and thus the dosage of the drug required by the patient.

Alternatively, nitroglycerin injection may be infused slowly via a syringe pump using a glass syringe or rigid plastic syringe (Gillette Sabre syringe, Brunswick Disposable, B.D. Plastipak syringes). A high pressure polyethylene tubing known to be compatible with nitroglycerin is the Lectrocath tubing, Vygon, Gloucester.

6.3. Shelf-Life

3 years (36 months).

If only part of an ampoule is used, discard the remaining solution.

6.4. Special Precautions for Storage

Protect from light.

Store in a cool dry place.

6.5. Nature and Contents of Container

10ml, clear glass ampoules, glass type 1 Ph. Eur., packed in cardboard cartons to contain 5 x 10ml or 10 x 10ml ampoules.

6.6. Instructions for Use, Handling and Disposal

For administration by i.v. infusion only after dilution with a suitable vehicle such as 5% dextrose in water or 0.9% w/v sodium chloride.

Use as directed by the physician.

Keep out of reach of children.

If only part used, discard the remaining solution.

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,

Roscrea,

Co. Tipperary,

Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

PL 2848/0169.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

29 November 1991.

10. DATE OF (PARTIAL) REVISION OF THE TEXT

April 1999.