1 NAME OF THE MEDICINAL PRODUCT

Prostin VR 500 micrograms/ml Concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

500 micrograms/ml. Each 1 ml ampoule contains 500 micrograms of alprostadil.

Excipient with known effect:
Prostin VR contains 790 mg anhydrous ethanol in each 1 ml vial which is equivalent to 790 mg/ml (79% w/v).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (Sterile concentrate).

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prostin VR is indicated to temporarily maintain the patency of the ductus arteriosus until corrective or palliative surgery can be performed in infants who have congenital defects and who depend upon the patent ductus for survival. Such congenital heart defects include pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, co-arctation of the aorta, aortic stenosis, aortic atresia, mitral atresia, or transposition of the great vessels with or without other defects.

4.2 Posology and method of administration

Posology
The infusion is generally initiated at a rate of 0.05-0.1 micrograms/kg/min. The most experience has been with 0.1 micrograms/kg/min. After a therapeutic response (an increase in pO_2 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.

Paediatric population
Prostin VR contains a quantity of ethanol that is likely to affect children (see section 4.4).

Doses lower than 0.05 microgram/kg/min (as low as 0.005 microgram/kg/min) alprostadil have been used successfully in neonates, specifically when transport of the infant is necessary. No comparative trials exist and the efficacy and safety of this approach when compared to the generally initiated dosage rate of 0.05-0.1 micrograms/kg/min is currently unclear.

Method of administration
For administration by intravenous drip or constant rate infusion pump.

In infants with lesions restricting pulmonary blood flow (blood is flowing through the ductus arteriosus from the aorta to the pulmonary artery), Prostin VR may be administered by continuous infusion through an umbilical artery catheter placed at or just above the junction of the descending aorta and the ductus arteriosus, or intravenously. 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.

For instructions on dilution, see section 6.6. The diluted solution should contain no more than 20 micrograms/ml alprostadil.

PARTICULAR CARE SHOULD BE TAKEN IN CALCULATING AND PREPARING DILUTIONS OF PROSTIN VR.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prostin VR should be administered only by well trained healthcare professionals and in facilities with immediate access to paediatric intensive care.

Apnoea may occur in about 10-12% of neonates with congenital heart defects treated with alprostadil. There is some evidence that apnoea is dose related. 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 Prostin VR should be used where ventilatory assistance is immediately available.

Prostin VR should be infused for the shortest time possible and at the lowest dose that 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.

Pathologic studies of the ductus arteriosus and pulmonary arteries of infants treated with prostaglandin E1 have disclosed histologic changes related with the weakening effect upon these structures. The specificity or clinical relevance of these results is not known.

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.

Since prostaglandin E1 is a potent inhibitor of platelet aggregation, use Prostin VR cautiously in neonates with histories of bleeding tendencies.

Alprostadil should not be used in neonates (or infants) with respiratory distress syndrome (hyaline membrane disease). A differential diagnosis should always be made between respiratory distress syndrome and cyanotic heart disease (restricted pulmonary blood flow). In the event that 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 a restricted pulmonary blood flow.

Arterial pressure should be monitored by umbilical artery catheter, auscultation or with a Doppler transducer. **Should arterial pressure fall significantly, the rate of infusion should be immediately decreased.**

Weakening of the ductus arteriosus wall and pulmonary artery has been reported, particularly during prolonged administration.

The administration of alprostadil 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 at recommended doses for more than 120 hours should be closely monitored for evidence of antral hyperplasia and gastric outlet obstruction.

In neonates (or infants) with decreased pulmonary blood flow, the oxygenation increase is inversely proportional to the previous pO2 values; i.e., better responses are obtained in patients with low pO2 values (less than 40 mmHg), whereas patients with high pO2 values (more than 40 mmHg) have usually a minimal response.

In neonates (or infants) with decreased pulmonary blood flow, alprostadil efficacy is measured by monitoring blood oxygenation increase. In neonates (or infants) with decreased systemic blood flow, the efficacy is determined by monitoring the increase in systemic blood pressure and blood pH.

