SCHEDULING STATUS S 4

PROPRIETARY NAME AND DOSAGE FORM

PROSTIN VR™ 0,5 mg (Sterile Solution)

COMPOSITION

PROSTIN VR Sterile Solution contains 0,5 mg alprostadil (prostaglandin E_1) in 1 ml dehydrated alcohol.

PHARMACOLOGICAL CLASSIFICATION

A 7.1 Vasodilators

PHARMACOLOGICAL ACTION

PROSTIN VR (alprostadil) dilates the ductus arteriosus in neonates. The mechanism of action of alprostadil is undetermined.

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 a ductus-dependent congenital heart defect. 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.

CONTRAINDICATIONS

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.

WARNINGS and SPECIAL PRECAUTIONS

Pathological studies of the ductus arteriosus and pulmonary arteries of infants treated with prostaglandin E_1 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 following long-term infusions of alprostadil in neonates and dogs. The cortical proliferation in neonates regressed after withdrawal of the medication.

The administration of alprostadil (PGE_1) 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 medicine. Neonates receiving alprostadil (PGE_1) at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction. Alprostadil (PGE_1) 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 alprostadil (PGE_1) should be weighed against the possible benefits that critically ill infants may derive from its administration.

Use alprostadil (PGE_1) cautiously in neonates with histories of bleeding tendencies.
If full diagnostic facilities are not immediately available, cyanosis (PO_2 less than 40 mmHg) and restricted pulmonary blood flow apparent on an X-ray are good indicators of congenital heart defects.

Infusion rate should be decreased if arterial pressure falls.

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

DOSAGE AND DIRECTIONS FOR USE

Cyanotic neonates with congenital heart defects, treated with alprostadil, may experience apnoea. Apnoea is most often observed in cyanotic neonates weighing less than 2 kg at birth and usually appears during the first hour of drug infusion. Therefore, **PROSTIN VR** should be used only where ventilatory assistance is immediately available.

The preferable 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 the types of reactions are different. A higher incidence of flushing has been associated with intra-arterial than with intravenous administration.

Infusion should begin with 0,1 micrograms alprostadil per kilogram of body mass per minute. When an effect is achieved, decrease the infusion to the lowest possible dose while maintaining the desired effects.

DIRECTIONS FOR USE OF THE AMPOULES

No ampoule file is needed to open the ampoules. The neck of the ampoule is prescored at the point of constriction. A coloured dot on the ampoule helps to orientate the ampoule. Take the ampoule and face the coloured dot. The ampoule opens easily by placing the thumb on the coloured dot and gently pressing downwards.

DILUTION INSTRUCTIONS

To prepare infusion solutions, dilute 1 ml of **PROSTIN VR** with sterile sodium chloride injection USP or sterile dextrose (glucose) injection USP. Dilute to volumes appropriate for the pump delivery system available. Prepare fresh infusion solutions every 24 hours. **Discard any dilution more than 24 hours old**.

The following alprostadil concentrations (mcg/ml) are achieved by adding 1 ml (500 mcg) of alprostadil to various volumes of diluent:

TOTAL VOLUME OF DILUENT	**500 mcg(1 ml)** ALPROSTADIL ADDED TO ACHIEVE THESE FINAL ALPROSTADIL CONCENTRATIONS**
250 ml	2,0 mcg/ml
100 ml	5,0 mcg /ml
50 ml	10,0 mcg /ml
25 ml	20,0 mcg /ml

** Ampoule volume withdrawn

$$\text{Infusion rate (ml/hr)} = \frac{\text{dosage (mcg/kg/min) x patient weight (kg) x 60 min/hr}}{\text{Final concentration to be used (mcg/ml)}}$$

Example: To provide 0,1 mcg/kg/min to a 2,8 kg neonate, using a final alprostadil concentration of 5 mcg/ml:

$$\text{Infusion rate} = \frac{0.1 \text{ mcg/kg/min} \times 2{,}8 \text{ kg} \times 60 \text{ min/hr}}{5 \text{ mcg/ml}}$$

$$= 3{,}3 \text{ ml/hr}$$

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

SIDE EFFECTS

In the neonate whose ductus arteriosi must be kept patent, the most frequent adverse reactions observed with **PROSTIN VR** infusion are related to its known pharmacological effects.

Cardiovascular System:

The most common adverse reactions reported were flushing, bradycardia, hypotension, tachycardia, cardiac arrest, and oedema. The following reactions were also reported: congestive heart failure, hyperaemia, pneumopericardium, second degree heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia, ventricular fibrillation and ventricular hypertrophy.

Central Nervous System:

The most common adverse reactions reported were apnoea, fever and seizures. The following reactions were also reported: cerebral bleeding, hyperextension of the neck, hyperirritability, hypothermia, jitteriness, lethargy, microcephaly and stiffness.

Respiratory System:

Bradypnoea, bronchial wheezing, hypercapnia, hypoplastic lungs, pneumothorax, respiratory depression, respiratory distress and tachypnoea.

Gastro-intestinal System:

Diarrhoea, biliary atresia, gastric regurgitation and hyperbilirubinaemia.

Haematologic Events:

Disseminated intravascular coagulation, hypochromic anaemia, anaemia, bleeding and thrombocytopenia.

Excretory System:

Adverse reactions reported were anuria, haematuria, polycystic kidneys and renal failure.
Tachyphylaxis, sepsis and peritonitis were also reported.

Metabolic:

Hypokalaemia, hyperkalaemia and hypoglycaemia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Apnoea, bradycardia, pyrexia, hypotension and flushing may be signs of overdose. If apnoea 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.

IDENTIFICATION

A clear colourless sterile solution in a Type 1 clear glass ampoule.

PRESENTATION

PROSTIN VR 0,5 mg sterile solution is available in 1 ml ampoules containing 0,5 mg alprostadil in 1,0 ml dehydrated alcohol.

STORAGE INSTRUCTIONS

Store in a refrigerator at 2 °C to 8 °C.
Discard any dilution more than 24 hours old.
Keep out of reach of children.

REGISTRATION NUMBER

Q/7.1/32

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd
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