21 March 2024
EMA/260885/2024
Committee for Medicinal Products for Human Use (CHMP)

CHMP Assesment Report

Neoatricon

International non-proprietary name: Dopamine hydrochloride

Procedure No. EMEA/H/C/006044/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Neoatricon
Applicant:	BrePco Biopharma Limited Suite 1 The Avenue Beacon Court Sandyford Dublin 18 IRELAND
Active substance:	Dopamine / Dopamine hydrochloride
International Non-proprietary Name/Common Name:	Dopamine hydrochloride
Pharmaco-therapeutic group (ATC Code):	Cardiac therapy, adrenergic and dopaminergic agents
Therapeutic indication(s):	Treatment of hypotension in haemodynamically unstable neonates, infants and children < 18 years.
Pharmaceutical form(s):	Solution for infusion
Strength(s):	1.5 mg/ml and 4.5 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

Related to Quality

CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
EDQM	European Directorate for the Quality of Medicines
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IR	Infrared
MAH	Marketing Authorisation Holder
MO	Major Objection
PDCO	Paediatric Committee
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
Rec	Recommendation
SMBS	Sodium Metabisulfite
SmPC	Summary of Product Characteristics

Related to clinical

AE	Adverse Event
AR	Adverse Reaction
ABG	Arterial Blood gas
BP	Blood Pressure
BCRI	Boole Centre for Research Informatics
CAP	Caffeine for Apnoea of Prematurity
CA	Competent Authority
CNN	Canadian Neonatal Network
COIN CPAP	Continuous Positive Airway Pressure or Intubation at Birth Trial
CP	Collaborative Project
CPMP0	Committee for Proprietary Medical Products
CPSIP	Collaborative Project Supported Intellectual Property
CREC	Clinical research ethics committees
Ecrf	Electronic Case Report Form
CTA	Clinical Trial Authorisation
CTA	Clinical Trial Agreement
D/C	Infant Discharge from Hospital
DMC	Data Monitoring Committee
EAB	Ethics Advisory Board
ECHO	Echocardiography
EEG	Electroencephalography
aEEG	Amplitude integrated EEG
ELBW	Extremely Low Birth Weight (<1000g)
ELGAN	Extremely Low Gestational Age Newborn (<28 weeks)
EMA	European Medicines Agency
ENBC	European Neonatal Brain Club
ESPR	European Society for Paediatric Research
EURICON	European Neonatal Research Informed Consent
FDA	Food and Drug Administration
GA	Gestational Age
GABO:mi	Gesellschaft für Ablauforganisation: Milliarium (P8)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPvP	Good Pharmacovigilance Practice
HIP	Trial Acronym
IB	Investigators Brochure
IMP	Investigational Medicinal Product

IMPD	Investigational Medicinal Product dossier
ISF	Investigator Site File
IVH	Intraventricular Haemorrhage
Kg	Kilogramme
LVO	Left Ventricular Output
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Health care products Regulatory Agency
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
NIRS	Near Infrared spectroscopy
PD	Pharmacodynamics
PCC	Project Coordination Committee
PGB	Project Governing Board
PIP	Paediatric Investigation Plan
PIL	Parent Information Leaflet
PINT	Premature Infants in need of Transfusion Trial
PIS	Parent Information Sheet
PK	Pharmacokinetics
PNA	Post-natal Age
PUMA	Paediatric Use Marketing Authorisation
Pv	Pharmacovigilance
PVL	Periventricular Leukomalacia
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
REC	Research Ethics Committee
RVO	Right ventricular output
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SC	Study Co-ordinator
SME	Small to Medium-sized Enterprise
SmPC	Summary of Product Characteristics
SOP:	standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVC	Superior Vena Cava Flow
TIPP	Trial of Indomethacin Prophylaxis in the Preterm Infant
TMF	Trial Master File
UAR	Unexpected Adverse Reaction
UCC	University College Cork
WD	Patient Withdrawal from Clinical Trial

List of definitions

Corrected age (of preterm infant): age calculated from expected date of delivery (GA plus PNA).
Gestational age (GA): time between first day of last normal menstrual period and date of birth, usually expressed in weeks; GA is defined at birth.
Neonatal period: period from birth up to and including the age of 27 days or in case of preterm infants period from birth to Corrected age at term.
Post-natal age (PNA) or chronological age: age calculated from date of birth.
Preterm infant: < 37 weeks of gestational age.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant BrePco Biopharma Limited submitted on 24 August 2022 an application for a paediatric use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Neoatricon, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 December 2021.

The applicant applied for the following indication:

Treatment of hypotension in neonates including the extremely low gestational newborns.

Treatment of hypotension in infants and children.

1.2. Legal basis, dossier content

The legal basis for this application refers to: Article 10(3) of Directive 2001/83/EC, Hybrid application under Article 31 of Regulation (EC) No 1901/2006 - Paediatric Use Marketing Authorisation (PUMA)

Reference medicinal product

Sterile Dopamine Concentrate BP 40mg/mL, Ireland (MAH: Mercury Pharmaceuticals (Ireland) Ltd).

