

PRODUCT MONOGRAPH

<sup>Pr</sup> **ALPROSTADIL INJECTION USP**

Alprostadil

500 mcg/mL Injection

USP

Prostaglandin

Valeo Pharma Inc.  
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Pr **ALPROSTADIL INJECTION USP**

Alprostadil

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form/ Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Intravascular Injection Only	Injection/ 500 mcg/mL	Ethyl Alcohol Anhydrous

**INDICATIONS AND CLINICAL USE**

**Geriatrics**

No data is available.

**Pediatrics**

Alprostadil Injection USP (alprostadil) is indicated to temporarily maintain the patency of the ductus arteriosus until corrective or palliative surgery can be performed in neonates who have congenital heart defects and who depend upon a patent ductus arteriosus for survival.

Alprostadil should be administered only by medically trained personnel in facilities in which pediatric patients can receive or have access to pediatric intensive care.

**CONTRAINDICATIONS**

Alprostadil is contraindicated in the following patients:

- Cyanotic neonates with persistent fetal circulation.
- Neonates with total anomalous pulmonary venous return below the diaphragm, neonates with polysplenia or asplenia in whom pulmonary atresia is combined with anomalous pulmonary venous return which may be obstructed.

In such patients alprostadil may precipitate pulmonary edema because of increased pulmonary blood flow.

**WARNINGS AND PRECAUTIONS**

**PEDIATRICS**

## General

Since alprostadil appears most effective within 96 hours after birth due to a decreasing responsiveness of the ductus arteriosus with time after birth, every effort should be made to start infusion of the drug during this period.

Alprostadil sterile solution should be infused for the shortest period of time at the lowest dose which will produce the desired effects. Risk of long-term infusion of alprostadil should be weighed against the possible benefits that critically ill infants may derive from its administration.

Alprostadil should be used with caution in infants with suspected bleeding tendencies.

Cortical proliferation of the long bones has followed long-term infusions of alprostadil in infants. The proliferation appeared to regress after withdrawal of the drug. (see **Toxicology Section**)

## Carcinogenesis, Mutagenesis and Fertility

Long-term carcinogenicity and fertility studies have not been done.

The Ames and Alkaline Elution assays reveal no potential for mutagenesis.

## Cardiovascular

In all neonates, blood pressure should be monitored by appropriate methods such as an umbilical artery catheter, or by a Doppler transducer. **Should arterial pressure fall significantly, reduce the rate of infusion immediately.**

No drug interactions have been reported to occur between alprostadil and the standard therapy employed in neonates with congenital heart defects. Standard therapy includes antibiotics, such as penicillin or gentamicin; vasopressors, such as dopamine or isoproterenol; cardiac glycosides; and diuretics, such as furosemide.

## Gastrointestinal

The administration of alprostadil to neonates may result in gastric outlet obstruction secondary to antral hyperplasia. This effect appears to be related to duration of therapy and cumulative dose of the drug. Neonates receiving alprostadil at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction.

## Respiratory

Care should be taken to avoid the use of alprostadil in neonates with respiratory distress syndrome (hyaline membrane disease), which sometimes can be confused with cyanotic heart disease. If full diagnostic facilities are not immediately available, cyanosis ( $pO_2$  less than 40 mm Hg) and restricted pulmonary blood flow apparent on an X-ray are good indicators of congenital heart defects.

In infants with restricted pulmonary blood flow, the increase in blood oxygenation is inversely proportional to pretreatment  $pO_2$  values; that is, patients with low  $pO_2$  values (less than 40 torr) respond best, and patients with high  $pO_2$  values (greater than 40 torr) usually have little response.

In infants with restricted pulmonary blood flow, measure efficacy of alprostadil by monitoring an improvement in blood oxygenation. In infants with restricted systemic blood flow, measure efficacy by monitoring improvement of systemic blood pressure and blood pH.

Approximately 10 to 12% of neonates treated with alprostadil experienced apnea. Apnea is seen most often in neonates weighing less than 2 kg at birth and usually appears during the first hour of drug infusion. Therefore alprostadil should be used in facilities with immediately available intensive care for intubation and assisted ventilation.

Pathologic studies of the ductus arteriosus and pulmonary arteries of infants treated with prostaglandin E<sub>1</sub> have disclosed histologic changes compatible with a weakening effect upon these structures. The specificity or clinical relevance of these findings is not known.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

In infants whose ductus arteriosus must be kept patent, the most frequent adverse reactions observed with alprostadil infusion are related to its known pharmacological effects. The following incidences are based on experience in 436 patients.

