

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

PROSTIN VR 500 microgram/mL Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL ampoule of PROSTIN VR contains 500 micrograms of alprostadil.

Excipient(s) with known effect

Each mL contains 789 mg ethanol.

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

3. PHARMACEUTICAL FORM

Solution for Injection.

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 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 PO₂ values; that is, patients with low PO₂ values respond best, and patients with PO₂ values of 40 torr or more usually have little response.

4.2 Dose and method of administration

Dose

The infusion is generally initiated at a rate of 0.05 to 0.1 micrograms alprostadil (PGE₁) 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 PO₂ 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 (PGE₁) should be stored in a refrigerator at 2 - 8 degrees C (35.6 - 46.4 degrees F). Prepare fresh dilutions of alprostadil (PGE₁) every 24 hours. Discard any dilution more than 24 hours old.

Due to the low concentrations of alprostadil (PGE₁) to be employed, the following guidelines for the dilution of the drug are recommended.

Dilute 1 mL (ampoule) of alprostadil (PGE₁) with sterile sodium chloride injection or sterile dextrose or glucose injection. Dilute to volumes appropriate for the delivery system available. Also see Section 6.6 Special precautions for disposal and other handling.

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

1 Ampoule (500 micrograms alprostadil (PGE₁)) to:	Concentrations of resulting solution (microgram mL⁻¹)	Infusion rate (mL/min/kg-1)
250 mL	2	0.05
100 mL	5	0.02
50 mL	10	0.01
25 mL	20	0.005

Method of administration

Alprostadil (PGE₁) should be administered only by medically trained personnel in facilities in which paediatric patients can receive or have access to paediatric intensive care.

The preferred route of administration for alprostadil (PGE₁) 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 (PO₂) are similar by both routes of administration.

4.3 Contraindications

Hypersensitivity to alprostadil or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Alprostadil (PGE₁) should be administered only by medically trained personnel in facilities in which paediatric patients can receive or have access to paediatric intensive care.

Apnoea is experienced by about 10 to 12% of neonates with congenital heart defects treated with PROSTIN VR. Apnoea is most often seen in neonates weighing less than 2 kg at birth and usually appears during the first hour of drug infusion. Therefore, respiratory status

should be monitored throughout treatment, and PROSTIN VR 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 (PGE₁) 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 (PGE₁) at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction. Alprostadil (PGE₁) 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 VR should be weighed against the possible benefits that critically ill infants may derive from its administration.

Because alprostadil inhibits platelet aggregation, use PROSTIN VR cautiously in neonates with bleeding tendencies.

PROSTIN VR 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 (PO₂ 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 VR 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.

4.5 Interaction with other medicines and other forms of interaction

No drug interactions have been reported between PROSTIN VR 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.

4.6 Fertility, pregnancy and lactation

Fertility

Long-term fertility studies have not been done.

Pregnancy

Not relevant.

Lactation

Not relevant.

4.7 Effects on ability to drive and use machinery

Not relevant.

4.8 Undesirable effects

The most frequent adverse reactions observed with alprostadil (PGE₁) 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, thrombocytopenia, and anaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 PO₂ (mean increase about 14 torr and mean increase in oxygen saturation about 23%). In general, patients who responded best had low pre-treatment blood PO₂ 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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

Long-term carcinogenicity studies have not been done. The Ames and Alkaline Elution assays reveal no potential for mutagenesis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethnaol.

6.2 Incompatibilities

Diluted solutions of Prostin VR should be infused from glass or hard plastic containers, or PVC infusion bags. If undiluted Prostin VR comes in direct contact with a plastic container, plasticisers are leached from the sidewalls. This appears to be a concentration-dependent phenomenon. 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

24 months.

6.4 Special precautions for storage

Store between 2°C and 8°C.

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

If undiluted Prostin VR comes in direct contact with a plastic container, plasticisers are leached from the side walls. 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 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.

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

11 March 1982.

10. DATE OF REVISION OF THE TEXT

15 January 2019

Summary table of changes (15 Jan 2019)

Section changed	Summary of new information
All	Reformatting to SPC format.