Difference(s) compared to this reference medicinal product: Change in therapeutic indications, change in strength (quantitative change to the active substance(s)).

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP P/0209/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0209/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0209/2022.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
29 October 2019	EMEA/H/SA/4195/1/2019/PED/SME/III	*Dr Mario Miguel Rosa and Dr Peter Mol*
5 February 2021	EMA/SA/0000047014	*Prof Peter Mol and Dr Clemens Mittmann*

The scientific advice pertained to the following quality and clinical aspects:

Quality:

- Intended formulation for the MAA and the presence of an excipient.

Clinical:

- Systematic review of literature to support a MAA.
- Level of evidence in preterm babies from HIP trial to support a MAA.
- Dosing regimen.
- Proposed additional pharmacovigilance monitoring to monitor the safety of dopamine use.
- Acceptability of biomarkers, endpoints, clinical measurements and sample size calculations for a proposed post-approval study.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Alar Irs

PRAC Rapporteur: Maia Uusküla

The application was received by the EMA on	24 August 2022
The procedure started on	1 December 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 February 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 March 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	8 March 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 March 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 September 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	6 December 2023
SAG/Expert group/ Working Party experts (as appropriate) were convened to address questions raised by the CHMP on	12 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	17 January 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	23 January 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 January 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	7 March 2024

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Neoatricon on	21 March 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed therapeutic indication was:

Treatment of hypotension in neonates including the extremely low gestational new-borns.

Treatment of hypotension in infants and children.

The CHMP approved the following indication:

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

2.1.2. Epidemiology

Preterm birth is the second largest direct cause of child deaths in children younger than 5 years. Blencowe H et al. (The Lancet 2012; 379: 2162–72) have reported worldwide, regional, and national estimates of preterm birth rates for 184 countries in 2010. In 2010, an estimated 14·9 million babies (uncertainty range 12.3–18.1 million) were born preterm, 11.1% of all livebirths worldwide, ranging from about 5% in several European countries to 18% in some African countries. Among 131,296,785 live births in 41 countries, they calculated proportions of extremely preterm (<28 weeks GA): 5.2% (5.1–5.3); very preterm (28–<32 weeks GA):10.4% (10.3–10.5); and moderate or late preterm (32–<37 weeks GA): 84.3% (84.1–84.5). The regions with the highest preterm birth rates in 2010 were Southeastern Asia, South Asia, and sub-Saharan Africa (Figure 1 below). Only some of the very preterm infants develop hypotension and not all of these require drug therapy. It has to be considered that physiologically MABP increases by about 5 mmHg during the first day after delivery. Definitions as to whether drug treatment is necessary have changed over the last 1 – 2 decades. Lacking clear criteria for initiation of treatment, it is also difficult to estimate the proportion of ELGANs requiring therapy for insufficient cardiovascular function associated with hypotension.

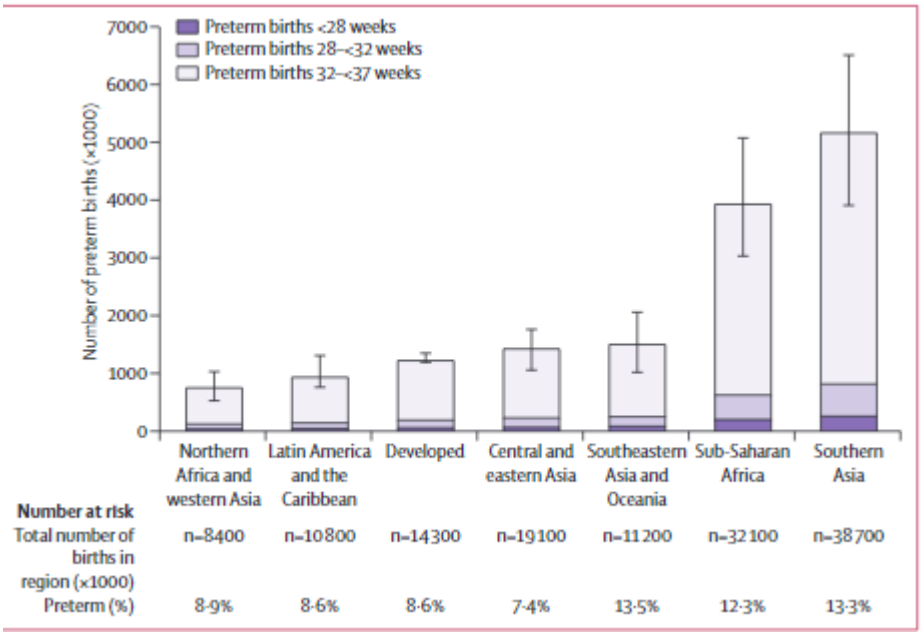

Figure 1. Estimated preterm births by region and by gestational age grouping for the year 2010.