### **Cardiovascular System**

The most common adverse reactions reported in these patients were flushing 10.1%, bradycardia 6.7%, hypotension 3.9%, tachycardia 2.8%, cardiac arrest 1.1% and edema 1.1%. The following reactions were reported in less than 1% of patients: congestive heart failure, hyperemia, pneumo-pericardium, second degree heart block, shock, spasm of the right infundibulum (conus arteriosus), supraventricular tachycardia, ventricular fibrillation, ventricular hypertrophy, tachyphylaxis.

### **Central Nervous System**

The most common adverse reactions reported were fever in 13.8% and seizures in 4.1% of patients. The following reactions were reported in less than 1% of patients: intracranial bleeding, hyperextension of neck, hyperirritability, hypothermia, jitteriness, lethargy, stiffness.

### **Respiratory System**

The most common adverse reaction reported was apnea in 11.5% of patients. The following reactions were reported in less than 1% of patients: bradypnea, bronchial wheezing, hypercapnea, pneumothorax, respiratory depression, respiratory distress, tachypnea.

### **Gastrointestinal System**

The most common adverse reaction reported was diarrhea in 2.6% of patients. The following reactions were reported in less than 1% of patients: gastric regurgitation, hyperbilirubinemia, peritonitis.

### **Hematologic**

The most common adverse reaction reported was disseminated intravascular coagulation in 1.1% of patients. The following reactions were reported in less than 1% of patients: anemia, bleeding, thrombocytopenia, hypochromic anemia.

### **Urinary Tract**

The following reactions were reported in less than 1% of patients: anuria, hematuria, renal failure.

### **Metabolic**

The most common adverse reaction reported was hypokalemia in 1.1% of patients. The following reactions were reported in less than 1% of patients: hypoglycemia, hyperkalemia.

## **Infection**

Sepsis was reported in 1.6% and peritonitis in less than 1% of patients.

## **Ductus Arteriosus Histological Changes**

One group of investigators reported edema of the media, separation of the medial components by clear spaces, pathological interruption of the internal elastic lamina, and intimal lacerations; some of which extended into the media in the ductus arteriosus of four patients.

## **Cortical Proliferation of Long Bones**

Following long term infusion of alprostadil, cortical proliferation of long bones has been reported.

This hypertrophic osteoarthropathy appeared to be reversible on discontinuation of the drug.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

Interactions with other drugs have not been established.

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Test Interactions**

Interactions with laboratory tests have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

If undiluted alprostadil comes in direct contact with a plastic container, plasticizers are leached from the sidewalls. The solution may turn hazy and the appearance of the container may change. Should this occur, the solution should be discarded and the plastic container replaced. This appears to be a concentration-dependent phenomenon. To minimize the possibility of haze formation, alprostadil should be added directly to the intravenous infusion solution avoiding contact with the walls of plastic containers (see **Dilution Instructions**).

### **Recommended Dose and Dosage Adjustment**

The initial infusion rate of alprostadil should be 0.1 mcg per kilogram of body weight per minute. When the desired effect on the ductus arteriosus is achieved, decrease infusion to the lowest possible dose while maintaining the desired effect. This may be accomplished by reducing the dosage from 0.1 to 0.05 to 0.025 to 0.01 mcg/kg of body weight per minute. Although doses up to 0.4 mcg/kg of body weight per minute have been used, doses above 0.1 mcg/kg of body weight per minute generally do not offer additional benefits.

The preferred route of administration for alprostadil is by continuous intravenous infusion into a large vein. Alternatively, alprostadil may be administered through an umbilical artery catheter placed at the

ductal opening. Adverse effects have occurred with both routes of administration, but higher incidence of flushing has been associated with interarterial than with intravenous administration.

## Reconstitution

### Dilution Instructions

To prepare infusion solutions, dilute 1 mL of alprostadil in PVC bags with sterile Sodium Chloride Injection or sterile Dextrose Injection. Dilute to volumes appropriate for the pump delivery system available. Prepare fresh infusion solution every 24 hours. Discard any solution more than 24 hours old. Unused portions of the 1 mL should be discarded.

