PRODUCT MONOGRAPH

NITROJECT®

Nitroglycerin Injection

Sterile Solution, 50 mg /10 mL (5 mg/mL)

USP

For Intravenous Infusion

VASODILATOR

Juno Pharma Canada Inc.
11 177 Hamon
Montreal, Canada
H3M 3E4

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Actions and Clinical Pharmacology

The principal pharmacological action of NITROJECT® (nitroglycerin injection) is relaxation of vascular smooth muscle and consequent dilation of peripheral arteries and veins, especially the latter. Nitrates probably act primarily by reducing oxygen demand rather than by increasing myocardial oxygen supply. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (preload). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (afterload). Dilation of the coronary arteries also occurs. The relative importance of preload reduction, afterload reduction, and coronary dilation remains undefined.

Blinded, placebo-controlled trials of intravenous nitroglycerin have not been reported, but multiple investigators have reported open-label studies, and there are scattered reports of studies in which intravenous nitroglycerin was tested in blinded fashion against sodium nitroprusside.

In each of these studies, therapeutic doses of intravenous nitroglycerin were found to reduce systolic and diastolic arterial blood pressure. The heart rate was usually increased, presumably as a reflexive response to the fall in blood pressure. Coronary perfusion pressure was usually, but not always, maintained.

Intravenous nitroglycerin reduced central venous pressure (CVP), right arterial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary-capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR). When these parameters were elevated, reducing them toward normal usually caused a rise in cardiac output. Conversely, intravenous nitroglycerin usually *reduced* cardiac output when it was given to patients whose CVP, RAP, PAP, PCWP, PVR, and SVR were all normal.

Dosing regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Several well-controlled clinical trials have used exercise testing to assess the anti-anginal efficacy of continuously-delivered nitrates. In the large majority of these trials, active agents were indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome nitrate tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored.

To avoid development of tolerance to nitroglycerin, drug free intervals of 10-12 hours are known to be sufficient; shorter intervals have not been well studied. In one well-controlled clinical trial, subjects receiving nitroglycerin appeared to exhibit a rebound or withdrawal effect, so that their exercise tolerance at the end of the daily drug-free interval was less than that exhibited by the parallel group receiving placebo. Most clinical trials of intravenous nitroglycerin have been brief and have typically followed hemodynamic parameters during a single surgical procedure. In one careful study, one of the few that lasted more than a few hours, continuous intravenous nitroglycerin had lost almost all of its hemodynamic effect after 48 hours. In the same study, patients who received nitroglycerin infusions for only 12 hours out of each 24 demonstrated no similar attenuation of effect. These results are consistent with those seen in multiple large, double-blind, placebo-controlled trials of other formulations of nitroglycerin and other nitrates.

Pharmacokinetics: The volume of distribution of nitroglycerin is about 3 L/kg, and nitroglycerin is cleared from this volume at extremely rapid rates, with a resulting serum half-life of about 1 - 4 minutes. The observed clearance rates (close to 1 L/kg/min) greatly exceed hepatic blood flow. Known sites of extrahepatic metabolism include red blood cells and vascular walls.

The first products in the metabolism of nitroglycerin are inorganic nitrate and the 1,2- and 1,3-dinitroglycerols. The dinitrates are less effective vasodilators than nitroglycerin, but are longer lived in the serum, and their net contribution to the overall effect of chronic nitroglycerin regimens is not known. Nitroglycerin is excreted by the renal route primarily as the 2 dinitrometabolites, which have excretion half-lives of approximately 3 to 4 hours.

Indication and Clinical Use

NITROJECT® (nitroglycerin injection) is indicated for:

- control of blood pressure in perioperative hypertension, i.e., hypertension associated with surgical procedures, especially cardiovascular procedures (hypertension seen during intratracheal intubation, anesthesia, skin incision, sternotomy, cardiac bypass) and in the immediate post-surgical period;
- control of congestive heart failure in the setting of acute myocardial infarction;
- treatment of angina pectoris in patients who have not responded to conventional antianginal agents;
- induction of controlled hypotension during surgery.

