PRODUCT MONOGRAPH

NITROJECT®

(Nitroglycerin for Injection,USP)

Sterile

For Intravenous Infusion

10 mg/10 mL (1 mg/mL)
&
50 mg/10 mL (5 mg/mL)

VASODILATOR

Omega Laboratories, Ltd.
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Montreal, Canada
H3M 3E4

Control Number: 153511

Date of Revision:
June 26, 2012

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Sterile

For Intravenous Infusion
1 mg/mL (10 mg/10 mL)
&
5 mg/mL (50 mg/10 mL)

CAUTION: SEVERAL PREPARATIONS OF NITROGLYCERIN FOR INJECTION ARE AVAILABLE. THEY DIFFER IN CONCENTRATION AND/OR VOLUME PER VIAL. WHEN SWITCHING FROM ONE PRODUCT TO ANOTHER ATTENTION MUST BE PAID TO DILUTION AND TO THE DOSAGE AND ADMINISTRATION INSTRUCTIONS.

THERAPEUTIC CLASSIFICATION

Vasodilator

ACTIONS AND CLINICAL PHARMACOLOGY

The principal pharmacological action of NITROJECT® (Nitroglycerin for Injection, USP) is the relaxation of vascular smooth muscle. Nitrates probably act primarily by reducing oxygen demand rather than increasing myocardial oxygen supply. Although venous effects predominate, nitroglycerin produces, in a dose-related manner, dilatation of both arterial and venous beds. Dilation of the postcapillary vessels, including large veins, promotes peripheral pooling of blood and decreases venous return to the heart, reducing left ventricular end-diastolic pressure (preload). Arteriolar relaxation reduces systemic vascular resistance and arterial pressure (afterload). Left ventricular end diastolic pressure and volume are decreased, resulting in reduction of ventricular wall tension results in a net decrease in myocardial oxygen consumption (as measured by the pressure-rate product, tension time index and stroke work index). A favorable net balance between myocardial oxygen supply and demand is achieved. Elevated central venous and pulmonary capillary wedge pressures, pulmonary vascular resistance and systemic vascular resistance are also reduced by nitroglycerin therapy.

Therapeutic doses of intravenous nitroglycerin reduce systolic, diastolic and mean arterial blood pressure. Effective coronary perfusion pressure is usually maintained, but can be compromised if blood pressure falls excessively or increased heart rate decreases the diastolic filling time.

Heart rate is usually slightly increased, presumably a reflex response to the fall in blood pressure. Nitroglycerin is widely distributed in the body with an apparent volume of distribution of approximately 200 litres in adult male subjects and is rapidly metabolized to dinitrates and mononitrates, with a short half-life, estimated at 1 to 4 minutes. This results in a low plasma concentration after intravenous infusion. At plasma concentrations of between 50 and 600

ng/mL, the binding of nitroglycerin to plasma proteins is approximately 60%, while those of the metabolites 1,2-dinitroglycerin and 1,3-dinitroglycerin are 60% and 30% respectively. The activity and half-life of 1,2-dinitroglycerin and 1,3-dinitroglycerin are not well characterized. The mononitrate is not active.

INDICATIONS

NITROJECT® (Nitroglycerin for Injection, USP) is indicated for:

1. CONTROL OF BLOOD PRESSURE IN PERIOPERATIVE HYPERTENSION, i.e., hypertension associated with surgical procedures, especially cardiovascular procedures, such as the hypertension seen during intratracheal intubation, anesthesia, skin incision, sternotomy, cardiac bypass, and in the immediate postsurgical period.
2. CONGESTIVE HEART FAILURE ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION.
3. TREATMENT OF ANGINA PECTORIS in patients who have not responded to recommended doses of conventional antianginal agents.
4. PRODUCTION OF CONTROLLED HYPOTENSION DURING SURGICAL PROCEDURES.

CONTRAINDICATIONS

NITROJECT® (Nitroglycerin for Injection, USP) should not be administered to individuals with:

1. A known hypersensitivity to nitroglycerin or a known idiosyncratic reaction to organic nitrates.
2. Hypotension or uncorrected hypovolemia, as the use of nitroglycerin for injection in such states could produce severe hypotension or shock.
3. Increased intracranial pressure (e.g., head trauma or cerebral hemorrhage).
4. Constrictive pericarditis and pericardial tamponade.

