PROSTIN® VR
STERILE SOLUTION
PRODUCT INFORMATION

PROSTIN® VR STERILE SOLUTION
(alprostadil; prostaglandin E₁)

DESCRIPTION

PROSTIN® VR Sterile Solution contains 500 micrograms alprostadil in 1.0 mL of dehydrated alcohol.

It is white to off-white crystalline powder with a melting point between 110°C and 116°C. Its solubility at 35°C is 8000 micrograms per 100 mL double distilled water.

The chemical formula for PROSTIN® VR is (11-a, 13E, 15S)-11, 15 dihydroxy-9-oxoprost-13-en- 1-oic acid, and its structural formula is as follows.

![Chemical structure of alprostadil](image)

The molecular weight of alprostadil is 354.49.

PHARMAACOLOGY

Alprostadil (also known as prostaglandin E₁) relaxes the ductus arteriosus in early post-natal 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 metabolised 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.

The mechanism of action of alprostadil is unknown but an active role for prostaglandin in maintaining ductus patency during foetal life is supported by the presence of biosynthetic pathways in the ductus, the constrictor effect of prostaglandin synthetase inhibitors and the relaxant action of \( \text{PGE}_2 \) and related agents.

**INDICATIONS**

PROSTIN® VR Sterile Solution (alprostadil) 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 a patent ductus for survival. Such congenital heart defects include pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, mitral atresia, or transposition of the great vessels with or without other defects.

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

**CONTRAINDICATIONS**

PROSTIN® VR is contraindicated in the following patients:

1. Cyanotic neonates with persistent foetal 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 oedema because of increased pulmonary blood flow.

**PRECAUTIONS**

Approximately 10% to 12% of neonates treated with PROSTIN® VR experienced apnoea. Apnoea is seen most often in neonates weighing less than 2 kg at birth and usually appears during the first hour of drug infusion. Therefore PROSTIN® VR should be used where facilities for ventilatory assistance and intubation are immediately available.

Some studies suggest that \( \text{PGE}_1 \) administration causes a weakening effect on the structure of the wall of the ductus arteriosus rendering the vessels prone to laceration. These effects may extend into the wall of the aorta and may cause problems in surgical procedures.

Cortical proliferation of the long bones has followed long-term infusions of alprostadil in infants and dogs. The proliferation in infants regressed after withdrawal of the drug.
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 should be infused for the shortest time and at the lowest dose which will produce the desired effects. The risk of long-term infusion of PROSTIN® VR should be weighed against the possible benefits that critically ill infants may derive from its administration.

In general, it is recommended that the preparation should not be administered for more than 2 or 3 days at a time. Since PROSTIN® VR appears most effective within 96 hours after birth every effort should be made to start infusion of the drug during this period.

Use PROSTIN® VR cautiously in neonates with histories of 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 (pO₂ less than 40 mm Hg) and restricted pulmonary blood flow apparent on X-ray are good indicators of congenital heart defects.

In all neonates, intermittently monitor arterial pressure by umbilical artery catheter, auscultation, or with a Doppler transducer. Should arterial pressure fall significantly, decrease the rate of infusion immediately.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long term carcinogenicity and fertility studies have not been done. No potential for mutagenic activity was revealed in assays of gene mutation in bacterial and mammalian cells, or in DNA damage assays; however, alprostadil has not been tested in assays for chromosomal damage.

Testicular atrophy and/or degeneration has been observed in rats receiving high doses (10 mg/day for 35 days or longer) of PGE₁. The relevance of this to the human neonate is not known.

ADVERSE EFFECTS

Cardiovascular System: The most common adverse reactions reported were flushing in 10.1% of patients, bradycardia in 6.7%, hypotension in 3.9%, tachycardia in 2.8%, cardiac arrest in 1.1% and oedema in 1.1%. The following reactions were reported in less than 1% of the patients: congestive heart failure, hyperaemia, pneumopericardium, second degree heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia, ventricular fibrillation, ventricular hypertrophy and tachyphylaxis.

Central Nervous System: Apnoea was reported in 11.5% of neonates treated. The other most common adverse reactions reported were fever in 13.8% of patients treated, and seizures in 4.1%. The following reactions were reported in less than 1% of the patients: cerebral
bleeding with recorded fatalities, hyperextension of the neck, hyperirritability, hypothermia, jitteriness, lethargy, microcephaly and stiffness.

**Respiratory System:** The following reactions were reported in less than 1% of the patients: bradypnoea, bronchial wheezing, hypercapnia, hypoplastic lungs, pneumothorax, respiratory depression, respiratory distress and tachypnoea.

**Gastrointestinal System:** The most common adverse reaction reported was diarrhoea in 2.6% of the patients. The following reactions were reported in less than 1% of the patients: biliary atresia, gastric regurgitation and hyperbilirubinaemia.