The aetiological frequency of the different causes of shock in the overall paediatric population varies worldwide and direct comparisons are difficult to make. In a study of paediatric patients who presented to the paediatric emergency department over an 8-year period in a single institution, Fisher et. al. (Fisher, J. D. Pediatr Emer Care 2010; 26: 622-625) identified sepsis as the leading cause of shock in 57% of patients, followed by hypovolaemic shock (24%), distributive shock (14%), and cardiogenic shock (5%).

2.1.3. Biologic features, aetiology and pathogenesis

Hypotension is a symptom of shock. Shock is defined as the inadequate delivery of substrates and oxygen to meet the metabolic needs of the tissues and is one of the most common, and often life-threatening, conditions encountered in paediatric intensive care. Shock is often categorized as follows:

• Hypovolaemic shock results from an absolute deficiency of intravascular blood volume. This can present in a variety of ways. In the developing world severe gastroenteritis is one of the most common causes. Children with gastroenteritis who may lose 10-20% of their circulating volume rapidly. Rapid loss of intravascular volume reduces ventricular preload, resulting in decreased stroke volume, cardiac output and decreased delivery of oxygen to the tissues. Other cases of hypovolaemic shock include haemorrhagic shock in trauma and capillary leak syndrome in sepsis and burns.

• Distributive shock includes shock secondary to anaphylaxis, traumatic brain injury or drug-related causes following poisoning. Traumatic brain injury is the leading cause of traumatic morbidity and mortality in children. Altered autonomic tone results in abnormal vasodilation resulting in a decrease in preload, reduced cardiac output and shock.

• Septic shock is defined as severe sepsis plus hypotension not reversed with fluid resuscitation. It results from a complex interaction between pathologic vasodilation, relative and absolute hypovolaemia, myocardial dysfunction, and altered blood flow distribution caused by the inflammatory response to infection.

• Cardiogenic shock results from a direct impairment of cardiac contractility as can occur in ischaemic heart disease, cardiomyopathy, drug ingestion, and sepsis, leading to decreased stroke volume, cardiac output and a reduction in delivery of oxygen to the cells. It is a rare cause of shock in the paediatric population but can occur in congenital heart disease.

Low blood pressure is a common phenomenon in the first three days after the birth of extremely low gestational age new-borns (gestational age < 28 weeks). Although hypotension of itself is not necessarily a condition that requires treatment, it can be indicative of more serious issues with organ perfusion, or shock as described above. Many hospital guidelines describe the threshold for intervention as a mean blood arterial pressure (MABP) in mmHg lower than the gestational age of the patient in weeks but there is a shift to a more permissive approach allowing for lower BP values depending on the clinical status. Systemic arterial hypotension is associated with periventricular haemorrhage and poor long-term neurodevelopmental outcome in preterm infants. Preterm infants with low cerebral blood flow are at risk of periventricular haemorrhage (Subhedar NV, Shaw NJ. Cochrane Database of Systematic Reviews 2003, Issue 3).

2.1.4. Clinical presentation, diagnosis and management

Preterm infants

The rationale for aggressively treating systemic hypotension in preterm infants has been to preserve adequate organ perfusion and, in particular, cerebral blood flow. It has been argued that sick preterm infants have impaired cerebral autoregulation resulting in a pressure-passive cerebral circulation. In this setting, hypotension may lead to low cerebral blood flow. However, data are conflicting in this regard and cerebral perfusion may be independent of systemic blood pressure (BP) based on an intact cerebral autoregulation. There is an ongoing discussion about the appropriate target BP in preterm infants. Although not based on scientific evidence, as a criterion for treatment a MABP below gestational age has been in widespread use. This threshold has been challenged and a more permissive approach allowing for lower values, depending on whether signs of impaired organ perfusion are present, is increasingly in use. Mean arterial blood pressure (MABP) may not be an optimal parameter, assessment of cardiac haemodynamics, tissue perfusion and cerebral haemodynamics may be better to guide treatment decisions in extremely low gestational age neonates (ELGANs). Avoidance of peak blood pressure values and of major fluctuations may protect vulnerable tissues like the germinal matrix, usually the origin of intraventricular bleedings in ELGANs. P persistent cerebral hypoperfusion is a relevant cofactor for the development of IVH or periventricular leukomalacia: (PVL). It is also associated with worse neurological outcome. Lower and prolonged phases of rScO2 <50-55% are associated with a worse clinical outcome at month 18/24. Overall, rScO2 is among the relevant parameters to assess cerebral perfusion.

In preterm hypotensive infants a number of therapeutic strategies including volume expansion, corticosteroids and inotropic agents have been used in an attempt to treat systemic hypotension in preterm neonates. Therapeutic strategies are shifting towards a more permissive approach allowing for lower BP values. In the clinical management intensified fluid management and administration of hydrocortisone where needed rather than early administration of a catecholamine is currently preferred, although robust long term data on clinical and in particular neurological outcome supporting one or the other strategy are currently not available.