Contraindications

NITROJECT® (nitroglycerin injection) should NOT be administered to individuals who:

- have a known hypersensitivity to NITROJECT® (nitroglycerin injection) or a known idiosyncratic reaction to organic nitrates;
- are taking any form of phosphodiesterase inhibitors, such as sildenafil, tadalafil, or vardenafil. Concomitant use can cause life-threatening hypotension, syncope, or myocardial ischemia;
- are taking the soluble guanylate cyclase stimulator (e.g. riociguat, vericiguat). Concomitant use can cause hypotension;
- have hypotension or uncorrected hypovolemia, as the use of NITROJECT® (nitroglycerin injection) in such states could produce severe hypotension or shock;
- have increased intracranial pressure, for example head trauma or cerebral hemorrhage;
- have constrictive pericarditis or pericardial tamponade.

Warnings

Nitroglycerin migration to plastics: Nitroglycerin readily migrates into many plastics. To avoid absorption of Nitroglycerin into plastic parenteral solution containers, the dilution and storage of NITROJECT® (nitroglycerin injection) should be made only in glass parenteral solution bottles.

Nitroglycerin formulations: Several formulations of nitroglycerin for injection are available. They differ in concentration and/or total volume per vial. When switching between products, careful attention must be paid to dilution factors and dosing instructions to avoid medication errors.

Infusion Set and Filter Used

Nitroglycerin readily migrates into many plastics, including the polyvinyl chloride (PVC) plastics commonly used for intravenous administration sets. Use of PVC tubing in infusion sets may lead to loss of active ingredient due to adsorption of nitroglycerin to PVC, therefore dosage is affected (see Dosage and Administration). Nitroglycerin adsorption by PVC tubing is increased when the tubing is long, the flow rates are low, and the nitroglycerin concentration of the solution is high. The delivered fraction of the solution's original nitroglycerin content has been 40 - 80% when using PVC tubing. The fraction varies with time during a single infusion, and no simple correction factor can be used. PVC tubing has been used in most published studies of intravenous nitroglycerin, but the reported doses have been calculated by simply multiplying the flow rate of the solution by the solution's original concentration of nitroglycerin. **THE ACTUAL DOSES DELIVERED HAVE BEEN LESS, SOMETIMES MUCH LESS, THAN THOSE REPORTED.** Relatively non-adsorptive intravenous administration sets are available. **IF INTRAVENOUS NITROGLYCERIN IS ADMINISTERED THROUGH NON-ADSORPTIVE TUBING, DOSES BASED UPON PUBLISHED REPORTS WILL GENERALLY BE TOO HIGH.** Some in-line intravenous filters also adsorb nitroglycerin and these should be avoided.

Fluid Overload

The intravenous administration of solutions may cause fluid overload resulting in dilution of serum electrolyte concentrations, overhydration and congested states of pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration of the injections.

Precautions

Hypotension and Shock

Severe hypotension and shock may occur with even small doses of nitroglycerin. This drug should be used with caution in patients who may be volume depleted or who are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Hypertrophic Cardiomyopathy

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Tolerance

Development of tolerance and occurrence of cross tolerance to other nitro compounds has been reported. As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates demonstrating the existence of true physical dependence.

Some clinical trials in angina patients have provided nitroglycerin for about 12 continuous hours of every 24-hour day. During the nitrate-free intervals in some of these trials, anginal attacks have been more easily provoked than before treatment, and patients have demonstrated hemodynamic rebound and decreased exercise tolerance. The importance of these observations to the routine, clinical use of intravenous nitroglycerin is not known.

Intracoronary Injection

Intracoronary injection of nitroglycerin injection has not been studied.

Use in the Elderly

When selecting the type of infusion solution and the volume/rate of infusion for a geriatric patient, consider that geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant drug therapy.

Patients with renal and/or hepatic insufficiency

NITROJECT® should be used with caution in patients who have severe hepatic or renal disease.

