

PRODUCT MONOGRAPH

^{Pr}PROSTIN* VR STERILE SOLUTION

(alprostadil injection USP)

0.5 mg/mL

Prostaglandin

Pfizer Canada ULC
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

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ACTION AND CLINICAL PHARMACOLOGY

Alprostadil (also known as prostaglandin E₁) 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 micrograms per kilogram per 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 pre-infusion arterial pO₂ is less than 40 mm Hg.

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.

INDICATIONS AND CLINICAL USE

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

PROSTIN VR (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.

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

CONTRAINDICATIONS

PROSTIN VR (alprostadil) is contraindicated in the following patients:

1. Cyanotic neonates with persistent fetal circulation.
2. 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 PROSTIN VR may precipitate pulmonary edema because of increased pulmonary blood flow.

WARNINGS

Pathologic studies of the ductus arteriosus and pulmonary arteries of infants treated with prostaglandin E₁ have disclosed histologic changes compatible with a weakening effect upon these structures. The specificity or clinical relevance of these findings is not known.

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

The administration of PROSTIN VR 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 PROSTIN VR at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction.

PROSTIN VR 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 treatment infusion of PROSTIN VR should be weighed against the possible benefits that critically ill infants may derive from its administration.

PRECAUTIONS

PROSTIN VR (alprostadil) should be used with caution in infants with suspected bleeding tendencies.

Care should be taken to avoid the use of PROSTIN VR 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 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.

Since PROSTIN VR (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.

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

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

In infants with restricted pulmonary blood flow, the increase in blood oxygenation is inversely proportional to pre-treatment 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 PROSTIN VR 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.

No drug interactions have been reported to occur between PROSTIN VR 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.

ADVERSE REACTIONS

In infants whose ductus arteriosus must be kept patent, the most frequent adverse reactions observed with PROSTIN VR (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, hyper-extension 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 PROSTIN VR cortical proliferation of long bones has been reported.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Apnea, bradycardia, pyrexia, hypotension and flushing may be signs of drug overdose. If apnea or bradycardia occur, 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.

DOSAGE AND ADMINISTRATION

The initial infusion rate of PROSTIN VR (alprostadil) should be 0.1 micrograms 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 micrograms per kilogram of body weight per minute. Although doses up to 0.4 micrograms per kilogram of body weight per minute have been used, doses above 0.1 micrograms per kilogram of body weight per minute generally do not offer additional benefits.

The preferred route of administration for PROSTIN VR is by continuous intravenous infusion into a large vein. Alternatively, PROSTIN VR 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 inter-arterial than with intravenous administration.

If undiluted PROSTIN VR 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, PROSTIN VR should be added directly to the intravenous infusion solution avoiding contact with the walls of plastic containers.

(Refer to Dilution Instructions on page 12)

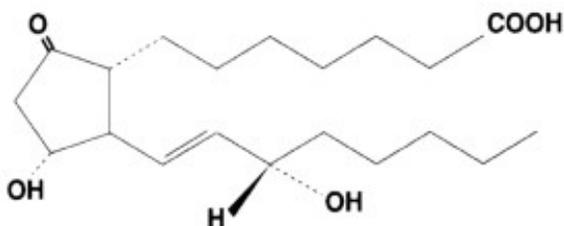
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: alprostadil (PGE₁)

Chemical Name: (11 α , 13E, 15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid

Structural Formula



Molecular Weight: 354.49

Alprostadil occurs as an odourless, white to off-white crystalline powder, which melts in the range of 110 to 116°C.

Composition:

Each mL of PROSTIN VR contains 500 micrograms in anhydrous ethanol

Stability and Storage Recommendations:

Store PROSTIN VR in a refrigerator at 2°C to 8°C. Prepare fresh dilutions of PROSTIN VR every 24 hours. Discard any dilution more than 24 hours old.

Dilution Instructions: To prepare infusion solutions, dilute 1 mL of PROSTIN VR 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.*

1. For administration using a pump capable of delivering small volume constant infusions (i.e., not limited to discrete infusion rates) dissolve 1 mL PROSTIN VR (500 mcg alprostadil) in 25 to 100mL 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 per kilogram of body weight per minute can be calculated as follows:

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

2. For administration using an infusion pump limited to discrete infusion rates, infuse 2 to 4 mL per hour. The volume of saline or glucose to be added to the 1mL PROSTIN VR is to be calculated as follows:

$$\text{Volume of saline or glucose needed (mL)} = \frac{\text{Pump rate (mL/hr)} \times 83.3}{\text{Body weight (kg)}}$$

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

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

AVAILABILITY

PROSTIN VR (alprostadil) is available in 1mL ampoules, each containing 500 micrograms alprostadil in anhydrous ethanol. *Prostin VR is packaged in cartons of 5's.*

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-PgE₁ and 13, 14-dihydro-15-oxo-PgE₁ were metabolized by β - and ω -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 α -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

<u>Species</u>	<u>Route</u>	<u>LD₅₀ (mg/kg)</u>
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 4th 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.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Pr **PROSTIN* VR STERILE SOLUTION**
(alprostadil injection USP)

Read this carefully before your baby receives **PROSTIN VR STERILE SOLUTION**. This leaflet is a summary and will not tell you everything about this drug. Talk to your baby's healthcare professional about your baby's medical condition and treatment and ask if there is any new information about **PROSTIN VR STERILE SOLUTION**.