Excipient information

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

An example of ethanol exposure based on maximum single dose (see section 4.2) is as follows: Administration of 0.576ml of this medicine to a child 1 month of age and weighing 2 kg would result in exposure to 227.52 mg/kg of ethanol 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 ethanol content in this preparation is likely to affect children. These effects may include somnolence and changes in behaviour.

Because this medication is administered slowly over 24 hours the effects of ethanol may be reduced (see section 4.2).

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

The ethanol content in this medicinal product should be carefully considered in the following patient groups who may be at higher risk of ethanol-related adverse effects:

- Patients with liver disease
- Patients with epilepsy

The amount of ethanol in this medicinal product may alter the effects of other medicines.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions have been reported to occur between Prostin VR and the standard therapy employed in neonates with congenital heart defects. Standard therapy includes antibiotics (such as penicillin or gentamicin), vasopressors (such as dopamine or isoproterenol), cardiac glycosides and diuretics (such as frusemide).

4.6 Fertility, pregnancy and lactation

Not relevant.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The most frequent adverse reactions observed with Prostin VR infusion in neonates with ductal-dependent congenital heart defects are related to the drug's known pharmacological effects.

The following undesirable effects have been observed and reported during treatment with alprostadil (436 neonates treated) with the following frequencies: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000).

System Organ Class	Frequency	Undesirable effects
Nervous system disorders	Common	Seizures
Cardiac disorders	Common	Bradycardia, hypotension, tachycardia
Vascular disorders	Uncommon	Vascular fragility

Respiratory, thoracic and mediastinal disorders	Very common	Apnoea
Metabolism and nutrition disorders	Common	Hypokalaemia
Gastrointestinal disorders	Common	Diarrhoea
	Uncommon	Gastric obstruction, gastric mucosal hypertrophy
Musculoskeletal and connective tissue disorders	Uncommon	Exostosis
General disorders and administration site conditions	Very common	Transient pyrexia
	Common	Cutaneous vasodilatation (flushing)*

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

The relationship of the following adverse events to the drug, in decreasing frequency, is unknown: sepsis, cardiac arrest, disseminated intravascular coagulation, and oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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. 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

Prostaglandins are potent vasoactive derivatives of arachidonic acid that exert vasomotor, metabolic and cellular effects on the pulmonary and coronary circulation. The E series of prostaglandins produces vasodilation of the systemic and coronary circulation in most species: these prostaglandins have been used for maintaining the patency of the ductus arteriosus in children.

5.2 Pharmacokinetic properties

Distribution

Based on studies in several animal species, intravenous or arterially administered prostaglandin E1 is very rapidly distributed throughout the entire body, with the exception of the central nervous system, where distribution, though detectable, is markedly reduced.

Biotransformation

Prostaglandin E1 is very rapidly metabolised. The primary organs for metabolism and inactivation of prostaglandin E1 are probably the lung, liver and kidney which remove and metabolise 40-95% of the prostaglandin E1 in a single pass through the organ. A number of other tissues possess lesser, but significant, capacity to metabolise prostaglandin E1. The predominant metabolites found in plasma, 15-oxo-prostaglandin E1 and 13, 14-dihydro-15 oxo-prostaglandin E1 are extensively metabolised by β- and ω-oxidation prior to excretion, primarily by the kidney. Few urinary metabolites of prostaglandin E1 have been characterised, but are widely believed to be analogous to those reported in detail for prostaglandin E2 and prostaglandin F2.

Elimination

Excretion is essentially complete within 24 hours after dosing, with no intact prostaglandin E1 being found in urine and no evidence of tissue retention of prostaglandin E1 or metabolites. In three species (rat, rabbit and lamb), the prostaglandin metabolising activity of lung from near-term fetal animals has been shown to be at least as effective as that of adults.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol, anhydrous

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 section 6.6.

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

6.3 Shelf life

3 years.

Diluted solutions should be used within 24 hours.

6.4 Special precautions for storage

Store in a refrigerator.

6.5 Nature and contents of container

1ml Type I clear glass ampoule.

6.6 Special precautions for disposal and other handling

Dilution instructions

To prepare infusion solutions, dilute 1 ml of Prostin VR with sterile 0.9% sodium chloride intravenous infusion or sterile 5% dextrose intravenous infusion.

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

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 0032/0083

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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