EU Risk Management Plan for Dopamine HCl

RMP version to be assessed as part of this application:

RMP Version number: 0.4

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Rationale for submitting an updated RMP: Not applicable

Summary of significant changes in this RMP: Not applicable

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Dopamine Hydrochloride
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: adrenergic and dopaminergic agents ATC Code: C01CA04
Marketing Authorisation Applicant	BrePco Biopharma Limited
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	Neoatricon
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Dopamine Hydrochloride is the hydrochloride salt form of Dopamine, a monoamine compound with positive inotropic activity.
	Summary of mode of action: Dopamine Hydrochloride binds to alpha-1- and beta-1-adrenergic receptors. Mediated through myocardial beta-1-adrenergic receptors, dopamine increases heart rate and force, thereby increasing cardiac output. Alpha-1-adrenergic receptor stimulation on vascular smooth muscle, leads to vasoconstriction and results in an increase in systemic vascular resistance. Stimulation of dopaminergic receptors in renal vasculature, leads to renal blood vessel dilation, and an increase in glomerular filtration rate, renal blood flow, sodium excretion, and urine output.
	Important information about its composition: [redacted] The key starting material is [2-(3,4-dimethoxyphenyl)ethyl]amine (Homoveratrylamine). The key starting material is treated with hydrochloric acid to obtain wet purified Dopamine HCl.

	[redacted]
Hyperlink to the Product Information	*Hyper link to Product Information*
Indication(s) in the EEA	Current: Treatment of hypotension in hemodynamically unstable neonates, infants and children < 18 years.
Dosage in the EEA	Current: • Infusion of dopamine hydrochloride solution should begin at a rate of 5 µg /kg/min and increase gradually in 5 µg /kg/min increments. The recommended dose range is 5 – 10 µg/kg/min. • Doses above 10 µg/kg/min up to a maximum of 20 µg /kg/min may be administered if considered justified.
Pharmaceutical form(s) and strengths	Current: Dopamine Hydrochloride Ready-to-Use Sterile Solution for Infusion. (1) 30 mL vial containing 1.5 mg/mL of Dopamine Hydrochloride. (2) 50 mL vial containing 4.5 mg/mL of Dopamine Hydrochloride.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication:

Treatment of hypotension in hemodynamically unstable neonates, infants and children < 18 years.

Target population:

Neonates, infants and children < 18 years.

Incidence:

The precise epidemiology of hypotension is highly variable and depends on the exact etiology.[1]

Hypotension is a common problem in the neonatal intensive care unit (NICU). The incidence of neonatal hypertension in the NICU ranges from 0.2% to 3% and most commonly affects term and preterm infants in the intensive care setting.[2]

Prevalence:

There are no definitive or generally accepted figures on prevalence.[3] Wide differences exist in the prevalence of hypotension among NICUs.[4]

Risk factors for the disease:

The aetiology of hemodynamic instability in the neonatal period is often multifactorial, but an assessment of the clinical risk factors, in combination with physical exam, can provide valuable insight. Blood pressure is equal to blood flow multiplied by resistance and is, therefore, a reflection of both cardiac function and systemic vascular resistance. Whereas mean arterial pressure (MAP) is commonly used for routine blood pressure monitoring, the systolic and diastolic components can be reflective of underlying vascular status. Systolic blood pressure is a measure of left ventricular (LV) stroke volume, which is the composite of preload, contractility, and afterload.[5]

Systolic hypotension can result when any or all of these factors are impaired.
1. Preload is compromised by hypovolemia or cardiac tamponade as well as conditions of limited pulmonary blood flow, including persistent pulmonary hypertension of the newborn (PPHN).
2. Contractility is compromised by structural heart disease, myocardial injury/ischemia, or arrhythmia.
3. Afterload is compromised after patent ductus arteriosus (PDA) ligation as well as failed cardiovascular transition after removal of the placental circuit.[5]

In contrast, diastolic blood pressure is a measure of systemic vascular resistance, which can be compromised by sepsis, capillary leak, a hemodynamically significant PDA, and arteriovenous malformations.[5]