Laboratory Tests

Because of the propylene glycol content of intravenous nitroglycerin, serum triglyceride assays that rely on glycerol oxidase may give falsely elevated results in patients receiving this medication.

Pregnancy

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

Lactation

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

Pediatric Use

Safety and effectiveness in children have not been established.

Drug Interactions

Administration of NITROJECT® (nitroglycerin injection) through the same infusion set as blood can result in pseudoagglutination and hemolysis. More generally, NITROJECT® (nitroglycerin injection) should not be mixed with any other medication of any kind.

Phosphodiesterase inhibitors: Concomitant use of NITROJECT® (nitroglycerin injection) with phosphodiesterase inhibitors (e.g. sildenafil, tadalafil, or vardenafil) can potentiate the hypotensive effects (see **Contraindications**).

Soluble guanylate cyclase stimulator: Concomitant use of NITROJECT® (nitroglycerin injection) with soluble guanylate cyclase stimulator (e.g. riociguat, vericiguat) can cause hypotension (see **Contraindications**).

Antihypertensive drugs: Concomitant use of nitroglycerin and other vasodilatating antihypertensives (e.g., beta-blockers, calcium channel blockers and tricyclic antidepressants) may cause increased hypotensive effects.

Tricyclic Antidepressants: Nitroglycerin may potentiate the hypotensive effects of tricyclic antidepressants.

Anticoagulants: Intravenous nitroglycerin at higher dosages may interfere with the anticoagulant effect of heparin. Intravenous nitroglycerin can induce heparin resistance. In patients receiving intravenous nitroglycerin, concomitant heparin therapy should be guided by frequent measurement of the activated partial thromboplastin time.

Adverse Reactions

Adverse reactions to nitroglycerin are generally dose-related and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

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.

Miscellaneous: Muscle twitching and retrosternal discomfort.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in apparently normal patients. Further discussion is listed under '**Overdosage**'.

Data are not available to allow estimation of the frequency of adverse reactions during treatment with NITROJECT® (nitroglycerin injection).

Post-marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

- **NERVOUS SYSTEM DISORDERS:** Headache
- **VASCULAR DISORDERS:** Hypotension (severe)
- **CARDIAC DISORDERS**: Cardiac arrest
- **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS**: Dyspnea
- **INVESTIGATIONS**: Blood pressure decreased

Other (Class) Reactions

- **IMMUNE SYSTEM DISORDERS:** Hypersensitivity
- **BLOOD AND LYMPHATIC SYSTEM DISORDERS:** Methemoglobinemia
- **VASCULAR DISORDERS:** Syncope

Symptoms and Treatment of Overdosage

Signs and symptoms of overdose generally reflect the mechanism of action of nitroglycerin (see **Adverse Reactions**). There is no specific antidote for overdose of nitroglycerin. The risk of overdose can be minimized by close monitoring during treatment.

Hemodynamic Effects: The noxious effects of nitroglycerin overdose are generally the results of nitroglycerin's capacity to induce vasodilation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g. maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia: Use of nitroglycerin has been associated with methemoglobinemia as nitrate ions liberated during metabolism of organic nitrates can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant productions of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2 - 4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%. This was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without colour change on exposure to air.

Treatment of nitrate-induced methemoglobinemia consists of discontinuing the medication and when necessary, administering 1mg/kg of intravenous methylene blue.

In the event of an overdose, the use of epinephrine or other arterial vasoconstrictors may be harmful.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada’s toll-free number, 1-844 POISON-X (1-844-764-7669).

Dosage and Administration

NITROJECT® (nitroglycerin injection) is intended for intravenous infusion only using sterile equipment. It should be administered only via an infusion pump that can maintain a constant infusion rate. A container which has lost its vacuum, or one in which particulate matter is visible, should not be used.