Burns ML et al. (Pediatr Crit Care Med (2016) 17:948–56) reported that dopamine was the most commonly used vasoactive agent with a median duration of administration of 46 h and a median maximum dose of 10 µg/kg/min, followed by epinephrine (33 h and 0.3 µg/kg/min, respectively) and dobutamine (22 h and 8.3 µg/kg/min, respectively), with the increasing use of milrinone,

norepinephrine, and vasopressin (for rev. see Chloe J. and Po-Yin C. (Front Pediatr. 2018; 6: 86). Meanwhile a shift in the approaches has been taking place and some centres try to avoid treatment with dopamine in general. The inotropic and peripheral vasoconstrictor effects of dopamine predominate in the newborn period, although there is controversy surrounding the existence of any vasodilator effects in renal, coronary and cerebral circulations. Dobutamine is a synthetic catecholamine with beta adrenergic actions with inotropic effects but without the tendency for peripheral vasoconstriction. Epinephrine is an endogenous catecholamine that acts directly and dose-dependently on α-1 (>0.1 µg/kg/min) and α-2, β-1 and β-2 (0.02–0.1 µg/kg/min) adrenoreceptors, with vasopressive and inotropic actions, respectively. There may be a modest decrease in pulmonary vascular resistance as well as vasodilation of renal and mesenteric vasculature at low doses. As doses escalate, vasoconstriction can become intense, tachycardia is pronounced, blood flow to the gut and kidneys decreases, and increased oxygen consumption occurs, although there is still some inotropic action and blood flow is increased to the brain and heart. (Chloe J. and Po-Yin C Front Pediatr. 2018; 6: 86).

Norepinephrine is often used as a second- or a third-line antihypotensive agent as an endogenous sympathomimetic amine that acts on the vascular and myocardial α-1 receptors with a mild to moderate β-1 adrenoreceptor agonism. As the effect on β-2 adrenoreceptors is minimal, norepinephrine has combined inotropic and peripheral vasoconstrictive effects. The clinical literature on norepinephrine use in neonates is predominantly involving refractory shock and demonstrates increased BP, improved oxygenation, and decreased serum lactate within hours of initiation. (Chloe J. and Po-Yin C Front Pediatr. 2018; 6: 86).

Milrinone may improve left ventricular function and reduce pulmonary (venous and arterial) hypertension. A randomized controlled trial of milrinone in preterm neonates showed no clear benefit to prevent low SVC flow in the first few days of life (Paradisis M et al., J Pediatr (2009) 154:189–95).

The neonatal use of vasopressin has been predominantly for catecholamine-resistant shock, hypothetically tackling the hypotension via the depletion of endogenous AVP in a critically ill state as well as the vasoplegia unresponsive to catecholamines. An increase in the mean BP and the ability to decrease inotrope score were not accompanied by an improved survival and an increased end-organ perfusion (Masarwa R, et al., Crit Care (2017) 21:1).

The available literature contains conflicting results regarding the hypotension and its treatment in extremely preterm infants. For extremely pre-term (GA ≤ 28 weeks) infants who have adequate perfusion, it remains unclear whether the interventions have a clinically meaningful impact, and if so, whether they are beneficial or harmful. There are numerous studies indicating potential harm of interventions and hypotension treatment (see below, Discussion on clinical efficacy).

2.2. About the product

The applicant filed an application for marketing authorisation of Dopamine 1.5 and 4.5 mg/mL Solution for infusion, in accordance with Article 10.3 of Directive 2001/83/EC, so called hybrid application, as amended. Dopamine Hydrochloride Ready-to-Use Sterile Solution for infusion is an equivalent formulation of the reference product. The reference medicinal product is Sterile Dopamine Concentrate BP 40mg/mL, Ireland (MAH: Mercury Pharmaceuticals (Ireland) Ltd, Authorisation Number: PA 73/108/1 and Date of first authorization: 17 August 1989). The widely available formulations of dopamine across EU are indicated only for adults and the wording of the indications varies considerably.

The approved indications for the reference product Sterile Dopamine Concentrate BP 40mg/mL, Ireland (MAH: Mercury Pharmaceuticals (Ireland) Ltd, Authorisation Number: PA 73/108/1 is: "*For the*

correction of haemodynamic imbalance such as is seen in circulatory decompensation accompanying myocardial infarction, trauma, endotoxic septicaemia, renal failure, congestive cardiac failure and open heart surgery".

It has been approved for more than 10 years in various European countries.

The proposed formulation is developed for use in paediatric population and hence the strength and indication differ to the reference product in terms of target population and a change in strength (quantitative change to the active substance(s)). The product is developed specifically for paediatric use; the applicant submitted this application under PUMA (Paediatric Use Marketing Authorisation). Dopamine hydrochloride is widely available across Europe in 40 mg/mL and 160 mg/mL presentations and is indicated for 'correction of haemodynamic imbalance present in: acute hypotension or shock associated with myocardial infarction, endotoxic septicaemia, trauma and renal failure; as an adjunct after open heart surgery where there is persistent hypotension after correction of hypovolaemia; or for use in chronic cardiac decompensation as in congestive failure' in adults for doses up to 50 µg/kg/min.