WARNINGS

NITROGLYCERIN READILY MIGRATES INTO MANY PLASTICS. TO AVOID ABSORPTION OF NITROGLYCERIN INTO PLASTIC PARENTERAL SOLUTION CONTAINERS, THE DILUTION AND STORAGE OF NITROJECT® (NITROGLYCERIN for INJECTION, USP) SHOULD BE MADE ONLY IN GLASS PARENTERAL SOLUTION BOTTLES.

Some filters absorb nitroglycerin; therefore all filters should be avoided.
Important: Prior to the initiation of infusion check carefully which type of infusion set is going to be used:

a) A conventional administration set with absorbable tubing (most frequently made of polyvinyl chloride); or
b) A special administration set which will not absorb any significant amount of nitroglycerin from the infusion solution.

Please read carefully points A and B below taking into account the highly significant difference in the amount of nitroglycerin being delivered depending on the type (A or B) of the set used.

A. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by polyvinyl chloride (PVC) intravenous administration sets. The higher rates of absorption occur when flow rates are low, nitroglycerin concentrations are high, and the administration set is long. Although the rate of loss is highest during the early phase of infusion (when flow rates are lowest), the loss is neither constant nor self-limiting. Consequently, no simple calculation or correction can be performed to convert the theoretical infusion rate (based on the concentration of the infusion solution) to the actual delivery rate.

B. Because of this problem, special administration sets in which loss of nitroglycerin is minimal have been developed. When these sets are used the calculated dose will be delivered, because the loss of nitroglycerin due to absorption into the set will be negligible. Because the tubing of such infusion sets may be less pliable than conventional PVC tubing, occlusion of the infusion set by some pumps may not be complete. The result may be excessive flow at low infusion rate settings, causing alarms, or unregulated gravity flow when the infusion pump is stopped which could lead to over-infusion of nitroglycerin. To minimize the potential for such occurrence, one should consider the following before using an infusion pump:

1. All infusion pumps should be tested with an appropriate infusion set to ensure their ability to deliver nitroglycerin accurately at low flow rates, and to occlude the infusion set properly when the infusion pump is stopped.
2. If the infusion pump alarms frequently, the tubing may be made more pliable by manipulating and warming the tubing with your hands before installing the i.v. set into the unit.
3. To prevent the possibility of a runaway infusion, locate the set's roller clamp above the pump unit, and use it to establish the approximate desired drip rate manually. Then insert the infusion set into the unit, setting the unit at the desired drip rate. (It should be noted that this procedure may be contrary to usually recommended procedures with some infusion pumps).
4. In accordance with good operating practices, when turning off the pump, close the roller clamp to assure complete occlusion.
5. Hospitals that use volumetric pumps for infusion of nitroglycerin should note that some volumetric pumps require a special cassette or special integrated administration set with disposal pump components made of assorted nitroglycerin-absorbing materials. If such pump is used with the set connected from the bottle to the pump, you should be aware that some loss of nitroglycerin will occur.

Additionally, care should be taken to fill the set drip chamber at least half full to prevent the aspiration of air bubbles into the line during the fill cycle of the volumetric cassette.

As with all potent drugs, no matter what means for infusion of nitroglycerin is chosen, critical care personnel must carefully monitor the patient's status. Due to variation in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (e.g. blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate) must be performed to achieve the correct dose. Adequate blood pressure and coronary perfusion pressure must be maintained.

DOSING INSTRUCTIONS MUST BE FOLLOWED WITH CARE. IT SHOULD BE NOTED THAT WHEN SPECIAL NON-ABSORBING TYPE OF SET (TYPE B) IS USED THE CALCULATED DOSE WILL BE DELIVERED TO THE PATIENT BECAUSE THE LOSS OF NITROGLYCERIN DUE TO ABSORPTION IN STANDARD PVC TUBING WILL BE KEPT TO A MINIMUM. NOTE THAT THE DOSAGES COMMONLY USED IN PUBLISHED STUDIES UTILIZED GENERAL-USE PVC ADMINISTRATION SETS, AND RECOMMENDED DOSES BASED ON THIS EXPERIENCE ARE TOO HIGH WHEN SPECIAL NON-ABSORBING TYPE OF SET (TYPE B) IS USED.