1. For administration using a **pump capable of delivering small volume constant infusions** (i.e. not limited to discrete infusion rates) dissolve 1 mL alprostadil (500 mcg alprostadil) in 25 to 100 mL sterile 0.9% Sodium Chloride Injection USP or sterile 5% Dextrose Injection USP to provide a solution containing 500 mcg alprostadil. The infusion rate to deliver 0.1 mcg/kg of body weight per minute can be calculated as follows:

$$\text{Infusion rate (mL/hr)} = \frac{\text{Volume containing 500 mcg alprostadil} \times \text{body weight (kg)}}{83.3}$$

2. For administration using an infusion pump limited to discrete infusion rates, infuse 2 to 4 mL per hour. The volume of 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP to be added to the 1 mL alprostadil is to be calculated as follows:

$$\text{Volume of 0.9\% Sodium Chloride Injection USP or 5\% Dextrose Injection USP needed (mL)} = \frac{\text{Pump rate (mL/hr)} \times 83.3}{\text{Body weight (kg)}}$$

The infusion solution may be mixed conveniently in a graduated mixing chamber inserted between the IV bottle and the pump.

Change the dosage from 0.1 mcg/kg of body weight per minute to 0.05 mcg/kg of body weight per minute by reducing the pump rate to one-half the original rate.

## OVERDOSAGE

Apnea, bradycardia, pyrexia, hypotension and flushing may be signs of drug overdose. If apnea or bradycardia occurs, the infusion should be discontinued and the appropriate medical treatment initiated. Caution should be used if the infusion is restarted. If pyrexia or hypotension occur, the infusion rate should be reduced until these symptoms subside. Flushing is usually attributed to incorrect intra-arterial catheter placement and is usually alleviated by repositioning the tip of the catheter.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

Alprostadil (also known as *prostaglandin E<sub>1</sub>*) relaxes the ductus arteriosus in early postnatal life and supports its patency when continuously infused intravenously or intra-arterially in neonates with congenital heart defects who depend on a patent ductus for survival. The desired pharmacological effects are obtained with an initial dosage of 0.1 mcg/kg/minute. Higher doses do not offer added benefit. Postnatally the ductus arteriosus rapidly loses its responsiveness to alprostadil and consequently alprostadil appears to be most effective within 96 hours after birth, particularly when the preinfusion arterial pO<sub>2</sub> is less than 40 mm Hg.

### **Pharmacokinetics**

The estimated half-life of alprostadil is 5 to 10 minutes. Intravenously administered alprostadil is rapidly distributed and metabolized and the pulmonary vascular bed removes about 68% of the drug in a single pass. Alprostadil is weakly bound to serum albumin. The major route of elimination of alprostadil and its metabolites is *via* the kidneys. In laboratory animals and humans, alprostadil can lower blood pressure, probably by relaxing the smooth muscle of the cardiovascular system. Alprostadil can elevate body temperature and this effect has been observed in some neonates receiving the drug.

## **STORAGE AND STABILITY**

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Refrigerate between 2 and 8°C. Protect from light and freezing. Discard unused portion.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Alprostadil Injection USP is available in 1 mL fill in 2 mL vials, boxes of 1.

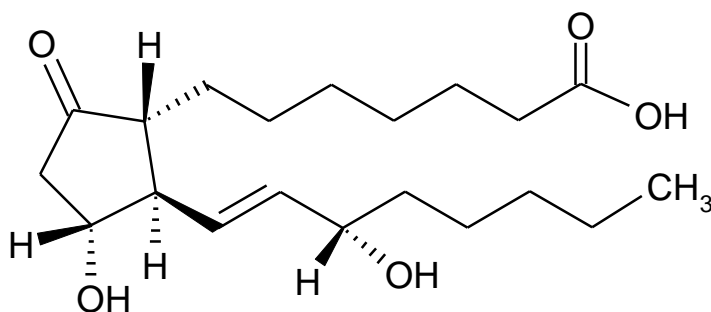
Each mL contains: alprostadil 500 mcg and ethyl alcohol anhydrous (solvent).

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name:	Alprostadil
Chemical name:	Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-, (11 $\alpha$ ,13 <i>E</i> , 15 <i>S</i> )- (1 <i>R</i> ,2 <i>R</i> ,3 <i>R</i> )-3-Hydroxy-2-(( <i>E</i> )-(3 <i>S</i> )-3-hydroxyl-1-octenyl)-5-oxocyclopentane heptanoic acid
Molecular formula:	C <sub>20</sub> H <sub>34</sub> O <sub>5</sub>
Molecular mass:	354.5 g/mol
Structural formula:	



Physicochemical properties: Clear sterile solution.

Aqueous Solution pH: Not applicable since the finished product is not an aqueous solution.

