PROSTIN VR®

Alprostadil

0.5 mg/ml concentrate for solution for infusion

Common Export Pack

Reference market: Belgium

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PROSTIN VR 0.5 mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PROSTIN VR 0.5 mg/ml concentrate for solution for infusion contains 500 micrograms alprostadil per ml of concentrate for solution.

Excipient with known effect: anhydrous ethanol
This medicine contains 790 mg of alcohol (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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PROSTIN VR 0.5 mg/ml concentrate for solution for infusion is indicated as palliative treatment for maintaining temporary patency of the ductus arteriosus in neonates with congenital cardiac defects, whose survival while waiting to undergo corrective or palliative surgery depends on the patency of their ductus arteriosus. These congenital cardiac defects include pulmonary atresia, pulmonary stenosis, tricuspid atresia, tetralogy of Fallot, aortic arch interruption, coarctation of the aorta, mitral atresia and transposition of the great vessels with or without other defects.

4.2 Posology and method of administration

Posology

The infusion is usually initiated with 0.05 to 0.1 microgram/kg/min of alprostadil. Good results have apparently also been obtained with lower initial doses. Experience with these doses is however limited. The most experience has been with the dose of 0.1 microgram/kg/min. When a therapeutic effect is obtained (an increase in pO_2 in children with pulmonary blood flow disorders, or increase in systemic arterial pressure and blood pH in children with systemic circulation disorders), the rate of administration must be reduced to the lowest possible dose for maintaining the desired effect. If the dose of 0.1 micrograms/kg/min is not sufficient, it may be increased to 0.4 micrograms/kg/min, although higher infusion rates do not always produce more pronounced effects.
The preferred administration route for PROSTIN VR 0.5 mg/ml concentrate for solution for infusion is by continuous IV infusion into a large vein. It is also possible to administer it using a catheter introduced into the umbilical artery oriented towards the ductal opening. Intra-arterial administration produces a higher incidence of facial flushing, apnoea and bradycardia than does intravenous administration.

Method of administration

PROSTIN VR is a concentrate for solution for infusion intended for intraarterial or intravenous use.

Instructions for dilution
Prepare a new solution every 24 hours, and keep it in the refrigerator. Solutions more than 24 hours old may no longer be used.
To prepare a solution for infusion, the desired quantity of PROSTIN VR 0.5 mg/ml concentrate for solution for infusion must be diluted in a sterile glucose solution (first choice of diluent) or a sterile saline solution. When the non diluted PROSTIN VR concentrate for infusion comes into contact with plastic containers, plasticising agents may be absorbed from the plastic material. The solution then becomes cloudy and the appearance of the container may be modified. If this happens, the solution and the container must be replaced. This phenomenon depends on the concentration. It is consequently advisable to add PROSTIN VR 0.5 mg/ml concentrate for solution for infusion directly to the diluent and to avoid all contact with plastic materials. The dilution must be decided depending on the pump system.

The following concentrations of alprostadil (in micrograms/ml) are obtained by diluting the 500 micrograms ampoules of alprostadil with the following volumes:

Total volume	Number of micrograms of Alprostadil -500 micrograms (1 ml)
250 ml	2.0 micrograms/ml
100 ml	5.0 micrograms/ml
50 ml	10.0 micrograms/ml
25 ml	20.0 micrograms/ml

EXAMPLE:
Rate of infusion desired: 0.1 microgram/kg/min.
Weight of the neonate: 2.8 kg
Solution for infusion prepared: 5 micrograms/ml

With the prepared solution for infusion of 5 micrograms/ml, the infusion rate must be as follows:

$$\frac{0.1 \text{ microgram/kg/min}}{5 \text{ micrograms/ml}} = 0.02 \text{ ml/kg/min.}$$

For a neonate weighing 2.8 kg, the infusion rate is:
0.02 ml/kg/min x 2.8 = 0.056 ml/min or 3.36 ml/hour

Paediatric population
The alcohol in this preparation is likely to affect children (see section 4.4).

4.3 Contraindications

PROSTIN VR concentrate for solution for infusion is contraindicated in case of hypersensitivity to the active substance (alprostadil) or to any of the excipients listed in section 6.1.
PROSTIN VR 0.5 mg/ml concentrate for solution for infusion must never be administered to neonates (or infants) with respiratory distress syndrome (hyaline membrane disease), which can sometimes be confused with a cyanotic cardiopathy. If adequate means of making a correct diagnosis are not available, the diagnosis should be based on the presence of cyanosis (pO_2 less than 40 mm Hg) and x-ray evidence showing decreased pulmonary blood flow.

4.4 Special warnings and precautions for use

- Solutions prepared more than 24 hours previously may no longer be used.
- This product must be used exclusively in the hospital environment.
- Bearing in mind the severity of certain undesirable effects, PROSTIN VR 0.5 mg/ml concentrate for solution for infusion may only be administered by qualified medical staff in specialist hospitals where intensive care facilities for neonates are immediately available (paediatric cardiology, cardiac surgery).
- Permanent cardiorespiratory monitoring is necessary for neonates treated with PROSTIN VR. It is also required to monitor arterial pressure and body temperature and to measure transcutaneous blood gases (pO_2, pCO_2).
- Apnoea may occur in about 10-12% of neonates with congenital heart defects treated with alprostadil (PGE1). Apnoea is most often observed in neonates, especially those weighing less than 2.0 kg at birth, and usually appears during the first hour of drug infusion. Therefore, alprostadil (PGE1) should only be used where ventilatory assistance is immediately available.
- Alprostadil should be infused for the shortest time possible and at the lowest dose that may produce the desired therapeutic response. The risks of long-term infusion of alprostadil should be evaluated in relation to the possible benefits that these critically ill infants might 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.
- Weakening of ductus arteriosus wall and pulmonary arteries has been reported principally during prolonged administration.
- Cortical proliferation of the long bones has been reported in neonates during long-term infusions of alprostadil (PGE1) (14 days or more). The cortical proliferation in children regressed after withdrawal of the drug.
- Since prostaglandin E1 is a potent inhibitor of platelet aggregation, Alprostadil should be used with caution in neonates (and infants) with bleeding tendencies.
- 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.
- The administration of alprostadil to neonates (or infants) may result in a gastric outlet obstruction secondary to antral hyperplasia. This effect appears to be related to duration of therapy and cumulative dose of the drug. Neonates (or infants) receiving alprostadil at recommended doses for more than 120 hours should be carefully 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; ie, better responses are obtained in patients with low pO2 values (less than 40mmHg), 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 determinated by monitoring the increase in systemic blood pressure and blood pH.
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Excipient information

