

# **PROSTIN V.R.**

**Alprostadil injection, USP (prostaglandin E1)**

**0.5mg/ml sterile solution**

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## **Presentation**

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Each ampoule of PROSTIN V.R. contains 500 micrograms of alprostadil in dehydrated alcohol.

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## **Uses**

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### **Actions**

Alprostadil (prostaglandin E) is one of a family of naturally occurring acidic lipids with various pharmacologic effects. Vasodilation, inhibition of platelet aggregation, and stimulation of intestinal and uterine smooth muscle are among the most notable of these effects. Intravenous doses of 1 to 10 micrograms of alprostadil per kilogram of body weight lower the blood pressure in mammals by decreasing peripheral resistance. Reflex increases in cardiac output and rate accompany the reduction in blood pressure.

Smooth muscle of the ductus arteriosus is especially sensitive to alprostadil, and strips of lamb ductus markedly relax in the presence of alprostadil. In addition, administration of alprostadil reopened the closing ductus of new-born rats, rabbits, and lambs. These observations led to the investigation of alprostadil in infants who had congenital defects which restricted the pulmonary or systemic blood flow and who depended on a patent ductus arteriosus for adequate blood oxygenation and lower body perfusion.

In infants with restricted pulmonary blood flow, about 50% responded to alprostadil infusion with at least a ten torr increase in blood PO<sub>2</sub> (mean increase about 14 torr and mean increase in oxygen saturation about 23%). In general, patients who responded best had low pre-treatment blood PO<sub>2</sub> and were four days old or less.

In infants with restricted systemic blood flow, alprostadil often increased pH in those having acidosis, increased systemic blood pressure and decreased the ratio of pulmonary artery pressure to aortic pressure.

Alprostadil must be infused continuously because it is very rapidly metabolised. As much as 80% of the circulating alprostadil may be metabolised in one pass through the lungs, primarily by B- and W- oxidation. The metabolites are excreted primarily by the kidney, and excretion is essentially complete within 24 hours after administration. No unchanged alprostadil has been found in the urine, and there is no evidence of tissue retention of alprostadil or its metabolites.

## Indications

PROSTIN V.R. Paediatric Sterile Solution is indicated for palliative, not definitive, therapy 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 the patent ductus for survival. Such congenital heart defects include mitral atresia, pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, or transposition of the great vessels with or without other defects.

In infants with restricted pulmonary blood flow, the increase in blood oxygenation is inversely proportional to pre-treatment PO<sub>2</sub> values; that is, patients with low PO<sub>2</sub> values respond best, and patients with PO<sub>2</sub> values of 40 torr or more usually have little response.

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## Dosage and Administration

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The preferred route of administration for alprostadil (PGE<sub>1</sub>) is by continuous intravenous infusion into a large vein. Alternately, the drug may be infused through an umbilical artery catheter with its tip positioned at the ductal opening. Increases in blood oxygenation (PO<sub>2</sub>) are similar by both routes of administration.

The infusion is generally initiated at a rate of 0.05 to 0.1 micrograms alprostadil (PGE<sub>1</sub>) per kilogram of body weight per minute. Starting dosages lower than that have been used with apparent good response, but this experience has been largely anecdotal. The most experience has been with 0.1 micrograms/kg/min. After a therapeutic response (an increase in PO<sub>2</sub> in neonates with restricted pulmonary blood flow or an increase in systemic blood pressure and blood pH in neonates with restricted systemic blood flow) has been obtained, the infusion rate should be reduced to the lowest possible dosage that will maintain the desired response.

In the event that the initial rate of 0.1 microgram/kg/min. is inadequate, the dosage may be cautiously increased up to 0.4 microgram/kg/min. However, in general, higher infusion rates do not produce greater effects.

Due to its instability, alprostadil (PGE<sub>1</sub>) should be stored in a refrigerator at 2 - 8 degrees C (35.6 - 46.4 degrees F). Prepare fresh dilutions of alprostadil (PGE<sub>1</sub>) every 24 hours. Discard any dilution more than 24 hours old.

Due to the low concentrations of alprostadil (PGE<sub>1</sub>) to be employed, the following guidelines for the dilution of the drug are recommended -

Dilute 1ml (ampoule) of alprostadil (PGE<sub>1</sub>) with sterile sodium chloride injection USP or sterile dextrose or glucose injection USP. Dilute to volumes appropriate for the delivery system available.

Sample dilutions and infusion rates to provide a dosage of 0.1 micrograms/kgbw/min-1:

1 Ampoule 500 Micrograms Alprostadil (PGE <sub>1</sub> ) to:	Concentrations of Resulting solution (Microgram ml <sup>-1</sup> )	Infusion rate (ml/min/kg-1)
250ml	2	0.05
100ml	5	0.02
50ml	10	0.01
25ml	20	0.005

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## Contraindications

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Nil

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## Warnings and Precautions

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Apnoea is experienced by about 10 to 12% of neonates with congenital heart defects treated with PROSTIN V.R. paediatric sterile solution. Apnoea is most often seen in neonates weighing less than 2kg at birth and usually appears during the first hour of drug infusion. Therefore, respiratory status should be monitored throughout treatment, and PROSTIN V.R. paediatric should be used where ventilatory assistance is immediately available.