PRECAUTIONS

NITROJECT® (Nitroglycerin for Injection, USP) should be used with caution in patients who have severe hepatic or renal disease.

Nitroglycerin can cause sudden severe hypotension. Excessive hypotension, especially for prolonged periods of time, must be avoided because of possible deleterious effects on the brain, heart, liver and kidney from poor perfusion and the attendant risk of ischemia, thrombosis, and altered function of these organs. Paradoxical bradycardia and increased angina pectoris may accompany nitroglycerin-induced hypotension. Patients with depleted blood volumes such as those with dehydration due to vomiting, diarrhea, or GI fluid loss, significant hemorrhage or intensive diuretic therapy may be subject to hypotensive crises with i.v. nitroglycerin. The hypovolemic state should be corrected prior to therapy to ensure that adequate ventricular filling is maintained. Patients with normal or low pulmonary capillary wedge pressure are especially sensitive to the hypotensive effects of intravenous nitroglycerin. If pulmonary capillary wedge pressure is being monitored, it will be noted that a fall in wedge pressure precedes the onset of arterial hypotension, and the pulmonary capillary wedge pressure is thus a useful guide to safe titration of the drug.

Tolerance to nitroglycerin and cross tolerance to other nitrates may occur. Nitrate tolerance and dependence in patients with chronic use of nitrates has been well documented. Tolerance to nitroglycerin has been readily produced in animals and it was reported that even a single dose of nitroglycerin in rats can produce some tolerance.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No long term studies in animals were performed to evaluate the carcinogenic potential of nitroglycerin.

Pregnancy:
Animal reproduction studies have not been conducted with nitroglycerin. It is not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers:
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when intravenous nitroglycerin is administered to a nursing woman.

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

Drug Interactions:
Nitroglycerin prolongs pentobarbital sleep time. Nitroglycerin potentiates the hypotensive and anticholinergic effects of tricyclic antidepressants. Patients receiving hypotensive agents and nitroglycerin should be observed for possible additive hypotensive effect. If nitroglycerin is used in surgical procedures, the choice of anesthetic agents may influence the response to nitroglycerin.

ADVERSE REACTIONS

The most frequent adverse reaction in patients treated with NITROJECT® (Nitroglycerin for Injection, USP) by intravenous infusion is headache, which occurs in approximately 14.5% of patients. However, considerable variation in frequency is observed according to the indication and dosage utilized. Symptomatic hypotension (2.7%) is the second most common adverse reaction. Other adverse reactions occurring in less than 1% of patients are:

Cardiovascular: Reflex tachycardia, paradoxical increase of anginal pain, palpitations and bradycardia may also occur, the incidence again depending on the indication and on the dosage utilized. These effects can be reversed or minimized by discontinuing the drug or by carefully adjusting the rate of infusion with constant hemodynamic monitoring of the patient.

CNS: Weakness, dizziness, apprehension and restlessness.

Gastrointestinal: Nausea, vomiting, abdominal pain.

Metabolic: Methemoglobinemia especially in the presence of methemoglobin reductase deficiencies or in congenital M hemoglobin variants (for treatment see Overdosage).

Miscellaneous: Muscle twitching and retrosternal discomfort.

The following additional adverse reactions have been reported with the oral and/or topical use of nitroglycerin: cutaneous flushing, weakness, and occasionally drug rash or exfoliative dermatitis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms of overdosage include headache, dizziness, flushing of skin, vomiting, marked fall in blood pressure, methemoglobinemia and coma. Most of these effects can be obviated by discontinuing the drug immediately. Reflex tachycardia can be treated by elevating the legs and decreasing or temporarily terminating the infusion until the patient's condition stabilizes. Since the duration of the hemodynamic effects following nitroglycerin administration is quite short, additional corrective measures are usually not required.

However, if further therapy is indicated, administration of an intravenous alpha adrenergic agonist (eg, methoxamine or phenylephrine) should be considered. Methemoglobinemia has been reported following the use of nitroglycerin. The diagnosis of methemoglobinemia must be considered in any cyanotic patient. Methylene blue 1-2 mg/kg as a 1% solution should be given intravenously only if stupor or coma occurs.