Serious Warnings and Precautions

About 10 to 12% of newborns that received PROSTIN VR STERILE SOLUTION had interrupted breathing (apnea). Apnea is seen most often in newborns weighing less than 2 kg at birth. It usually appears during the first hour of drug infusion. PROSTIN VR STERILE SOLUTION should be used by trained healthcare professionals in places where your baby has access to the proper equipment for intensive care.

What is PROSTIN VR STERILE SOLUTION used for?

PROSTIN VR STERILE SOLUTION is used in newborns that have congenital heart defects. It is used to keep a blood vessel called the ductus arteriosus open for a short time after your child is born. The ductus arteriosus is a temporary blood vessel found in unborn babies. It normally closes soon after birth. For babies born with some congenital heart defects this blood vessel needs to be kept open for a longer time until surgery can be done to fix or treat the heart condition.

How does PROSTIN VR STERILE SOLUTION work?

PROSTIN VR STERILE SOLUTION relaxes the muscle in the wall of the ductus arteriosus to keep it open while the newborn needs it.

What are the ingredients in PROSTIN VR STERILE SOLUTION?

Medicinal ingredient: alprostadil

Non-medicinal ingredient: anhydrous ethanol

PROSTIN VR STERILE SOLUTION comes in the following dosage form:

Solution for injection: 0.5 mg / mL

Your newborn must not receive PROSTIN VR STERILE SOLUTION if he or she:

- Has blueness or lividness of the skin with persistent pulmonary hypertension.
- Has a rare congenital defect of the pulmonary veins.
- Has multiple small accessory spleens or absence of normal spleen function in whom the pulmonary valve of the heart does not form properly and that have a rare heart defect that occurs when the pulmonary veins fail to form normally.

To help avoid side effects and ensure proper use, talk to your newborn's healthcare professional before your newborn takes PROSTIN VR STERILE SOLUTION. Talk about any health conditions or problems he or she may have, including:

- Respiratory distress syndrome (a breathing problem that makes it hard for your baby to breath)
- Weakening of the temporary blood vessel (ductus arteriosus) and of the arteries going from the heart to lungs
- Bone and tissue changes
- A history of bleeding tendencies

Other warnings you should know about:

Increased cell reproduction at the lower part of the stomach (antral hyperplasia): PROSTIN VR STERILE SOLUTION may cause an increase in cell reproduction at the lower part of your newborn's stomach if it given for more than 5 days. This can cause a blockage between the stomach and the small intestine. Your newborn's doctor will closely monitor your baby for this condition if PROSTIN VR STERILE SOLUTION is given for more than 5 days.

Tell your newborn's healthcare professional about all the medicines he or she takes, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How PROSTIN VR STERILE SOLUTION will be given:

PROSTIN VR STERILE SOLUTION is to be used:

- by a trained healthcare professional
- in a place with the proper equipment available to your baby for intensive care

Treatment will usually start within 4 days after birth. It will be given for the shortest time possible to treat your baby properly.

It will be given to your baby as a continuous infusion into either their:

- vein (intravenously) or
- umbilical artery through a long, soft, hollow tube (called a catheter)

Your newborn's blood pressure will be closely monitored while PROSTIN VR STERILE SOLUTION is being given.

Usual dose:

Your newborn's doctor will decide the dose and for how long PROSTIN VR STERILE SOLUTION will be given.

Overdose:

If you think your baby has been given too much PROSTIN VR STERILE SOLUTION, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Signs of an overdose include:

- interrupted breathing (apnea)
- a slow heart rate
- fever
- low blood pressure
- flushing

What are possible side effects from using PROSTIN VR STERILE SOLUTION?

These are not all the possible side effects your baby may feel when taking PROSTIN VR STERILE SOLUTION. If your baby experiences any side effects not listed here, contact your healthcare professional.