**Haematological:** The most common adverse reaction reported was disseminated intravascular coagulation in 1.1% of patients. The following events were reported in less than 1% of the patients: anaemia, bleeding, thrombocytopenia and hypochromic anaemia.

**Excretory System:** No adverse reactions were reported in more than 1% of the patients. Those reported in less than 1% of the patients were anuria, haematuria, polycystic kidneys and renal failure.

**Infection:** Sepsis was reported in 1.6% of the patients. Peritonitis was reported in less than 1% of the patients.

**Metabolic:** The most common adverse reaction reported was hypokalaemia in 1.1% of the patients. Hypoglycaemia and hyperkalaemia were reported in less than 1% of the patients.

**Ductus Arteriosus Histological Changes:** One group of investigators reported "oedema of the media, separation of the medial components by clear spaces, pathological interruption of the internal elastic lamina and intimal laceration some of which extended into the media" in the ducti arteriosi of four patients.

**Cortical Proliferation of the Long Bones:** Following long-term infusion of PROSTIN® VR, cortical proliferation of long bones has been reported.

**DOSAGE AND ADMINISTRATION**

Infusion should begin with 0.1 micrograms alprostadil per kilogram of body weight per minute. Doses above 0.1 micrograms per kilogram per minute, do not appear to offer additional benefits. When an effect is achieved, decrease the infusion to the lowest possible dose while maintaining the desired effects.

The preferable route of administration for PROSTIN® VR (alprostadil) 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 the types of reactions are different. A higher incidence of flushing has been associated with intra-arterial than with intravenous administration.
Dilution Instructions

Withdraw the appropriate volume of PROSTIN® VR (alprostadil) from the ampoule and
dissolve in sterile sodium chloride injection USP. Dilute to volumes appropriate for the pump
delivery system available.

Prepare fresh infusion solutions every 24 hours. Discard any solution more than 24 hours old.

Neither PROSTIN® VR nor the further diluted solutions contain an antimicrobial agent. To
avoid microbial contamination hazards, the further diluted solutions should be used as soon as
practicable. Any solution not used within 24 hours should be discarded.

The following alprostadil concentrations (μg/mL) are achieved by adding 500 μg of
alprostadil to various volumes of diluent:

<table>
<thead>
<tr>
<th>Alprostadil Added</th>
<th>Total Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 μg (1 mL)**</td>
<td>250 mL</td>
</tr>
<tr>
<td></td>
<td>2.0 μg/mL</td>
</tr>
<tr>
<td>2.0 μg/mL</td>
<td>100 mL</td>
</tr>
<tr>
<td></td>
<td>5.0 μg/mL</td>
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<td>5.0 μg/mL</td>
<td>50 mL</td>
</tr>
<tr>
<td></td>
<td>10.0 μg/mL</td>
</tr>
<tr>
<td>10.0 μg/mL</td>
<td>25 mL</td>
</tr>
<tr>
<td></td>
<td>20.0 μg/mL</td>
</tr>
</tbody>
</table>

** Volume of alprostadil withdrawn from ampoule

Infusion Rate (mL/hr)=Dosage (μg/kg/min x patient weight (kg)x60 min/hr

Final Concentration to be used (μg/mL)

Example: To provide 0.1 μg/kg/min to a 2.8 kg neonate, using a final alprostadil
concentration of 5 μg/ml

\[
\text{Infusion Rate} = \frac{0.1 \text{ μg/kg/min} \times 2.8 \text{ kg} \times 60 \text{ min/hr}}{5 \text{ μg/mL}} = 3.36 \text{ mL/hr}
\]

With an infusion pump limited to discrete infusion rates, infuse 2 or 4 mL per hour.

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 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.

If undiluted PROSTIN® VR comes in direct contact with a plastic container the solution may
turn hazy. Should this occur the solution should be discarded.
OVERDOSAGE

Overdose data is limited. Apnoea, bradycardia, pyrexia, hypotension and flushing may be signs of drug overdose. If apnoea or bradycardia occur, the infusion should be discontinued and the appropriate medical treatment initiated.

There is no antidote for alprostadil overdose. Treatment is symptomatic and supportive. Support respiratory and cardiac function. Monitor pulmonary function, vital signs, ECG and pulse oximetry, and fluid and electrolyte status in patients with significant diarrhoea.

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.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

PROSTIN® VR (alprostadil) Sterile Solution is available in ampoules containing:

1 mL of 500 μg/mL alprostadil in ethanol: 5's.

0.5 mL of 250 μg/mL alprostadil in ethanol: 5’s (not marketed)

0.2 mL of 100 μg/mL alprostadil in ethanol: 5’s (not marketed)

STORAGE CONDITIONS

Store at 2°C to 8°C (Refrigerate. Do not freeze)

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

Approved by TGA 14 January 1994

Date of most recent amendment: 15 November 2006

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