SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

PROSTIN VR®, 0,5 mg/mL sterile solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROSTIN VR Sterile solution contains 0,5 mg alprostadil (prostaglandin E_1) in 1 mL anhydrous alcohol.

Sugar free.

Excipient with known effect

PROSTIN VR contains 790 mg anhydrous alcohol in each 1 mL vial which is equivalent to 790 mg/mL (79 % w/v).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile solution for infusion.

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 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.

4.2 Posology and method of administration

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.

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 medicine infusion. Therefore, PROSTIN VR should be used only where ventilatory assistance is immediately available.

Posology

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.

Method of administration

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.

Directions for use of the ampoules

No ampoule file is needed to open the ampoules. The neck of the ampoule is pre-scored 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.

For instructions on dilution of PROSTIN VR before administration, see section 6.6.

Paediatric population

PROSTIN VR contains a quantity of alcohol that is likely to affect children (see section 4.4).

4.3 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.

4.4 Special warnings and precautions for use

Pathological studies of the ductus arteriosus and pulmonary arteries of infants treated with PROSTIN VR 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 PROSTIN VR in neonates and dogs. The cortical proliferation in neonates regressed after withdrawal of the medicine.

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 medicine. 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.

Use PROSTIN VR 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.

Excipient information

Each 1 mL vial of PROSTIN VR contains 790 mg anhydrous alcohol (see section 2), which is equivalent to less than 20 mL beer or 8 mL wine.

An example of alcohol exposure based on maximum single dose (see section 4.2) is as follows:
Administration of 0,576 mL of this medicine to a child 1 month of age and weighing 2 kg would result in exposure to 227,52 mg/kg of alcohol which may cause a rise in blood alcohol concentration (BAC) of about 37,9 mg/100 mL.

For comparison, for an adult drinking a glass of wine or 500 mL of beer, the BAC is likely to be about 50 mg/100 mL

The alcohol content in this preparation is likely to affect children. These effects may include somnolence and changes in behaviour.

Because PROSTIN VR is administered slowly over 24 hours the effects of alcohol may be reduced (see section 4.2).

Co-administration with medicines containing e.g. propylene glycol or alcohol may lead to accumulation of ethanol and induce adverse effects, particularly in young children with low or immature metabolic capacity.

The alcohol content in PROSTIN VR should be carefully considered in the following patient groups who may be at higher risk of alcohol-related adverse effects:

- Patients with liver disease
- Patients with epilepsy

The amount of alcohol in PROSTIN VR may alter the effects of other medicines.

4.5 Interaction with other medicines and other forms of interaction

Not applicable

4.6 Fertility, pregnancy and lactation

Not applicable

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Summary of the safety profile

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.

Cardiac disorders

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.

Nervous system disorder

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, thoracic, and mediastinal disorders

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

Gastrointestinal disorders

Diarrhoea, biliary atresia, gastric regurgitation and hyperbilirubinaemia.

Blood and lymphatic system disorders

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

Renal and urinary disorders

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

Metabolism and nutrition disorders

Hypokalaemia, hyperkalaemia and hypoglycaemia.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prostaglandins ATC code: C01EA01

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

5.2 Pharmacokinetic properties

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous alcohol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

Discard any dilution more than 24 hours old.

6.4 Special precautions for storage

Store in a refrigerator at 2 °C to 8 °C.

6.5 Nature and contents of containers

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

6.6 Special precautions for disposal and other handling

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 PROSTIN VR concentrations (mcg/mL) are achieved by adding 1 mL (500 mcg) of PROSTIN VR to various volumes of diluent:

Total volume of diluent	**500 mcg (1 mL)** PROSTIN VR added to achieve these final PROSTIN VR 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	

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 PROSTIN VR concentration of 5 mcg/mL:

Infusion rate $= \frac{\text{0,1 mcg/kg/min x 2,8 kg x 60 min/hr}}{\text{5 mcg/mL}}$

= 3,3 mL/hr

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

Building 2, 1st Floor, Maxwell Office Park, Magwa Crescent, Waterfall City

Midrand, Gauteng, 1685

South Africa

Tel: +27(0)11) 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBER

Q/7.1/32

9. DATE OF FIRST AUTHORISATION

14 February 1983

10. DATE OF REVISION OF THE TEXT

07 August 2025

Manufacturer:

Pfizer Manufacturing Belgium NV, Rijksweg 12, 2870 Puurs-Sint-Amands, Belgium

BOTSWANA: S2

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NAMIBIA: S2

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