Summary of risk management plan for Neupedix 500 µg Konzentrat zur Herstellung einer Infusionslösung (alprostadil)

This is a summary of the risk management plan (RMP) for Neupedix 500 µg Konzentrat zur Herstellung einer Infusionslösung (hereafter referred to as Neupedix). The RMP details important risks of Neupedix, how these risks can be minimised, and how more information will be obtained about Neupedix's risks and uncertainties (missing information).

Neupedix's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Neupedix 500 µg Konzentrat zur Herstellung einer Infusionslösung (alprostadil) should be used.

Important new concerns or changes to the current ones will be included in updates of Neupedix's RMP

I. The medicine and what it is used for

Neupedix 500 µg Konzentrat zur Herstellung einer Infusionslösung (alprostadil) is authorised for Temporarily maintaining the patency of the ductus arteriosus Botalli,

Neupedix 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 (see SmPC for the full indication).

It contains Alprostadil as the active substance and it is given intravenously.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Neupedix 500 µg Konzentrat zur Herstellung einer Infusionslösung (alprostadil), together with measures to minimise such risks, and the proposed studies for learning more about Neupedix's risks, are outlined below.

Measures to minimise the risks identified for medicinal products are:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Neupedix are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Neupedix. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the product).

List of important risks and missing information	
Important identified risks	Hypotension (Decreased blood pressure)
Important potential risks	Gastric outlet obstruction secondary to antral hyperplasia (Thickening of the stomach wall such that emptying of the stomach contents may be difficult)
Missing information	None

II.B Summary of important risks

Important identified risk: Hypotension (Decreased blood pressure)	
Evidence for linking the risk to the medicine	Alprostadil induces widening of the blood vessels (vasodilation) (Olsson and Carlson 1976) and uniformly lowered blood pressure of mammals when administered intravenously in doses between 1 and 10 mcg/kg (SA, 2003, Alprostadil Monograph, 2019). As a reaction to this Alprostadil-induced lowered blood pressure, cardiac output and heart rate increased (Lewis et al., 1981; Roehl and Townsend 1982; Hew and Gerriets 2021). Lucron et al. 2005 in a retrospective study in 62 neonates with congenital heart disease (average age 1.6 days) investigated the tolerance and efficacy of Alprostadil (average Age 1.6 days: 35 boys: weight: 3.1 +/- 0.6 Kg). This side effect was observed in 6.5% of the patients. Hypotension was more common in cases of poor neonatal adaptation. Short-term adverse effects of PGE_1 include hypotension (Akkinapally et al., 2018).
	Hypotension may also be a sign of drug overdose (Cole and Townsend, 1982).

Risk factors and risk groups	Unknown.
Risk minimization measures	Routine Risk minimization: SmPC: Section 4.8 Undesirable effects • Listing hypotension as undesireable effect under SOC Cardiac disorders with frequency "common" Section 4.9 Overdose • Listing hypotension as a potential sign of overdose. • Advise in case of occurring hypotension, to reduce the infusion rate until this symptom subsides. PIL: Section 2 What you need to know before you use Neupedix Warnings and precautions • Mentioning that reduced blood pressure can indicate an excessive alprostadil effect and the need for a dose reduction. • Section 3. How to use Neupedix • Advise that in case low blood pressure occurs, the infusion rate should be reduced until these symptoms subside. • Section 4. Possible side effects • Listing Low blood pressure as common side effect (may affect up to 1 in 10 people) The product is handled and administered by health care professionals only.
Important potential risk: Gastric outlet obstruction secondary to antral hyperplasia (Thickening of the stomach wall such that emptying of the stomach contents may be difficult)	
Evidence for linking the risk to the medicine	Several studies investigated the long-term effects of the group of drugs Alprostadil belongs to (so called Prostaglandins") administration on stomach and intestine in neonates. In a study by Babyn and colleagues, 1995, eight out of 74 newborns receiving Alprostadil had thickening of the stomach wall. From this it was concluded that long-term administration of Alprostadil can cause this thickening of the stomach wall such that emptying of the stomach contents may be difficult (Babyn et al., 1995; Lacher 2007; Peled 1992; Perme 2013, Calder 1984; Gittenberger-de Groot 1978; Talosi et al, 2007).
Risk factors and risk groups	Unknown.
Risk minimization measures	Routine Risk minimization measures:

	SmPC: Section 4.4. Special warnings and precautions for use • Mentioning that the administration of alprostadil to newborns may result in hyperplasia of the gastric outlet mucosa in the antrum and secondary to gastric outlet obstruction. • Mention, that this effect appears to be related to duration of therapy and cumulative dose of the drug. • Request that newborns receiving alprostadil at recommended doses for more than 5 days should be closely monitored for evidence of dose-dependent antral hyperplasia and gastric outlet obstruction. • Mentioning of frequency (to occur in 7% of patients). Section 4.8 Undesirable effects • Listing hyperplasia of the gastric mucosa in the antrum including occlusion of the gastric outlet (gastric obstruction) with long-term therapy (dose-dependent) under SOC Gastrointestinal disorders with frequency "common". PIL: Section 2. What you need to know before you use Neupedix Warnings and precautions • Mentioning that in newborns receiving alprostadil for more than 5 days, the occurrence of dose-dependent thickening of the gastric mucosa in the area of the gastric outlet or occlusion of the gastric outlet must be closely monitored. • Mentioning of the frequency of this side effect (to occur in 7% of patients) • Cross reference to PIL section 4. Section 4. Possible side effects • Listing "thickening of the gastric mucosa with obstruction of the gastric outlet in long-term therapy (dose-dependent)" as side effect with frequency "Common" • Cross reference to section 2

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Neupedix.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Neupedix.