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**Ihr Zeichen:**

**Betreff: Alprostadil – hältige Arzneispezialitäten – Änderungen der Fach- und Gebrauchsinformationen aufgrund des HBD – PSUR Worksharing Projektes**

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummer: AT/H/PSUR/0037/001) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Alprostadil- hältige Arzneispezialitäten mit der Indikation Ductus arteriosus Botalli aufzunehmen.

Sollten diese bereits aufgenommen worden sein, betrachten Sie dieses Schreiben als gegenstandslos.

## Fachinformation

### 4.3 Contraindications

Hypersensitivity to the active substance (alprostadil) or to any of the excipients.

### 4.4 Special Warnings and Special Precautions for Use

Alprostadil should be administered only by well trained healthcare professionals and in facilities with access to pediatric intensive care.

Apnea may occur in about 10-12% of neonates with congenital heart defects treated with alprostadil (PGE1). Apnea 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.

Cortical proliferation of the long bones has been reported in neonates during long-term infusions of alprostadil (PGE1). 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.

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 is not immediately available, the diagnosis should be based on the presence of cyanosis (pO<sub>2</sub> 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 ductus arteriosus wall and pulmonary arteries has been reported principally during prolonged administration

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 pO<sub>2</sub> values; ie, better responses are obtained in patients with low pO<sub>2</sub> values (less than 40 mmHg), whereas patients with high pO<sub>2</sub> 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.

#### **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 isoproterenol; cardiac glycosides; and diuretics such as furosemide.

#### **4.6 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

System Organ Class	Frequency	Undesirable effects
<b>Nervous system disorders</b>	Common	Seizures
<b>Cardiac disorders</b>	Common	Bradycardia, hypotension, tachycardia
<b>Respiratory, thoracic and medicinal disorders</b>	Very common	Apnea
<b>Gastrointestinal disorders</b>	Common	Diarrhea
	Uncommon	Obstruction gastric, gastric mucosal hypertrophy
<b>Musculoskeletal and connective tissue disorders</b>	Uncommon	Exostosis
<b>Vascular disorders</b>	Uncommon	Vascular fragility
<b>General disorders and administration site conditions</b>	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.





#### 4.9 Overdose

Apnea, bradycardia, pyrexia, hypotension and flushing may be signs of drug overdose. If apnea 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.

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.