This medicine contains 790 mg of alcohol (ethanol) in each 1 ml vial which is equivalent to 790 mg/ml (79% w/v) (see section 2). The amount in each 1 ml vial of this medicine 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 0.576 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 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.

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

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

Because this medicine is usually given slowly over 24 hours, the effects of alcohol may be reduced (see section 4.2).

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 alcohol in this medicine 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 alprostadil and the standard therapy employed in neonates (or infants) with congenital heart defects.
Standard therapy includes antibiotics, such as penicillin or gentamicin; vasopressors, such as dopamine or isoprenaline; cardiac glycosides; and diuretics such as furosemide.

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The most frequent adverse reactions observed with alprostadil infusion in neonates (and infants) with ductal-dependent congenital heart defect treated with alprostadil were related to the drug's 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
Blood and lymphatic system disorders	Common	Disseminated intravascular coagulation,
	Uncommon	Anaemia, thrombocytopenia

	Rare	Septicaemia
Metabolism and nutrition disorders	Common	Hypokalaemia
Endocrine disorders	Uncommon	Hypoglycaemia
Nervous system disorders	Common	Seizures
Cardiac disorders	Common	Bradycardia, hypotension, tachycardia
	Rare	Cardiac arrest
Respiratory, thoracic and mediastinal disorders	Very common	Apnoea
Gastrointestinal disorders	Common	Diarrhea
	Uncommon	Obstruction gastric, gastric mucosal hypertrophy
Hepatobiliary disorders	Uncommon	Hyperbilirubinemia
Musculoskeletal and connective tissue disorders	Uncommon	Exostosis
Vascular disorders	Uncommon	Vascular fragility
General disorders and administration site conditions	Very common	Transient pyrexia
	Common	Cutaneous vasodilatation (flushing)*
	Rare	Oedema

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

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 according to their local country requirements.

4.9 Overdose

Apnoea, bradycardia, pyrexia, hypotension and flushing may be signs of drug overdose. If apnoea or bradycardia occurs, the infusion should be discontinued and the appropriate corrective treatment initiated. Caution should be used if treatment is restarted. If pyrexia or hypotension occurs, 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: cardiac therapy
ATC code: C01E A01

Alprostadil (prostaglandin E_1) belongs to a group of naturally occurring fatty acids with various pharmacological effects. Vasodilatation, inhibition of platelet aggregation and stimulation of the intestinal and uterine smooth muscle tissue are among the most important effects. In mammals, doses of IV alprostadil of 1 to 10 micrograms/kg lower arterial pressure by reducing peripheral resistance. This reduction in pressure is accompanied by a reflex increase in cardiac output and heart rate.
The smooth muscle tissue of the ductus arteriosus is particularly sensitive to alprostadil and in the presence of the drug, strips of lamb ductus arteriosus relax markedly. In addition, the closing ductus arteriosus of newborn rats, rabbits and lambs has been reopened by administering alprostadil. These observations led to trials being undertaken with alprostadil in human neonates with congenital defects restricting systemic or pulmonary blood flow, and in whom the ductus arteriosus had to be kept patent to ensure adequate blood oxygenation and lower body perfusion.
In about 50% of the infants with restricted pulmonary blood flow, the blood pO_2 increased following the infusion of alprostadil by at least 10 mm Hg (mean increase of about 14 mm Hg and mean increase in oxygen saturation of about 23%). In general, the best results were obtained in infants who were less than 4 days old and who had low initial blood pO_2.
In infants with restricted systemic blood flow, alprostadil often increases the pH in those having acidosis, increases the systemic arterial pressure and reduces the ratio between pulmonary artery and aortic pressure.

5.2 Pharmacokinetic properties

Since it is rapidly metabolised alprostadil must be administered as a continuous infusion. Up to 80% of the circulating alprostadil may be metabolised in a single pass through the lungs, primarily by beta and omega oxidation. The metabolites are mainly excreted by the kidneys and 24 hours after administration, the drug will have been almost totally eliminated. No unchanged alprostadil is found in the urine and there is no indication of tissue retention of alprostadil or of its metabolites.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous ethanol.

6.2 Incompatibilities

It is advisable to avoid all contact between PROSTIN VR 0.5 mg/ml concentrate for solution for infusion and plastic material, see section 4.2.

6.3 Shelf life

Do not use Prostin VR after the expiry date which is stated on the carton / label after EXP:. The

expiry date refers to the last day of that month.

Diluted solutions must be used within 24 hours and must be stored in the refrigerator.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ampoule containing 1 ml concentrate for solution for infusion.
For use in hospital only.

6.6 Special precaution for disposal and other handling

Keep out of the sight and reach of children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. MANUFACTURER

Pfizer Manufacturing Belgium N.V Rijkisweg 12 2870 Puurs , Belgium

Classification for dispensing: medicinal product subject to medical prescription.

8. DATE OF REVISION OF THE TEXT

July 2021