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 been reported in dogs and neonates during long-term infusions of alprostadil. The cortical proliferation in infants regressed after withdrawal of the drug.

The administration of alprostadil (PGE<sub>1</sub>) 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 (PGE<sub>1</sub>) at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction. Alprostadil (PGE<sub>1</sub>) should be infused for the shortest time possible and at the lowest dose that will produce the desired effects. The risks of long-term infusion of PROSTIN V.R. paediatric should be weighed against the possible benefits that critically ill infants may derive from its administration.

Because alprostadil inhibits platelet aggregation, use PROSTIN V.R. paediatric cautiously in neonates with bleeding tendencies.

PROSTIN V.R. paediatric should not be used in neonates with respiratory distress syndrome (hyaline membrane disease). A differential diagnosis should be made between respiratory distress syndrome and cyanotic heart disease (restricted pulmonary blood flow). If full diagnostic facilities are not immediately available, the diagnosis should be based on the presence of cyanosis (pO<sub>2</sub> less than 40 torr) and x-ray evidence of restricted pulmonary blood flow.

*Necessary Monitoring:* In all neonates, arterial pressure should be monitored intermittently by umbilical artery catheter, auscultation, or with a Doppler transducer. Should arterial pressure fall significantly, decrease the rate of infusion immediately.

In infants with restricted pulmonary blood flow, measure efficacy of PROSTIN V.R. paediatric by monitoring improvement in blood oxygenation. In infants with restricted systemic blood flow, measure efficacy by monitoring improvement of systemic blood pressure and blood pH.

*Carcinogenicity and fertility:* long-term carcinogenicity and fertility studies have not been done. The Ames and Alkaline Elution assays reveal no potential for mutagenesis.

Alprostadil (PGE<sub>1</sub>) should be administered only by medically trained personnel in facilities in which paediatric patients can receive or have access to paediatric intensive care.

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## **Adverse Effects**

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The most frequent adverse reactions observed with alprostadil (PGE<sub>1</sub>) infusion in neonates with ductal-dependent congenital heart defects were related to the drug's known pharmacological effects. Of 436 neonates treated, transient pyrexia occurred in 13.8%, apnoea in 11.5%, bradycardia in 6.7%, seizures in 4.1%, hypotension in 3.9%, tachycardia in 2.8% and diarrhoea in 2.6%. Cutaneous vasodilation (flushing) (7-10%) was the only event related to the route of administration, occurring more frequently during intra-arterial administration.

The relationship of the following adverse events to the drug is unknown. In order of decreasing frequency, they were: sepsis (1.6%), cardiac arrest (1.1%), disseminated intravascular coagulation (1.1%), hypokalaemia (1.1%) and oedema (1.1%). The following events have been reported in less than 1% of the neonates: shock, congestive heart failure, hyperbilirubinaemia, bleeding, lethargy, bradypnoea, respiratory distress, tachypnoea, anuria, renal failure, hypoglycaemia, ventricular fibrillation, second degree heart block, supraventricular tachycardia, hyperextension of the neck, hyperirritability, hypothermia, jitteriness, hypercapnia, hyperaemia, hypochromic anaemia, haematuria, peritonitis, tachyphylaxis, hyperkalaemia, thrombocytopaenia, and anaemia.

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## **Interactions**

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No drug interactions have been reported between PROSTIN V.R. paediatric and the therapy standard in neonates with restricted pulmonary or systemic blood flow. Standard therapy includes antibiotics, such as penicillin and gentamicin; vasopressors, such as dopamine and isoproterenol; cardiac glycosides; and diuretics, such as furosemide.

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## **Overdosage**

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Apnoea, bradycardia, pyrexia, hypotension, and flushing may be signs of drug overdosage. If apnoea or bradycardia occurs, discontinue the infusion, and provide appropriate medical treatment. Caution should be used in restarting the infusion. If pyrexia or hypotension occurs, reduce the infusion rate until these symptoms subside. Flushing is usually a result of incorrect intra-arterial catheter placement, and the catheter should be repositioned.

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## **Pharmaceutical Precautions**

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Store between 2 degrees and 8 degrees C.

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## **Medicine Classification**

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Prescription medicine.

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## **Package Quantities**

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PROSTIN V.R. is available in ampoules of 1 ml.

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## **Further Information**

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Due to the low concentration of alprostadil (PGE<sub>1</sub>) to be employed, the following guidelines for the dilution of the drug are recommended:

Dilute desired amount of alprostadil (PGE<sub>1</sub>) with sterile sodium chloride injection or sterile dextrose (or glucose) injection. If undiluted PROSTIN VR PAEDIATRIC Sterile Solution comes in direct contact with a plastic container, plasticisers 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 should be replaced. This appears to be a concentration-dependent

phenomenon. To minimise the possibility of haze formation, PROSTIN VR PAEDIATRIC Sterile Solution should be added directly to the intravenous, infusion solution avoiding contact with the walls of plastic containers. Dilute to volumes appropriate for the delivery system available.

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