Among the risk factors, the birth weight, small for gestational age (SGA) status, Apgar score, neonatal resuscitation (cardiac massage or epinephrine administration), neonatal body temperature, neonatal pH, symptomatic PDA, early onset sepsis (EOS), prenatal steroid administration, amniotic fluid volume, chorioamnionitis, and multiple birth status were identified as factors associated with treatment for hypotension within the first postnatal week. Regression analysis demonstrated a significant relationship between a lower birth weight and 1-minute Apgar score ≤ 3 and a higher incidence of hypotension. Additionally, in infants who underwent neonatal resuscitation, had pH at admission < 7.20, were diagnosed with symptomatic PDA or EOS, whose mother had polyhydramnios, and were multiple births, the rate of hypotension was high. However, in the logistic regression analysis after matching, the incidence of hypotension was significantly higher in infants when the 1-minute Apgar score was ≤ 3, when neonatal resuscitation was performed, and when infants were diagnosed with symptomatic PDA or EOS. The rate of hypotension was significantly lower in infants with mothers with chorioamnionitis than in those without.[6]

<u>The main existing treatment options:</u>

The basis of treatment of hypotension in newborns is specifying and treating the underlying cause. The objective should be to correct organ perfusion rather than only obtaining a normal BP value.[7,8,9,10] Therefore, the patient should be intermittently assessed during the treatment period and at the end of treatment using clinical criteria, TE, tissue perfusion, and oxygenation.[11]

Drugs for neonatal hypotension primarily act on three classes of G-protein coupled receptors: α- and β-adrenergic receptors as well as dopaminergic receptors. Alpha$_1$-adrenergic receptors and peripherally located a$_2$-adrenergic receptors cause systemic vasoconstriction, including in blood vessels of the intestines and kidney. Beta$_1$ receptors increase cardiac output by increasing heart rate (chronotropy), contractility (inotropy), and conduction velocity (dromotropy); activation of these receptors also promotes renin secretion. Beta$_2$ receptors cause smooth muscle relaxation and vasodilation. Dopaminergic stimulation has both cardiopulmonary and renal effects. Myocardial dopaminergic receptors increase contractility without increasing heart rate. Dopaminergic receptors in the kidney mediate diuresis and natriuresis.[5]

Adequate volume expansion is the prerequisite for nearly all cardiovascular support in the neonate. The administration of crystalloid or colloid improves preload and can temporarily counter a decrease in systemic vascular resistance. In preterm infants, isotonic saline is equally effective to 5 percent albumin in the treatment of hypotension. However, resuscitation with albumin is associated with increased fluid retention in the first 48 hours of life.[12] Albumin administration is also associated with impaired oxygenation in hypotensive preterm infants.[13] If there is a history of haemorrhage, then resuscitation with blood products may be preferred in the management of hypotension.[5]

The mainstay of pharmacologic therapy includes exogenous administration of various catecholamine agonists each of which have different mechanisms. The selection of a specific catecholamine should consider specific developmental and pathophysiological factors unique to the index case. These drugs interact with a population of myocardial and peripheral

adrenoreceptors including 2 major types (α and β), each of which has multiple subtypes.[14] In addition to the catecholamine agents, two other classes of medications are increasingly used in the management of hemodynamic instability in neonates. These are the hormone vasopressin and its analogues and phosphodiesterase inhibitors (e.g., milrinone). Cardiovascular therapeutic agents may be divided into drugs that have predominantly vasopressor activity (e.g., dopamine, vasopressin, norepinephrine) and those with predominantly inotropic activity (e.g., dobutamine, milrinone) based on their receptor profile and mechanism of action. Epinephrine is an inotropic agent with variable dose dependent vasoactive effects. The effects of hydrocortisone are complex with multiple interacting mechanisms of action.[15] Intravenous fluids and steroids are also frequently used in the treatment of hypotension.[11]

Although the drugs are classified as inotropics and vasopressors, some (e.g., dopamine and adrenalin) show both effects according to the dose given. Differences in maturation according to gestational week and postnatal age change adrenergic (alpha and beta) and dopaminergic receptor expression and thus the cardiovascular response. Inotropics improve cardiac contraction by acting on the myocardium and increase cardiac output. Vasopressors lead to an increase in BP by way of vasoconstriction in the vascular bed. They basically act via the adrenergic system. Resuscitation guidelines recommend use of inotropics and/or vasopressors in hypotension that persists despite volume replacement.[16] Which agent to be preferred in which newborn is still an issue of debate.[17] There are insufficient clinical studies showing long-term results of treatment of hypotension in newborns. The most frequently used agents in the treatment of hypotension and hemodynamic disruption in newborns and their mechanisms of action are Dopamine, Dobutamine, Epinephrine, Norepinephrine, Vasopressin, Terlipressin, Hydrocortisone, Milrinon and Levosimendan.[11]