The proposed therapeutic indications were:

Treatment of hypotension in neonates including the extremely low gestational new-borns.

Treatment of hypotension in infants and children

Based on a documented use of dopamine in the paediatric population the applicant stated that providing an age appropriate formulation ready for use would provide a significant advantage for handling and for the safety of patients. The applicant stated that use of existing adult presentations which are diluted, introduce unnecessary danger to the NICU and PICU patient. Frequent dosage errors in paediatrics are a well known concern, as individual dosage calculations and preparations are more often necessary than in adult patients. In the field of neonatology, it often becomes difficult depending on the desired dosage. On the one hand, sometimes very low doses have to be administered to very small children. Since at the lower end the running speed of the perfusers is limited and a drug may be administered with too much of a variation at very low running speeds of a perfuser (also depending on a possible bypass), a dilution of the standard solution is often preferred, even though this is a potential source of error. On the other hand, infusion of a standard concentration can be accompanied by a considerable volume load, depending on the concentration of the drug and the necessary dosage, so that individual approaches are also followed in this regard sometimes. Therefore, the development of an age appropriate ready to use formulation has the potential to reduce such errors.

2.3. Type of application and aspects on development

The application is based on two lines of evidence.

a) A pivotal study was submitted in order to support an indication in extremely low gestational age newborns (ELGANs): HIP study with CAR substudy.

This claim was supported by a literature review on the administration of dopamine in this patient population.

An additional PAES was proposed by the applicant to be performed post-authorisation.

b) A comprehensive literature review was submitted to support an indication in hypotension/shock in different conditions: sepsis, shock in the context of cardiac diseases including cardiosurgery, Traumatic Brain Injury, Hypoxic Ischaemic Brain Injury, toxicology including drug overdose.

EMA scientific advice was provided twice.

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The EMA scientific advice discussed the following quality aspects (reformulation of Neoatricon): drug product stability aspects, the use of antioxidant and the chosen formulation. Notably, using the antioxidant SMBS at the lowest possible concentration in the formulation was agreed if adequately justified.

For the clinical development the following issues were discussed. The appropriateness of the review of the available literature for the paediatric population 0 – 18 years, methodological issues regarding a meta-analysis. The proposal to close the HIP trial and use the results to support an MAA with the indication 'Treatment of hypotension in neonates including the extremely low gestational age newborn' and to further support the application by a PAES which was considered difficult to assess with regards to efficacy and safety. It was considered that the available HIP data will be useful from a safety and short-term efficacy standpoint but could not support any claims of longer-term benefit on survival or neurological outcome. The proposed dosing regimen up to 20 µg/kg/min, titrated at the discretion of the clinician which was considered reasonable.

The follow up advice discussed specific questions pertaining to the proposed PAES in 25 - 34 hypotensive extremely low gestational age neonates (ELGANs, Gestational age from 23 weeks at birth to less than 28 completed weeks) and alternative endpoints. Whether the impact of dopamine on rScO2 is a relevant biomarker and is predictive value for clinical outcomes discussed. At that time it was agreed that key questions to be assessed at the time of a marketing authorisation application are not only dose selection and short- and long-term efficacy and safety but also the appropriate characterisation of patients and therapeutic decision trees. The classification of hypotension, clinical relevance of therapeutic interventions and treatment decisions are extensively debated in the scientific community and treatment recommendations differ between centres.

It was questioned in the scientific advice provided that the proposed PAES would provide sufficient information on relevant treatment decisions. A study including a comparator groups was endorsed. It was agreed that MABP may not be an optimal parameter, assessment of cardiac haemodynamics, tissue perfusion and cerebral haemodynamic may be better to guide treatment decisions in ELGANs. Overall, rScO2 is among the relevant parameters to assess cerebral perfusion. When considering rScO2 as determined by NIRS as a primary endpoint in an efficacy study it may therefore have some advantages over BP values alone, as it is a prognostic factor for outcome that integrates not only effects of BP on cerebral perfusion but also other relevant parameters like hypoxia and acidosis. There is evidence of the prognostic value of cerebral perfusion and rScO2 in ELGANs. NIRS is an appropriate tool for the assessment of rScO2. The predictive value of using NIRS to guide therapy is, however, less well established and it cannot a priori be assumed that treatment associated changes in rScO2 as assessed by NIRS translate into long-term clinical benefit. Therefore, rScO2 cannot be considered as an established surrogate for clinically relevant outcome. Correlation with long term clinical outcome should therefore still be established. It was concluded that the proposed observational study with change in rScO2 (primary endpoint) and TF Gain (% change in rScO2/mmHg, secondary endpoint) will not be sufficient to substitute to a relevant degree for missing information on efficacy, safety, and the appropriate definition of a patient population with a positive B/R. Considering that the exact relationship between rScO2 and cranial ultrasound abnormalities has not been established, investigation of hard clinical endpoints e.g. the co-primary endpoints of the HIP trial, i.e. survival free from neurodevelopmental disability at 2 years corrected gestational age (GA) and survival without significant brain injury at 36 weeks corrected GA, would be expected. It was agreed that no additional data on BP would be needed.

