

Prescribing Information

PROSTIN VR™ Concentrate for solution for infusion (Alprostadil)

Composition

PROSTIN VR™ 100µg Concentrate for solution for infusion

PROSTIN VR™ 250µg Concentrate for solution for infusion

PROSTIN VR™ 500µg Concentrate for solution for infusion

Each ml contains: Alprostadil 500µg – Dehydrated alcohol.

Forms, ways of administration and packages

Forms

Prostin VR™ is a concentrate for solution for infusion.

Ways of administration

Intra-arterial or intravenous administration.

Packages

PROSTIN VR™ 100µg Concentrate for solution for infusion

Packages of 1 x 0.2 ml or 5 x 0.2 ml ampoule(s) of PROSTIN VR™
Concentrate for solution for infusion 500 µg/ml.

PROSTIN VR™ 250 µg Concentrate for solution for infusion

Packages of 1 x 0.5 ml or 5 x 0.5 ml ampoule(s) of PROSTIN VR™
Concentrate for solution for infusion 500 µg/ml.

PROSTIN VR™ 500 Concentrate for solution for infusion

Packages of 1 x 1 ml or 5 x 1 ml ampoule(s) of PROSTIN VR™
Concentrate for solution for infusion 500 µg/ml.

Properties

Pharmacodynamics

Alprostadil (prostaglandin E₁) 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 the drug. 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 100 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 pretreatment blood pO₂ and were 4 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.

Pharmacokinetics

Alprostadil must be infused continuously because it is very rapidly metabolized. As much as 80% of the circulating alprostadil may be metabolized in one pass through the lungs, primarily by beta- and omega-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.

Indications

PROSTIN VR™ Sterile solution (alprostadil) is indicated for palliative 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 but are not limited to mitral atresia, pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, interruption of the aortic arch, coarctation of the aorta, transposition of the great vessels with or without other defects.

Special precautions

Discard any dilution more than 24 hours old.

PROSTIN VR™ Sterile solution should be administered only by medically trained personnel in facilities in which pediatric patients can receive or have access to pediatric intensive care. Approximately 10-12% of neonates with congenital heart defects treated with PROSTIN VR™ Sterile solution experienced apnea. Apnea is most often seen in neonates, especially those weighing less than 2 kg at birth, and usually appears during the first hour of drug infusion. Therefore, PROSTIN VR™ Sterile solution should only 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 only occurred during long-term infusions of alprostadil in neonates and dogs (14 days or more). The proliferation in infants regressed after withdrawal of the drug.

Use PROSTIN VR™ Sterile solution cautiously in neonates with histories of bleeding tendencies.

Care should be taken to avoid the use of PROSTIN VR™ Sterile solution in neonates with respiratory distress syndrome (hyaline membrane disease), which sometimes can be confused with cyanotic heart disease. 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.

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 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.

PROSTIN VR™ Sterile solution 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™ Sterile solution should be weighed against the possible benefits that these critically ill infants might derive from its administration.

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.

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

Dosage and administration

The infusion is generally initiated at a rate of 0.05 to 0.1 micrograms alprostadil 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 microgram/kg/min.

After a therapeutic response is achieved (increased pO₂ in infants with restricted pulmonary blood flow or increased systemic blood pressure and blood pH in infants with restricted systemic blood flow), reduce the infusion rate to provide the lowest possible dosage that maintains the response. If response to 0.1 microgram/kg/min is inadequate, dosage can be cautiously increased up to 0.4 microgram/kg/min although, in general, higher infusion rates do not produce greater effects.

The preferable route of administration for PROSTIN VR™ Sterile solution is by continuous intravenous infusion into a large vein. Alternatively, PROSTIN VR™ Sterile solution may be administered 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.

Dilution instructions

To prepare infusion solutions, dilute 0.2 ml, 0.5 ml or 1 ml of PROSTIN VR™ Concentrate for solution for infusion with sterile sodium chloride solution or sterile dextrose (or glucose) solution. If undiluted PROSTIN VR™ Concentrate for solution for infusion comes in direct contact with a

plastic container, plasticizers are leached from the sidewalls. 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 minimize the possibility of haze formation, PROSTIN VR™ Concentrate for solution for infusion should be added directly to the intravenous infusion solution avoiding contact with the walls of plastic containers. Dilute to volumes appropriate for the pump delivery system available. Prepare fresh dilution every 24 hours. Discard any dilution more than 24 hours old.

**Sample dilutions and infusion rates to provide
a dosage of 0.1 µg/kg/min**

	Micrograms alprostadil added		
Total volume	100 µg (0.2 ml)**	250 µg (0.5 ml)**	500 µg (1.0 ml)**
250 ml	0.4 µg/ml	1.0 µg/ml	2.0 µg/ml
100 ml) 0.4 µg/ml	2.5 µg/ml	5.0 µg/ml
50 ml) 0.4 µg/ml	5.0 µg/ml	10.0 µg/ml
25 ml	4.0 µg/ml	10.0 µg/ml	20.0 µg/ml

** Ampoule volume withdrawn

Calculations:

$$\text{Infusion rate (ml/hr)} = \frac{\text{Dosage } (\mu\text{g/kg/min}) \times \text{patient wt (kg)} \times 60 \text{ min/hr}}{\text{Final concentration to be used } (\mu\text{g/ml})}$$

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

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

IMPORTANT

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

[Diagrams]

Adverse reactions

In neonates whose ductus arteriosus must be kept patent, the most frequent adverse reactions observed with PROSTIN VR™ Sterile solution infusion are related to its known pharmacological effects. The incidences of the following most common (more than 1%) adverse reactions are based on U.S. and foreign experience in 436 patients.

Occurred rather frequently:

Apnea, flushing (but less frequent if administered intravenously), and bradycardia.

Occurred sporadically:

Seizures, hypotension, tachycardia, and diarrhea.

The relationship of the following adverse events to the drug is unknown. In order of decreasing frequency, they were: sepsis, cardiac arrest, disseminated intravascular coagulation, hypokalemia and edema.

Overdosage

Apnea, bradycardia, pyrexia, hypotension and flushing may be signs of drug overdosage. If apnea 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 is usually alleviated by repositioning the tip of the catheter.

Interactions

No drug interactions have been reported to occur between alprostadil 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 furosemide.

Storage

Store in refrigerator (2-8°C).

The expiry date (month/year) is mentioned on the package after "EXP.:" (EXP. = expiry date).

Dispensing in the country of origin

On medical prescription only and in hospitals.

Manufacturer

Pharmacia NV/SA , Puurs, Belgium

Importer

Agis Commercial Agencies (1989) Ltd., 29 Lehi St., Bnei Brak 51200

22.02.99

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