AUSTRALIAN PRODUCT INFORMATION – PROSTIN VR (ALPROSTADIL)

1. NAME OF THE MEDICINE

Alprostadil (also known as prostaglandin E_1).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL ampoule contains 500 micrograms alprostadil.

Excipient(s) with known effect

Ethanol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

PROSTIN VR is a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROSTIN VR 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.

4.2 Dose and method of administration

Dosage

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.

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.

Method of administration

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 although the types of reactions are different. The incidences of flushing were higher with intra-arterial than with intravenous administration. See section 4.8 Adverse effects (underiable effects).

Dilution instructions

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

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

Alprostadil concentration by volume of diluent added	
Total volume of diluent	**Alprostadil concentration by adding 500 μg (1 mL)****
250 mL	2.0 μg/mL
100 mL	5.0 μg/mL
50 mL	10.0 μg/mL
25 mL	20.0 μg/mL

** Volume of alprostadil withdrawn from ampoule

$$\text{Infusion Rate (mL/hr)} = \frac{\text{Dosage (μg/kg/min x patient weight (kg)x60 min/hr}}{\text{Final Concentration to be used (μg/mL)}}$$

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

$$\text{Infusion Rate} = \frac{0.1\ \mu g/kg/min \times 2.8\ kg \times 60\ min/hr}{5\ \mu g/mL} = 3.36\ mL/hr$$

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.

Neither PROSTIN VR nor the further diluted solutions contain an antimicrobial agent. To avoid microbial contamination hazards, the diluted infusion solutions should be used prepared fresh every 24 hours and used as soon as possible. Any solution not used within 24 hours should be discarded. See Section 6.4 Special precautions for storage.

Product is for single use in one patient only. Discard any residue.

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. Also see section 6.2 Incompatibilities

4.3 Contraindications

PROSTIN VR 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.

PROSTIN VR may precipitate pulmonary oedema because of increased pulmonary blood flow in these patients.

4.4 Special warnings and precautions for use

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 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 (pO_2 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.

Use in the elderly

No data available.

Paediatric use

Indicated for use in paediatric patients. See section 4.1. Inidcations.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

No data available.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Long term fertility studies have not been done.

Use in pregnancy

No data available.

Use in lactation

Alprostadil should not be used in lactating women.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Adverse effects (undesirable effects)

The following undesirable effects have been observed and reported during treatment with alprostadil.

System organ class	Frequency	Adverse effects
Infection and infestation	Common ≥1% to <10%	Sepsis (1.6%)
	Uncommon (<1%)	Peritonitis
Cardiac disorders	Common	Bradycardia (6.7%), tachycardia (2.8%), cardiac arrest (1.1%).
	Uncommon (<1%)	Congestive heart failure, pneumopericardium, second degree

		heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia, ventricular fibrillation, ventricular hypertrophy, tachyphylaxis.
Vascular disorders	Very common ≥10%	Flushing (10.1%)*
	Common ≥1% to <10%	hypotension (3.9%), oedema (1.1%).
	Uncommon (<1%)	Haemorrhage, hyperaemia
Nervous system disorders	Common ≥1% to <10%	Seizures (4.1%)
	Uncommon (<1%)	Cerebral haemorrhage with recorded fatalities, lethargy.
Blood and lymphatic system disorders	Common ≥1% to <10%	Disseminated intravascular coagulation (1.1%)
	Uncommon (<1%)	Anaemia, thrombocytopenia and hypochromic anaemia.
Metabolism and nutrition disorders	Common ≥1% to <10%	Hypokalaemia (1.1%)
	Uncommon (<1%)	Hypoglycaemia, hyperkalaemia
Congenital familial and genetic disorders	Uncommon (<1%)	Pulmonary hypoplasia. polycystic kidneys, biliary atresia, microcephaly
Gastrointestinal disorders	Common ≥1% to <10%	Diarrhoea (2.6%).
	Uncommon (<1%)	Gastric regurgitation
Hepatobiliary disorders	Uncommon (<1%)	Hyperbilirubinaemia.
Renal and urinary disorders	Uncommon (<1%)	Anuria, haematuria and renal failure.
General disorders and administration site conditions	Very common ≥10%	pyrexia (13.8%)
	Common ≥1% to <10%	Oedema (1.1%
	Uncommon <1%	Hypothermia, feeling jittery
Psychiatric disorders	Uncommon <1%	Hyperirritability
Respiratory, thoracic and mediastinal disorders	Very common ≥10%	Apnoea (11.5%)
	Uncommon <1%	Bradypnoea, bronchial wheezing, hypercapnia, pneumothorax, respiratory depression, respiratory distress and tachypnoea
Musculoskeletal and connective tissue disorders	Uncommon <1%	Stiffness
Injury, poisoning and procedural complications	Uncommon <1%	Hyperextension of the neck

* This adverse event is directly related to the route of administration, being more frequent with intra-arterial administration.

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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The mechanism of action of alprostadil is unknown but an active role for prostaglandin in maintaining ductus patency during fetal life is supported by the presence of biosynthetic pathways in the ductus, the constrictor effect of prostaglandin synthetase inhibitors and the relaxant action of PGE_2 and related agents.

Alprostadil 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 pO_2 is less than 40 mm Hg.

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Distribution

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.

Metabolism

The estimated half-life of alprostadil is 5 to 10 minutes.

Excretion

The major route of elimination of alprostadil and its metabolites is via the kidneys.

5.3 Preclinical safety data

Genotoxicity

Testicular atrophy and/or degeneration has been observed in rats receiving high doses (10 mg/day for 35 days or longer) of PGE_1. The relevance of this to the human neonate is not known.

Carcinogenicity

Long term carcinogenicity 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol.

6.2 Incompatibilities

If undiluted Prostin VR comes in direct contact with a plastic container, plasticisers are leached from the sidewalls and the solution may turn hazy. Should this occur the solution should be discarded. See information in Section 6.6 Special precautions for disposal and other handling.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

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

Neither PROSTIN VR nor the further diluted solutions contain an antimicrobial agent. From a microbiological point of view, fresh infusion solutions should be prepared every 24 hours and the medicinal product should be used immediately. Any solution more than 24 hours old should be discarded.

6.5 Nature and contents of container

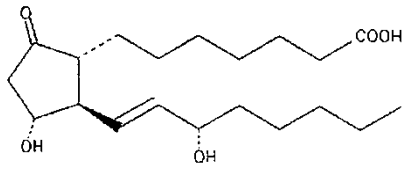
PROSTIN VR is available in 1 mL type I clear glass ampoules. Supplied in packs of 5 x 1 mL ampoules.

6.6 Special precautions for disposal and other handling

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



The chemical name is (11-a, 13E, 15S)-11, 15 dihydroxy-9-oxoprost-13-en-1-oic acid. The molecular weight of alprostadil is 354.49.

It is a 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.

CAS number

745-65-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4).

8. SPONSOR

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Toll Free Number: 1800 675 229.
www.pfizer.com.au.

9. DATE OF FIRST APPROVAL

14 January 1994.

10. DATE OF REVISION

08 October 2019

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Summary Table of Changes

Section changed	Summary of new information
All	Reformatting according to new Australian PI template.
4.6	New safety information added advising not to use in lactating women
4.8	Minor editorial change: Adverse events changed to MedRA terminology
8	Sponsor address change