DOSAGE AND ADMINISTRATION

General information:
Adequate facilities and personnel should be available for monitoring of the ECG and the blood pressure. In addition, whenever possible, the pulmonary capillary wedge pressure should be monitored to aid in the safe and effective infusion of nitroglycerin. Because of the rapid onset of action and potency of NITROJECT® (Nitroglycerin for Injection, USP), it should be administered with the use of an infusion pump in order to allow precise measurement of the flow rate.

BECAUSE OF THE LIKELY ALTERATIONS TO THE AMOUNT OF NITROGLYCERIN DELIVERED TO THE PATIENT CAUSED BY ADMINISTRATION SETS, PUMPS, ETC. AND THE GREAT VARIATIONS IN RESPONSIVENESS OF INDIVIDUAL PATIENTS TO NITROGLYCERIN, THERE IS NO FIXED, OPTIMUM DOSE OF NITROGLYCERIN. EACH PATIENT MUST BE TITRATED TO THE DESIRED LEVEL OF HEMODYNAMIC FUNCTION (SEE WARNINGS).

NOT FOR DIRECT INTRAVENOUS INJECTION. NITROJECT® (NITROGLYCERIN for INJECTION, USP IS A CONCENTRATED, POTENT DRUG WHICH MUST BE DILUTED IN DEXTROSE (5%) INJECTION, USP, OR SODIUM CHLORIDE (0.9%) INJECTION, USP, PRIOR TO ITS INFUSION. THE RESULTANT SOLUTION SHOULD BE USED WITHIN 24 HOURS. NITROJECT® (NITROGLYCERIN for INJECTION, USP) SHOULD NOT BE ADMIXED WITH OTHER DRUGS.

Dilution:
It is important to consider the fluid requirements of the patient as well as the expected duration of infusion in selecting the appropriate dilution of nitroglycerin.

Dosage: IMPORTANT NOTICE
Dosage is affected by the type of infusion set used (see WARNINGS). Although the usual starting adult dose range reported in clinical studies was 25 µg/min or more, those studies used PVC tubing.

THE USE OF NONABSORBING TUBING WILL RESULT IN THE NEED TO USE REDUCED DOSAGE.

The recommended dosage should initially be 5 µg/min delivered through an infusion pump capable of exact and constant delivery of the drug, such as a properly calibrated peristaltic-action pump which has been checked to determine proper operation with the appropriate infusion set. Subsequent titration must be adjusted to the clinical situation, with dose increments becoming more cautious as partial response is seen. Initial titration should be 5 µg/min increments, with increases every 3 to 5 minutes until some response is noted. If no response is seen at 20 µg/min, increments of 10 and later 20 µg/min can be used. Once a partial blood pressure response is observed, the rate of dose increase should be reduced and the interval between increments should be lengthened.

Patients with normal or low left ventricular filling pressure or pulmonary capillary wedge pressure (e.g., angina patients without other complications) may be hypersensitive to the effects of nitroglycerin and may respond fully to doses as small as 5 µg/min. These patients require especially careful titration and monitoring.

There is no fixed optimum dose of nitroglycerin. Due to variations in the responsiveness of individual patients to the drug, each patient must be titrated to the desired level of hemodynamic function. Therefore, continuous monitoring of physiologic parameters (blood pressure and heart rate in all patients, other measurements such as pulmonary capillary wedge pressure, as appropriate) MUST BE PERFORMED to achieve the correct dose. Adequate systemic blood pressure and coronary perfusion pressure must be maintained.

Nitroject® I.V. ADMINISTRATION TABLE NITROJECT® 1 mg/mL EACH 10 mL VIAL = 10 mg NITROGLYCERIN				
Mixing Instructions:	10 mL in 250 mL	20 mL in 250 mL	30 mL in 250 mL	
Concentration:	40 µg/mL (approx.)	75 µg/mL (approx.)	110 µg/mL (approx.)	
	µg/min	**µg/min**	**µg/min**	**µdrops/min(=mL/hour) (60 microdrops=1 mL)**
	5	10	15	8
	10	20	30	16
	15	30	45	24
	20	40	60	32
	30	60	90	48
	40	80	120	64