The applicant partially followed this scientific advice, for example assessing clinical outcome data in the proposed observational study was included but a parallel group was not included in the study.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

The assessor has been assured that proof of GMP compliance for all manufacturing and testing sites is available. A valid QP declaration for EU GMP compliance dated 02 October 2023 signed by QP of the batch release site has been provided for API manufacturer Siegfried, including all relevant API manufacturing sites.

GLP

Not applicable since the applicant conducted no non-clinical studies.

GCP

For the pivotal HIP study (Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn. Protocol number: 2010-023988-17) it was stated that the trial protocol was reviewed and approved by the appropriate ethical review committee(s) in each country. All trial personnel implemented the clinical trial with full respect and compliance of the legal and ethical European/Canadian institutional requirements and codes of practices. Procedures involving newborn infants were conform to the Declaration of Helsinki (Seoul 2008) and the EMA guidelines on clinical research in neonates; guidance document 267484/2007. The trial was carried out in accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines and the relevant regulatory requirements in each country. Legislation in each country has been transposed from the EU Clinical Trials Directive 2001/20/EC and the EU GCP Directive2005/28/EC.

During the assessment some inconsistencies were noted in the clinical study report of the HIP study. The CSR was corrected and proof read and missing information was included.

A request for a routine GCP inspection was adopted for the HIP study (Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn, Protocol number: 2010-023988-17). Two investigator sites (one in Ireland and one in Belgium) and the sponsor site (located in Ireland) were inspected. An integrated inspection report (EMA/IN/0000123873) was provided and dated 09-06-2023. The report revealed major deficiencies at the two investigator sites, but no critical issues. Several critical and major findings were however identified at the sponsor site. Based on these findings, related to trial management, data management, monitoring, statistical analysis and writing of the CSR, the inspectors concluded that the quality and integrity of the data generated in the HIP study cannot be reasonably assured and that the study was not conducted and reported in compliance with GCP.

Findings reported from the two investigator site inspections were overall not considered likely to materially impact on the reliability of the data for the full study. However, the following findings individual sites were considered likely to impact on the reliability of the data reported from each site. Site 1: protocol deviations and discrepancies identified through source data review and monitoring and Site 2: protocol deviations and monitoring.

The critical and major findings at the sponsor site were related to:

- Data management and monitoring: there were no data management resources assigned to the study, and as a result routine activities to ensure the quality, validity and integrity of all data collected during the study (for both the core HIP trial, and any sub-studies) were not conducted.
- Trial management: the accumulation of issues throughout the inspection raised questions as to whether the study was conducted in compliance with GCP.
- Statistical analysis and CSR: there was a lack of quality in approaches taken to both analysing and reporting on the trial data.

The applicant has provided additional responses regarding the GCP inspection findings together with the responses during the procedure and took the view that the data from the HiP trial can be relied upon.

Ultimately, considering also that the HiP trial was inconclusive for the primary endpoints, the applicant decided to not pursue the authorisation specifically for the population of ELGANs and therefore, since there were no other studies included in this dossier and conducted by the same sponsor, the inspection findings do not have an impact on the benefit-risk balance.

2.5. Quality aspects

2.5.1. Introduction

The finished product is presented as a solution for infusion in two strengths containing 1.5 mg/mL or 4.5 mg/mL of dopamine hydrochloride as the active substance.

Other ingredients are: sodium metabisulphite, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment), and water for injections.

The product is available in a type I clear glass vial with a bromobutyl rubber stopper, sealed with a flip-off aluminium seal as described in section 6.5 of the SmPC.

2.5.2. Active Substance

2.5.2.1. General information

The chemical name of dopamine hydrochloride is 4-(2-aminoethyl)-1,2-benzenediol hydrochloride corresponding to the molecular formula $C_8H_{12}ClNO_2$. It has a relative molecular mass of 189.6 g/mol and the following structure:

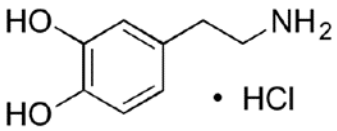


Figure 2. Active substance structure

There is a monograph for dopamine hydrochloride in the European Pharmacopoeia, and the manufacturer of the active substance has been granted a Certificate of Suitability of the European

Pharmacopoeia (CEP) for dopamine hydrochloride which has been provided within the current Marketing Authorisation Application.

2.5.2.2. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the CEP. According to the CEP, the active substance is packaged in fibre drums lined with 2 polyethylene bags.