Children are more likely to undergo intubation during the treatment of hypotension because their oxygen levels drop more rapidly than adults.[18]

Choice of therapeutic agent should depend on the pathophysiology of the underlying disease state and the intended effect.[15]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Early-onset hypotension in neonates is generally related with abnormal peripheral vasoregulation, myocardial dysfunction, and hypovolemia.[19]

Many studies show an association between hypotension and poor neurodevelopmental outcomes in neonates.[20,21] Although this does not prove causation, low BP does lead to impaired cerebral blood flow (CBF), particularly in preterm neonates who have immature cerebral autoregulation, and is a common rationale for treating hypotension in neonates.[22] Infants with symptomatic hypotension are more likely to have delayed motor development, hearing loss, and death.[23]

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Not applicable.

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes.

Dopamine Hydrochloride has no known abuse potential.

Part II: Module SVII - Identified and potential risks

Not applicable based on risk proportionality principle.

No new data in comparison to the information of the reference medicinal product is available.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Deterioration of tissue perfusion and hypoxia in hypovolaemic patients • Increased risk of infections
Important potential risks	• Increase in pulmonary artery pressure
Missing information	• Pregnancy, lactation and fertility

Part III Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

No special important risks have been identified for dopamine HCl, which require other routine PhV activities, beyond adverse drug reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV Plans for post-authorisation efficacy studies

Not applicable

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimization measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Deterioration of tissue perfusion and hypoxia in hypovolaemic patients	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 3 and 4 – Prescription only medicine Additional risk minimisation measures: None	Routine
Increased risk of infections	Routine risk minimisation measures: SmPC sections 4.4 and 4.8 PL sections 2 and 4 – Prescription only medicine Additional risk minimisation measures: None	Routine
Increase in pulmonary artery pressure	Routine risk minimisation measures: SmPC section 4.4 PL section 2 – Prescription only medicine Additional risk minimisation measures: None	Routine

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Pregnancy, lactation and fertility	Routine risk minimisation measures: SmPC section 4.6 PL section 2 – Prescription only medicine Additional risk minimisation measures: None	Routine

Part VI Summary of the risk management plan

Summary of risk management plan for Neoatricon (Dopamine hydrochloride)

This is a summary of the risk management plan (RMP) for Neoatricon. The RMP details important risks of Neoatricon, how these risks are minimised, and how more information will be obtained about Neoatricon's risks and uncertainties (missing information).

This summary of the RMP for Neoatricon should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. THE MEDICINE AND WHAT IT IS USED FOR

Neoatricon is authorised for the treatment of hypotension in hemodynamically unstable neonates, infants and children < 18 years.

It contains dopamine hydrochloride as the active substance and it is given by intravenous infusion.

Further information about the evaluation of Neoatricon's benefits can be found in Neoatricon's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage link to the EPAR summary landing page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Neoatricon, together with measures to minimise such risks and the proposed studies for learning more about Neoatricon's risks, are outlined below.

Measures to minimise the risks identified for medicinal products:

- Specific information, such as warnings, precautions, and advice on correct use have been included in the SmPC which is intended for healthcare professionals and in the package leaflet addressed to patients.
- Important advice has been incorporated on the medicine's packaging including "Protect from Light" and "Do not Dilute".
- Dopamine Hydrochloride lettering will be presented as **DOPamine Hydrochloride** on all secondary packaging and labelling to minimise confusion with similar compounds.
- The product is only intended for use in a Critical Care setting and its supply is specific to that setting.
- The product is POM and is only supplied on a doctor's restricted medical prescription.
- Hospital only product.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analysed including Periodic Benefit-Risk Evaluation Report assessment 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 Neoatricon 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 Neoatricon. 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 medicine).

List of important risks and missing information	
Important identified risks	• Deterioration of tissue perfusion and hypoxia in hypovolaemic patients • Increased risk of infections
Important potential risks	• Increase in pulmonary artery pressure
Missing information	• Pregnancy, lactation and fertility

Dopamine Hydrochloride solution for infusion has been in use since 1977. The important risks are well documented for this product and are included in the SmPC.

II.B: Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

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 Neoatricon.

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

There are no ongoing or planned additional pharmacovigilance studies or other activities in the pharmacovigilance plan.

Part VII Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

[redacted]

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable

[redacted]