As per DMF: Alprostadil is a white to off-white crystalline substance.

As per USP: Alprostadil is a white to off-white, crystalline powder.

As per EP: Alprostadil is a white or slightly yellowish, crystalline powder.

As per USP: Alprostadil is soluble in water, freely soluble in alcohol, soluble in acetone, slightly soluble in ethyl acetate, very slightly soluble in chloroform and in ether.

As per EP: Alprostadil is practically insoluble in water, freely soluble in alcohol, soluble in acetone, slightly soluble in ethyl acetate.

## DETAILED PHARMACOLOGY

### Animal Studies

Alprostadil uniformly lowered blood pressure of mammals when administered intravenously in doses between 1 and 10 mcg/kg. The depressor action was due to a decrease in peripheral resistance. Cardiac output and rate increased in association with alprostadil induced hypotension. The decreased vascular resistance occurred in the musculocutaneous, renal, mesenteric, coronary and pulmonary circulations and the dilatation was particularly apparent after intra-arterial administration close to the regional vascular beds.

*In vitro* experiments with strips of lamb or calf ductus arteriosus demonstrated that alprostadil markedly relaxed the strips in a low oxygen environment, but had little, if any, effect after the strips were exposed to oxygen. It was also demonstrated in newborn rats and rabbits that alprostadil administered subcutaneously reopened the closing ductus.

The administration of the prostaglandin synthetase inhibitors, indomethacin and sodium salicylate, to near-term pregnant rats or rabbits led to closure of the fetal ductus arteriosus *in utero*. Additionally, gastric administration of acetylsalicylic acid to the near-term fetus *in utero* resulted in constriction of the ductus arteriosus and redistribution of the cardiac output, an effect which could be reversed by the intravenous infusion of alprostadil into the fetus.

Large doses of alprostadil injected intraventricularly in the rat and monkey produced a reduction in spontaneous locomotion and unresponsiveness to stimuli, followed by stupor and eventually catatonia. By contrast, only a short-lived sedation followed the administration of very high doses by the parenteral route.

The administration of alprostadil into the ventricle or into the hypothalamus produced a prompt elevation of body temperature in the rat, rabbit, cat, monkey, sheep and chicken.

Alprostadil appeared to inhibit norepinephrine release from adrenergic nerve endings and inhibit effector responses which result from adrenergic nerve stimulation. Alprostadil appeared in most cases to enhance cholinergic responses with the exception of the heart and secretion from the gastric mucosa. The clinical significance of these observations is not known.

Alprostadil relaxed bronchial muscle tone in the cat, dog and monkey and briefly reduced pulmonary artery pressure when infused into the anaesthetized dog.

Alprostadil strongly inhibited ADP-induced platelet aggregation in rat, pig and human platelet rich plasma. The inhibition was short-lived (5 to 30 minutes) and in humans, no inhibition was produced at tolerable doses of 0.1 to 0.2 mcg/kg/minute.

In several animal species and man, intravenously or arterially administered alprostadil was very rapidly metabolized and distributed throughout the entire body with the exception of the CNS where concentrations though detectable, were very low. The primary organs for metabolism and inactivation of alprostadil were the lung, liver and kidney which removed and metabolized 40 to 95% of the alprostadil in a single pass. A number of other tissues possessed lesser, but significant, capacity to metabolize alprostadil. The predominant metabolites found in plasma, 15-oxo-PgE<sub>1</sub> and 13, 14-dihydro-15-oxo-PgE<sub>1</sub> were metabolized by  $\beta$ - and  $\omega$ -oxidation prior to excretion primarily via the kidney.

Excretion of drug-related materials was essentially complete within 24 hours after dosing with no intact alprostadil found in urine, and no evidence of tissue retention of alprostadil or metabolites. The primary urinary metabolite of alprostadil in man was 11  $\alpha$ -hydroxy-9, 15-dioxo 2,3,4,5-tetranorprosta-1,20-dioic acid, which is different from that found in either guinea pig or rat urine. In three species, rat, rabbit and lamb, the prostaglandin metabolizing activity of fetal lung - the primary organ for the initial metabolic conversion of parenterally administered alprostadil - has been shown to be at least as great as that of adults.

## TOXICOLOGY

### Acute Studies

Species	Route	LD <sub>50</sub> (mg/kg)
mouse	intravenous	96
	subcutaneous	12 (neonates)
rat		76
	intravenous	29
	subcutaneous	33 (neonates)
		25

The signs of toxicity in the above studies were diarrhea, depression and convulsions.