2.5.2.3. Specification

The specification for the active substance have been set based on the Ph. Eur. monograph with additional considerations related to the intended use in a sterile parenteral finished product. The active substance specification shown includes tests for: appearance, solubility (Ph. Eur.) identification (IR, Chlorides), assay (titration-Ph. Eur.), appearance of solution (Ph. Eur.), related substances (HPLC), acidity/alkalinity (Ph. Eur.), sulfated ash (Ph. Eur.), loss on drying (Ph. Eur.), microbiological quality (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The relevant methods are conducted in line with Ph. Eur. monograph requirements and the proposed limit for bacterial endotoxins is considered suitably justified.

Batch analysis data of eight commercial scale batches of the active substance are provided. The results are within specifications and consistent from batch to batch.

2.5.2.4. Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. According to the CEP, the re-test period of the substance is 18 months if stored under nitrogen at a temperature not exceeding 25°C in double polyethylene bags placed in a fibre drum.

2.5.3. Finished Medicinal Product

2.5.3.1. Description of the product and pharmaceutical development

The finished product is a sterile solution of dopamine hydrochloride in two strengths: 1.5 mg/mL and 4.5 mg/mL. It is a clear, colourless to pale yellow, solution in glass vials closed with rubber stoppers. The 1.5 mg/mL solution is available in a 30 mL fill volume (45 mg/30 mL). While the 4.5 mg/mL product is available in a 50 mL fill volume (225 mg/50 mL).

The excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the pharmaceutical development was to enable a “ready to use”, age appropriate formulation for the paediatric population. It was desired to create a formulation that required minimal manipulation for the treatment of the relevant age groups. The product was developed as a hybrid application with consideration to a reference product, Sterile dopamine Concentrate BP 40 mg/mL solution for infusion, from the Marketing Authorisation Holder (MAH) Mercury Pharmaceuticals. The strength and intended age groups are different for the proposed product as compared to the reference product, the reference product is used in the adult population. The proposed and reference product are qualitatively similar, contain the same active substance and excipients in different quantities.

The active substance is dissolved during the finished product manufacturing process and formulation, therefore physical characteristics of the active substance such as particle size or potential polymorphism are not relevant to the finished product performance.

A paediatric investigation plan (PIP) was relevant to the application and formulation development in question. As part of the development of an age appropriate formulation, the PDCO indicated that the antioxidant proposed for inclusion in the formulation, sodium metabisulfite (SMBS), should be included at the lowest level possible to ensure effective stability of the formulation. During the assessment it was initially not agreed that the ranges proposed for SMBS were justified and an overall multi-part major objection (MO) was raised on the suitability of the proposed formulation for the intended population. The MO concerned the wide ranges and limits initially proposed for the SMBS content, the formulation pH value range proposed, and the need to justify the suitability of the proposed formulation which did not contain a buffering agent. In response to this MO, the applicant tightened and justified the SMBS range proposed in the finished product specification. The pH range of the formulation was also tightened in the finished product specification and justified. The suitability of the formulation in view of the buffer capacity of the intended population was further justified considering the intended use and administration volumes, given the low administration volumes and infusion rates. This was considered acceptable and the MO was thus resolved.

An instability to oxidation is described by the applicant. This is mainly evident during significantly increased temperature conditions, such as those proposed for terminal sterilisation. The proposed terminal sterilisation conditions for the product involve the application of a sterilisation cycle of >121 °C for 20 minutes. Overall the inclusion of the antioxidant SMBS in the formulation is considered justified to enable terminal sterilisation. In the absence of SMBS discolouration occurs, and the formation of visible particles was observed. A need for the presence of some level of SMBS is therefore evident to enable terminal sterilisation. However, from the data provided, it is not yet evident that the lowest level of SMBS required to ensure acceptable product stability has been used. Considering this aspect a recommendation for further quality development is made, requesting the applicant to perform additional investigations to determine if suitable finished product stability can be achieved with lower levels of SMBS (REC 1). The applicant was requested to include in these investigations whether the standard Ph. Eur. sterilisation cycle could enable lower levels to be used (REC 2). In addition to this, demonstration batches of varying lower concentrations of SMBS were requested to be placed on stability, to determine if lower SMBS levels are possible and whether a revised lower limit for SMBS content at shelf life could be appropriate (REC 3).

It was confirmed that the product should not be diluted or mixed with other fluids. Compatibility with commercially available administration equipment has not been addressed because the product is intended for immediate use. These precautions are adequately addressed in SmPC sections 4.4, 4.5, 6.2 and 6.3.

The proposed manufacturing process was developed with the aim of enabling the terminal sterilisation described above, and creating a process that ensures product stability.

The primary packaging is a type I clear glass vial with a with bromobutyl rubber stopper. The material complies with Ph. Eur. requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.5.3.2. Manufacture of the product and process controls

The manufacturing process consists of five main steps.