Not for direct intravenous injection. NITROJECT® (nitroglycerin injection) is a concentrated, potent drug which must be diluted in Dextrose (5%) Injection USP, or 0.9 % Sodium Chloride (0.9%) Injection USP, prior to its infusion. The resultant solution should be used within 24 hours. NITROJECT® (nitroglycerin injection) 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 must be determined by individual patient requirements and patient response. Patient response should be based on blood pressure effects, as well as possible adverse events observed.

DOSAGE IS AFFECTED BY THE TYPE OF INFUSION SET USED (see **Warnings**). Although the usual adult starting dose in published studies has been 25 mcg/min or more, these studies used PVC tubing, so the delivered doses were less than those reported. WHEN NON-ADSORPTIVE TUBING IS USED, DOSES MUST BE REDUCED. When using non-adsorptive tubing, the dose necessary to achieve a given response will vary greatly from patient to patient. Patients with normal or low left-ventricular filling pressure (e.g., patients with uncomplicated angina pectoris) may respond fully to as little as 5 mcg/min, while other patients may require a dose that is one or even two orders of magnitude higher.

When using non-adsorptive tubing, the initial adult dosage of NITROJECT® (nitroglycerin injection) should be 5 mcg/min. Subsequent titration must be guided by the clinical results, with dose increments becoming more cautious as partial response is seen. Initial titration should be in 5 mcg/min increments at intervals of 3 to 5 minutes. If no response is seen at 20 mcg/min, increments of 10 and even 20 mcg/min can be used. Once some hemodynamic response is observed, dosage increments should be smaller and less frequent.

When the concentration is changed, the tubing must be disconnected from the patient and flushed with the new solution before therapy is continued. If this precaution is not taken, then depending upon the tubing, pump, and flow rate used, it might be several hours before nitroglycerin is delivered at the desired rate.

Because non-adsorptive tubing 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. 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.

Continuous monitoring of blood pressure and heart rate is necessary in all patients receiving this medication; in many cases, invasive monitoring of pulmonary capillary wedge pressure will also be indicated.

Lower concentrations of NITROJECT® (nitroglycerin injection) increase the potential precision of dosing, but these concentrations increase the total fluid volume that must be delivered to the patient. Total fluid load may be a dominant consideration in patients with compromised function of the heart, liver, and/or kidneys. The mixing instructions and necessary flow rates to achieve various dose rates with the different concentrations achieved after dilution are shown in Tables 1 and 2 (see **Availability of Dosage Forms**).

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

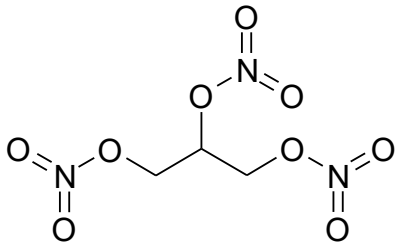
Do not add any concomitant medication to NITROJECT®.

Discard any unused portion.

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® (nitroglycerin injection) 5 mg/mL is a sterile, non-pyrogenic and non-explosive solution for intravenous infusion after dilution. The solution is clear and colourless. Each mL contains 5 mg of nitroglycerin, 30% ethanol v/v, 30% propylene glycol v/v and Water for Injection, USP, q.s. to 1 mL.

Stability and Storage Recommendations:

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

Dilution: Solution preparation for an infusion pump

Aseptically transfer 10 mL (50 mg Nitroglycerin) NITROJECT® (nitroglycerin injection) 5 mg/mL into a glass, IV bottle containing 1000 mL of 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP and mix well. The resultant solution will contain approximately 50 mcg/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 1 (see **Availability of Dosage Forms**). 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) 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 injection) 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**).

Availability of Dosage Forms:

NITROJECT® 5 mg/mL (nitroglycerin injection) 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.