Nitroject® I.V. ADMINISTRATION TABLE NITROJECT® 5 mg/mL EACH 10 mL VIAL = 50 mg NITROGLYCERIN				
Mixing Instructions:	10 mL in 1000 mL	10 mL in 500 mL 20 mL in 1000 mL	10 mL in 250 mL 20 mL in 500 mL 40 mL in 1000 mL	
Concentration:	50 µg/mL (approx.)	100 µg/mL (approx.)	200 µg/mL (approx.)	
	µg/min	**µg/min**	**µg/min**	**µdrops/min(=mL/hour) (60 microdrops=1 mL)**
	2.5	5	10	3
	5	10	20	6
	10	20	40	12
	20	40	80	24
	40	80	160	48
	60	120	240	72
	80	160	320	96

Invert the glass parenteral bottle several times following admixture to ensure uniform dilution of NITROJECT® IV. As with all intravenous admixtures, dilution should be made just prior to administration and the solution used within 24 hours.

NOTE: If the concentration is adjusted, it is imperative to flush or replace the nitroglycerin infusion set before a new concentration is utilized. Depending on the length of the dead space and the flow rate, the time required for the new concentration to reach the patient may vary (e.g. if the dead space of the set is approximately 15 mL and depending on the flow rate, it could take from 9 minutes to 3 hours for the new concentration to reach the patient if the set has not been flushed or replaced).

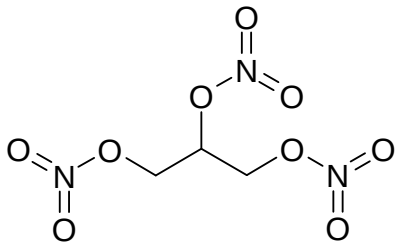
PHARMACEUTICAL INFORMATION

Drug substance:

Proper name: Nitroglycerin, USP

Chemical name: 1,2,3-Propanetriol, trinitrate

Structural formula: $C_3H_5N_3O_9$



Molecular weight: 227.09

Physical form: A colourless, slightly volatile, odourless, oily liquid, with a sweet, aromatic and pungent taste.

Solubility: 1 g in 800 mL of water, 1 g in 4 g of alcohol, 1 g in 18 g methanol, 1 g in 120 g of carbon disulphide, and 1 g in 6 g of almond oil; miscible with acetone, chloroform, ether glacial acetic acid, ethyl acetate, benzene, nitrobenzene, pyridine, ethylene bromide, dichloroethylene; sparingly soluble in glycerol and light petroleum.

Melting point: Crystallizes in 2 forms: labile form, mp + 2.8°C; stable form, mp + 13.5°C.

Composition:

NITROJECT® 1 mg/mL (Nitroglycerin for Injection, USP) is a clear, colorless solution for intravenous infusion after dilution. Each mL contains 1.0 mg of nitroglycerin, 10% ethanol v/v and Water for Injection, USP, q.s. to 1 mL.

NITROJECT® 5 mg/mL (Nitroglycerin for Injection, USP) is a clear, colorless solution for intravenous infusion after dilution. Each mL contains 5.0 mg of nitroglycerin, 30% ethanol v/v, 30% propylene glycol v/v and Water for Injection, USP, q.s. to 1 mL.

These solutions are sterile, non-pyrogenic and non-explosive.

Stability and storage recommendations:

Store between 15 and 30°C. Protect from freezing. Protect from light.

Under these storage conditions NITROJECT® 1 mg/mL (Nitroglycerin for Injection, USP) is stable for 18 months.

Under these storage conditions NITROJECT® 5 mg/mL (Nitroglycerin for Injection, USP) is stable for 36 months.

Dilution: SOLUTION PREPARATION FOR AN INFUSION PUMP

Aseptically transfer 10 mL (10 mg nitroglycerin) of NITROJECT® 1 mg/mL (Nitroglycerin for Injection, USP) into a glass, IV bottle containing 250 mL of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, and mix well. The resultant solution will contain approximately

40 µg/mL of nitroglycerin and is stable for at least 24 hours at controlled room temperature (15 to 30°C). For other concentrations, refer to Table. Invert the glass parenteral bottle several times following admixture to assure uniform dilution.

STABILITY AND STORAGE OF DILUTED SOLUTION

The diluted NITROJECT® (Nitroglycerin for Injection, USP) is stable for at least 24 hours at controlled room temperature (15 to 30°C). Discard all unused solution after 24 hours.