### SUBACUTE AND CHRONIC STUDIES

#### 5 Day Study (Rabbit)

Alprostadil was administered to the nasal mucosa of rabbits at a dose of 0.06 mg/kg once per day for 5 days. There was no evidence of damage to the nasal mucosa.

#### 7 Day Studies (Rat, Dog)

Rats were administered alprostadil intra-arterially at 50 ng/kg/minute for 10 minutes each hour and the only adverse effect noted was a slight repression of body weight.

Alprostadil was administered to the dog via the left femoral artery at 10 ng/kg/minute for 10 minutes every hour or via the anterior vena cava at 1 mcg/kg/minute for 7 days.

In the intra-arterial study, there was little evidence of drug effect with the exception of edema in the infused extremity.

In the intravenous study, clinical responses in drug recipients included anorexia, diarrhea, vomiting, and apparent abdominal cramps. Drug recipients were lethargic, appeared weak and 3 of 4 animals developed a moist cough. Subcutaneous edema was found in the anterior limbs of drug recipients after 6 days of treatment. Treated animals showed droopy eyelids and an accumulation of mucous of the conjunctiva and palpebra.

Mean arterial blood pressure showed a transient decrease which returned to normal after the first day of drug treatment. The heart rate increased after the first day of drug treatment.

Necropsy examination showed subcutaneous edema of the anterior limbs in drug recipients. Widespread thrombosis and infarction was found in vehicle controls and drug recipients at necropsy or by microscopic examination. These changes may have been related to the infusion procedure or to the

vehicle which contained 20% ethanol. In any event, no differences were noted between drug-treated and the vehicle control groups in distribution or intensity of the thromboses except that overt pulmonary infarcts were seen only in the drug recipients (2 out of 4 animals).

### **8 Day Study (Monkey)**

Monkeys were administered alprostadil intramuscularly at doses ranging from 0.5 to 1.0 mg/kg/day for 8 days. The signs of drug effect included depression, emesis and sialorrhoea.

### **1 Month Studies (Rat, Dog)**

Alprostadil was given intravenously to rats at a dosage level of 0.18 mg/kg 10 times per day for 30 days. Signs of drug effect included slightly repressed body weight gain in male rats, less efficient food conversion ratios in both males and females and slightly elevated hematocrit and haemoglobin levels.

Beagle dogs were treated intravenously with alprostadil for 30 days at a dose level of 25, 80 and 250 ng/kg/minute. A fourth group received diluent. There were two dogs per sex per group.

The dogs receiving 250 ng/kg/minute had swelling of the distal limbs which was first observed on the 4<sup>th</sup> day of infusion. Other clinical signs in this dose group included injection of the scleral blood vessels, ptosis of the lower eyelids, tearing, anorexia, muscle tremors, apparent discomfort and reluctance to stand.

The dogs receiving 80 ng/kg/minute had distal limb swelling, scleral injection, ptosis and tearing but the incidence was variable and to a lesser degree. Only injection of the scleral vessels was observed in the dogs in the low dose group (25 ng/kg/minute).

Hematologic changes were limited to an increased sedimentation rate in the blood from dogs in the mid and high dose group which corresponded with increased fibrinogen levels.

Clinical chemistry changes, in addition to the increased fibrinogen levels, included increased alkaline phosphatase levels and decreased serum albumin and blood urea nitrogen (high dose group only).

The occurrence of bone lesions was observed on gross necropsy. The bony proliferation was present in the long bones of the limbs of the dogs receiving 250 and 80 ng/kg/minute. The degree of change appeared to be directly dose dependent.

The proliferative bone lesions were observed at the end of the 30 day infusion, and were not anticipated. Thus because there was no stage killing or post-discontinuation observation in these studies, no other information is currently available.

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## IMPORTANT: PLEASE READ

### PART III: CONSUMER INFORMATION

#### Pr **ALPROSTADIL INJECTION USP** ( Alprostadil )

This leaflet is part III of a three-part "Product Monograph" published when Alprostadil Injection USP was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Alprostadil Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

Alprostadil Injection USP is used for temporary treatment of patent ductus arteriosus, a heart defect in infants, until surgery can be done.

##### What it does:

Alprostadil Injection USP is used to keep a blood vessel (ductus arteriosus) open temporarily after the child is born. Normally this blood vessel closes soon after birth. In some children who are born with heart defects, this blood vessel needs to be kept open for a longer time so that enough blood can reach the rest of the body.