Side effects include:

- flushing
- fever
- feeling irritable
- feeling tired or sleepy
- feeling jittery
- stiffness
- diarrhea
- gastric regurgitation

Serious side effects and what to do about them			
Symptom / effect	Talk to your baby's healthcare professional		Stop the drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Apnea (Interrupted breathing)			✓
COMMON			
Bradycardia (slower than normal heartbeat): dizziness, feeling tired, shortness of breath, chest pains, memory problems			✓
Hypotension (low blood pressure): dizziness or lightheadedness, fainting, blurred vision, nausea, feeling tired.			✓
Tachycardia (faster than normal heartbeat): shortness of breath, lightheadedness, rapid pulse rate, irregular heartbeat, chest pain, fainting.			✓
Cardiac arrest			✓
Edema: swelling of the arms and legs			✓

Seizure			✓
Disseminated intravascular coagulation (a condition in which blood clots form throughout the body, blocking small blood vessels): bleeding which may be severe			✓
Sepsis (serious infection that causes your immune system to attack your body)			✓
Hypokalemia (low level of potassium in the blood): muscle weakness, feeling tired and muscle cramps			✓
UNCOMMON/RARE			
Congestive heart failure (a condition in which the heart can't pump enough blood): shortness of breath, feeling tired, weakness, swelling in your legs, ankle and feet, rapid or irregular heartbeat			✓
Spasm of the right infundibulum [conus arteriosus] (upper right ventricle of the heart)			✓
Second degree heart block (a disease of the electrical conduction system of the heart)			✓
Ventricular fibrillation (heart rhythm problem that occurs when the heart beats with rapid, erratic electrical impulses): chest pain, rapid heartbeat, dizziness, shortness of breath, loss of consciousness			✓
Ventricular hypertrophy (enlargement and thickening of the walls of the heart (left ventricle)): shortness of breath, feeling tired, sensation of rapid, fluttering or pounding heartbeats, dizziness or fainting			✓
Intracranial bleeding (bleeding in the brain): sudden, extremely severe headache			✓
Hypothermia (abnormal low body temperature): shivering,			✓

slow, shallow breathing; slurred speech, drowsiness, confusion or memory loss, loss of consciousness			
Shock (a sudden drop in blood flow through the body): cool, clammy skin, paleness, rapid pulse, rapid breathing, nausea or vomiting, enlarged pupils, weakness, dizziness or fainting			✓
Bradypnea (abnormally slow breathing): lightheadedness, dizziness, feeling tired			✓
Pneumothorax (collapsed lung): sudden chest pain and shortness of breath			✓
Difficulty breathing			✓
Jaundice (liver condition that causes yellowing of a newborn's skin and eyes)			✓
Peritonitis (inflammation of the membrane covering the inside of the abdomen and its organs): abdominal pain, bloating, fever, nausea and vomiting, loss of appetite, diarrhea, thirst, inability to pass stool or gas, feeling tired			✓
Peritonsillitis (inflammation of the connective tissue above and behind the tonsil): fever, chills, difficulty swallowing or opening the mouth fully, swelling of the face and neck, headache			✓
Thrombocytopenia (low levels of platelets in the blood): easy or excessive bruising, a rash of pinpoint-sized reddish-purple spots usually on the legs, prolonged bleeding from cuts, bleeding from the gums or nose			✓
Anuria (failure of the kidneys to produce urine)			✓
Hematuria (blood in the urine)			✓
Whiplash (hyperextension of the neck)			✓
Bronchial wheezing: a high-pitched whistling sound while breathing.			✓

Hyperkalemia (high level of potassium in the blood): feeling tired or weak, a feeling of numbness or tingling, nausea or vomiting, chest pain, irregular heartbeats			✓
Anemia (low levels of red blood cells in the blood): feeling tired, weakness, pale or yellowish skin, shortness of breath, dizziness or lightheadedness, chest pain, irregular heartbeats			✓
Hypoglycemia (low blood sugar): feeling tired, pale skin, sweating, chills and clammy skin, feeling shaky, confusion, fast heartbeat, feeling weak or having no energy			✓
Hypercapnia (too much carbon dioxide in the blood): flushed skin, drowsiness, headache, feeling dizzy, shortness of breath, feeling exhausted			✓
Hyperemia (excess blood in parts of your body)			✓
Pneumopericardium (air entering the cavity surrounding the heart): chest pain, rapid heart rate, pain in the upper abdomen, nausea, shortness of breath, fainting, drop in blood pressure			✓
Tachyphylaxis (a decrease in response to the medicine)			✓
Hypoventilation: bluish colour of the skin, feeling tired			✓
Tachypnea (abnormally rapid breathing)			✓

If your baby has a troublesome symptom or side effect that is not listed here or their side effects worsen, talk to your healthcare professional.

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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

PROSTIN VR STERILE SOLUTION will be stored in the refrigerator (2°C - 8°C) by your healthcare professional.

If you want more information about PROSTIN VR STERILE SOLUTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website (<http://www.pfizer.ca>), or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

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