INCOMPATIBILITIES

NITROJECT® (Nitroglycerin for Injection, USP) is incompatible with alkalies. Nitroglycerin readily migrates into many plastics (see WARNINGS). Some filters also absorb nitroglycerin and should be avoided. Forty to 80% of the total amount of nitroglycerin in the final diluted solution for infusion is absorbed by polyvinyl chloride (PVC) intravenous administration sets (see WARNINGS).

DOSAGE FORMS

Availability
NITROJECT® 1 mg/mL (Nitroglycerin for Injection, USP) is available in 10 mL single-dose vials containing 10 mg of nitroglycerin. Each mL contains 1 mg of nitroglycerin. Boxes of 5 x 10 mL.

NITROJECT® 5 mg/mL (Nitroglycerin for Injection, USP) is available in 10 mL single-dose vials containing 50 mg of nitroglycerin. Each mL contains 5 mg of nitroglycerin. Boxes of 5 x 10 mL.

The NITROJECT® dosage forms consist of concentrated solutions of nitroglycerin which **must be diluted** in Dextrose (5%) Injection, USP, or Sodium Chloride (0.9%) Injection, USP, prior to intravenous infusion.

PHARMACOLOGY

It has been shown that intravenous nitroglycerin in anesthetized dogs produced a significant dilation of the large coronary arteries. Similarly, a marked dilation of large coronary arteries was observed in conscious dogs although only a slight effect was seen in the small coronary arteries.

Nitroglycerin caused a decrease in the ST segment elevations which accompany myocardial ischemia when administered intravenously to dogs with occluded coronary arteries. Although coronary blood flow was increased by 45% in the subendocardium of the ischemic areas, prolonged i.v. administration of nitroglycerin did not decrease the size of the infarct.

Nitroglycerin administered in low concentrations produced dilation of the veins which predominated over the arterioles. In anesthetized dogs, nitroglycerin decreased mean arterial pressure due to vasodilation of peripheral arteries.

CLINICAL PHARMACOLOGY

Studies on blood flow in the human forearm have demonstrated a significant decrease in venous tone after sublingual administration of nitroglycerin. This caused a pooling of blood in the peripheral veins and a decrease in venous return to the heart. A slight decrease in systemic arterial pressure was observed with a corresponding fall in vascular resistance in the forearm. Administration of nitroglycerin reduced towards normal left ventricular end diastolic pressure which has been found to be markedly elevated in patients with coronary artery disease. The result was disappearance of anginal pain. Intravenous nitroglycerin given to patients with congestive heart failure produced a significant decrease in pulmonary capillary wedge pressure and an improvement of the cardiac index.

Pharmacokinetics

Nitroglycerin shows essentially single compartment kinetics in rats when administered by the intracardiac route; the half-life was about 4 minutes and the mean apparent volume of distribution was about 3 litres/kg. Intravenous nitroglycerin in rabbits has a 20 second distribution phase, followed by rapid metabolism with a half-life of about 4 minutes.

In animal studies, nitroglycerin was rapidly degraded in the liver by glutathione-organic nitrate reductase. The metabolites are 1,3 or 1,2-glyceryl dinitrate, 1 or 2-glyceryl-mononitrate and oxidized glutathione.
Elimination was by the urine, feces and expired air.

TOXICOLOGY

Acute Toxicity

The acute intravenous toxicity in various species is summarized below:

Species	**Test**	**Dose (mg/kg)**
Guinea pig	LD	83.5
Rabbit	LD_{50}	43
Rabbit	MLD	45
Dog	LD	>10
Dog	LD	>30

Lethal doses of nitroglycerin in common laboratory animals by other routes of administration ranged from 80 to 500 mg/kg.

Signs of toxicity included methemoglobinemia and circulatory collapse, leading to convulsions and death.

It has been reported that most cats receiving 7.5 or 15 mg/kg, subcutaneously, survived 50 daily doses. Albuminuria and icterus were noted in the animals; and, at sacrifice, hemorrhage of the cerebellum, heart, liver and spleen were observed. Cats exposed to saturated atmospheres of nitroglycerin for 68 days developed anemia and moderate leucocytosis. Longer exposures

produced tolerance in the cats. Methemoglobinemia and peripheral vasodilation with an accompanying fall in blood pressure were produced.

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