##### When it should not be used:

Alprostadil Injection USP should not be given to patients with:

- A blue appearance of the lips, skin and nails due to poor flow through the lungs;
- Abnormal or unusual blood flow between the lungs and the heart.

##### What the medicinal ingredient is:

Alprostadil.

##### What the important nonmedicinal ingredient is:

Ethyl alcohol anhydrous.

##### What dosage forms it comes in:

Alprostadil Injection USP is available in 1 mL fill in 2 mL vials, boxes of 1.

Each mL contains alprostadil 500 mcg in intravascular injection.

#### WARNINGS AND PRECAUTIONS

##### This medication is for use in infants only.

- Since alprostadil appears most effective within 96 hours after birth due to a decreasing responsiveness of the ductus arteriosus with time after birth, every effort should be made to start infusion of the drug during this period.

- Blood pressure should be monitored by appropriate methods.
- Administration may result in gastric outlet obstruction and should be monitored for evidence of enlargement of gastric chamber.
- Care should be taken to avoid the use of alprostadil in neonates with respiratory distress syndrome and restricted pulmonary blood flow.
- Neonates may experience interrupted breathing (apnea).

#### INTERACTIONS WITH THIS MEDICATION

Interactions with other drugs, foods or herbal products have not been established.

#### PROPER USE OF THIS MEDICATION

##### Usual dose:

Your child's doctor will decide what dose will be given.

##### Overdose:

Symptoms of overdose may include interrupted breathing, slow heartbeat, fever, low blood pressure, weakness, or flushing.

##### Missed dose:

A missed dose is unlikely as treatment will follow hospital protocol and be given by trained medical personnel.

#### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The patient will be watched closely since seizures, a rapid or slow heart rate and breathing trouble can occur while using this medication.

#### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Advise your doctor	
		Only if severe	In all cases
Common	<b>Cardiovascular</b> (flushing 10.1%; slow heartbeat 6.7%; low blood pressure 3.9%; accelerated heartbeat 2.8%; cardiac arrest 1.1%; edema 1.1%). <b>Central Nervous System</b> (fever 13.8%; seizures 4.1%). <b>Respiratory</b> (interrupted breathing 11.5%).		✓ ✓ ✓

	<p><b>Gastrointestinal</b> (diarrhea 2.6%).</p> <p><b>Hematologic</b> (coagulation of the blood 1.1%).</p> <p><b>Metabolic</b> (low concentration of potassium ions in the blood 1.1%).</p> <p><b>Infection</b> (toxins in the blood 1.6%).</p>		<p>✓</p> <p>✓</p> <p>✓</p> <p>✓</p>
Uncommon	<p><b>Cardiovascular</b> (congestive heart failure; increased blood flow to body parts; shock; rapid heart rate; etc).</p> <p><b>Central Nervous System</b> (intracranial bleeding; hyperextension of neck; jitteriness; stiffness; unconsciousness).</p> <p><b>Respiratory</b> (slowness of respiration; wheezing; hyperventilation; respiratory depression; distress).</p> <p><b>Gastrointestinal</b> (gastric regurgitation; inflammation of the peritoneum).</p> <p><b>Hematologic</b> (anemia; bleeding).</p> <p><b>Urinary Track</b> (absence of urine formation, presence of blood in urine, renal failure).</p> <p><b>Metabolic</b> (low level of sugar in blood).</p> <p><b>Infection</b> (inflammation of the tonsils).</p>		<p>✓</p> <p>✓</p> <p>✓</p> <p>✓</p> <p>✓</p> <p>✓</p> <p>✓</p>

*This is not a complete list of side effects. For any unexpected effects after your child has been administered Alprostadil Injection USP, advise your doctor.*

## HOW TO STORE IT

Alprostadil Injection USP should be refrigerated between 2 and 8°C and should be protected from light and freezing. Unused portions should be discarded. Keep out of reach of children.

## REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345

Toll-free fax: 1-866-678-6789

By email: [cadrpm@hc-sc.gc.ca](mailto:cadrpm@hc-sc.gc.ca)

By regular mail:  
National AR Centre  
Marketed Health Products Safety and Effectiveness  
Information Division  
Marketed Health Products Directorate  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

**NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.**

## MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting the sponsor, Valeo Pharma Inc., at:  
1-866-694-0150

or

by written request at:  
16667 Boul. Hymus  
Kirkland, (QC), Canada  
H9H 4R9

or by e-mail at :  
[info@valeopharma.com](mailto:info@valeopharma.com)

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