Table 1

I.V. Administration Table for NITROJECT® 5 mg/mL
Each 10 mL Vial = 50 mg Nitroglycerin

Concentration (approx.)	Mixing Instructions
50 mcg/mL	10 mL in 1000 mL
100 mcg/mL	10 mL in 500 mL or 20 mL in 1000 mL
200 mcg/mL	10 mL in 250 mL or 20 mL in 500 mL or 40 mL in 1000 mL

Table 2
Necessary Flow Rates (mL/hr*)

Desired Dose	Initial Solution Concentration (mcg/mL)		
(mcg/min)	50	100	200
2.5	3	---	---
5	6	3	---
10	12	6	3
20	24	12	6
40	48	24	12
60	72	---	---
80	96	48	24
120	---	72	---
160	---	96	48
240	---	---	72
320	---	---	96

*With a set that produces 60 drops/mL, 1 mL/hr = 1 drop/min.

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).

Information for the Consumer

If you are using NITROJECT® (nitroglycerin injection), you must not take VIAGRA or REVATIO (sildenafil), CIALIS or ADCIRCA (tadalafil), LEVITRA or STAXYN (vardenafil), VERQUVO (vericiguat) or ADEMPAS (riociguat). Such combinations can produce severe lowering of blood pressure, loss of consciousness, heart attack or death.

Pharmacology

The primary pharmacological action of nitroglycerin is its smooth muscle relaxant effect. Therapeutic effectiveness is due to its action on vascular smooth muscle. Response from both the venous and arterial beds is dose related, however, venous effects predominate.

In anesthetized dogs, large conductive coronary arteries dilated upon intravenous infusion of nitroglycerin. A similar effect was found in conscious dogs. While there was some effect on the small coronary vessels, marked dilation of the large coronary arteries occurred. Further experiments in anaesthetized dogs have shown a vasodilation of peripheral arteries resulting in a decrease in mean arterial pressure.

In a study of human forearm bloodflow, administration of sublingual nitroglycerin caused a significant decline in venous tone. The result was pooling of blood in the peripheral veins, a decrease in the return of blood to the heart and a mild decrease in systemic arterial pressure. A corresponding fall in the forearm vascular resistance was also observed.

Congestive heart failure patients given intravenous nitroglycerin showed a significant fall in capillary wedge pressure. Cardiac index improved.

Intracardiac administration. Rats exhibited one compartment kinetics, average half-life of 4 minutes, and mean apparent volume of distribution of 3 L/kg.

Intravenous administration. In normal volunteers, the half life of intravenous nitroglycerin was 2.8 minutes.

Nitroglycerin is rapidly degraded in the liver by the enzyme glutathione-organic nitrate reductase. The process is initiated by a redox reaction. One molecule of nitroglycerin reacts with two of reduced glutathione to release one inorganic nitrate ion from either the 2 or 3 position. This produces 1,3- or 1,2- glyceryl dinitrate and oxidized glutathione.

Elimination - Essentially all metabolites are eliminated in the urine.

Toxicology

Intravenous administration. Rabbits exhibited an LD_{50} of 43 mg/Kg and guinea pigs an LD_{50} of 83.5mg/Kg. Dogs survived doses of 10-30 mg/Kg.

Non-intravenous administration. LD_{50}'s ranged from 80 to 500 mg/Kg in various animal studies. Death was a result of methemogloninemia, circulatory collapse and convulsions.

When cats were given 7.5 or 15 mg/Kg nitroglycerin injected subcutaneously, they survived fifty daily doses on average. Albuminuria and icterus were noted. At autopsy, hemorrhage of the cerebellum, heart, liver and spleen were observed.

Cats exposed to saturated atmospheres of nitroglycerin for 68 days developed anemia and moderate leukocytosis. Methemoglobinemia, peripheral vasodilation causing a fall in blood pressure, and tolerance developed when exposures were longer than 68 days.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: No long-term studies in animals were performed to evaluate the carcinogenic potential of nitroglycerin, and studies have not been performed to evaluate the potential for mutagenicity or impairment of fertility.

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Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about NITROJECT®

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals by visiting the Health Canada Drug Product Database website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website, https://www.junopharma.com, or by calling 1 800 363 0584.

This leaflet was prepared by Juno Pharma Canada Inc.

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