The manufacturing process is considered standard, therefore the provision of commercial scale validation data for the manufacturing process is not required at the time of marketing authorisation. The applicant did provide data from pilot scale batches of both strengths. A process validation scheme was also provided outlining the validation to be performed for the first three commercial batches before placing the product on the market.

Critical process steps and respective process parameters with limits and ranges as well as in-process controls are in general sufficiently described. The proposed in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.5.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification of dopamine (HPLC, PDA), identification of sodium metabisulfite (Ph. Eur.), pH (Ph. Eur.), assay of active substance (HPLC), assay of antioxidant (HPLC), organic impurities (HPLC), colour of solution (Ph. Eur.), light transmission (Ph. Eur.), extractable volume (Ph. Eur.), particulate levels (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.).

The limits for degradation impurities are set in line with ICH Q3B requirements, and no impurities above the qualification threshold are observed. The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 pilot scale batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

In line with the relevant resolution of the MO raised, the revised ranges of the SMBS antioxidant are considered adequate. It appears that further tightening of the proposed limits for pH at shelf life may be possible. The applicant is therefore recommended to review the data when the final timepoint from the stability batches are available to determine if the specification can be further tightened (REC 1).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. As mentioned above, no impurities are present at levels above the qualification threshold. Mass spectroscopic analysis has been conducted to identify a specified impurity. The applicant has commenced work to build up a reference standard for said impurity and is recommended to perform supplemental method validation when the standard has been finalised (REC 4).

Batch analysis results are provided for three pilot scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.5.3.4. Stability of the product

Stability data from three pilot scale batches of each strength of the finished product stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested in accordance with the same specification applied to finished product release. The analytical procedures used are stability indicating. At long term and accelerated conditions all results are within the proposed specification limits and no significant trend is observed. A freeze-thaw study was also conducted that revealed several vial breakages.

With respect to ongoing studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability study did not reveal any out of specification results. However considering the totality of the trends observed, with decreasing assay and antioxidant levels, along with the reported photosensitivity of the active substance it was considered that an instruction to keep the product in the outer carton to protect from light was appropriate (SmPC section 6.4).

The product is intended for immediate use and single dosing, this is reflected in the product information and therefore, no further in-use stability data was provided.

Based on available stability data, the proposed shelf-life of 24 months and store in the original package to protect from light and do not freeze as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.5.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.5.4. Discussion on chemical and pharmaceutical aspects

The finished product is a dopamine hydrochloride solution for infusion available in two strengths 1.5 mg/mL or 4.5 mg/mL. It is intended for the treatment of a paediatric population including infants and small children. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure one major objection (MO) was raised on quality aspects. The formulation and relevant ranges for critical criteria had not been sufficiently justified and were considered too wide. The initially wide limits proposed for pH and the antioxidant levels were not considered acceptable. In addition to this, justification was sought related to the absence of a buffering agent in a formulation intended for this patient population. The MO was resolved by the tightening of the pH range and the

antioxidant levels. Justification was also provided for the overall suitability of the formulation and absence of a buffering agent.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These pertain to further investigations into the tightening of shelf-life pH values, the ability to reduce SMBS content, and to further build a reference standard for a specified impurity. These points are put forward and agreed as recommendations for future quality development.

2.5.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.5.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to review the finished product stability data and tighten the finished product shelf-life specification acceptance limits with respect to pH when results from the final stability time-point are available. Timeline: July 2024
2. The applicant is recommended to investigate the reduction of the SMBS antioxidant concentration to the lowest feasible level. As part of these investigations the Ph. Eur. standard sterilisation conditions should be employed for the manufacture of a future product formulation. Timeline: March 2027
3. The applicant is recommended to review the final 24 month time point stability data when this is available and initiate the manufacture of “demonstration batches” of each strength having lower SMBS antioxidant levels and to place these on stability. The need for a lower limit for the shelf-life limits of SMBS will be discussed with the agency if appropriate. Timeline: March 2025
4. The applicant is recommended to build up a reference standard for a potential impurity and should confirm the retention time using the “Related substance HPLC” analytical method. Upon confirmation of the relative retention time, supplemental method validation of related substances by HPLC using the impurity standard should be performed. Timeline: September 2025.

2.6. Non-clinical aspects

2.6.1. Introduction

This non-clinical overview is entirely based on information available from published scientific literature, and no pharmacological, pharmacokinetic, or toxicological studies have been performed by the applicant.

2.6.2. Pharmacology

Dopamine is an endogenous catecholamine, precursor in the synthesis of noradrenaline and adrenaline. It is available for clinical use since the 1970s. Dopamine has positive inotropic, chronotropic and dromotropic effects, leading to increased cardiac output, blood pressure (BP) and heart rate (HR). Dopamine stimulates adrenergic receptors of the sympathetic nervous system. Dopamine stimulates ß1-adrenergic receptors, but with no effects on ß2-adrenergic receptors. Dopamine has an indirect effect by affecting the release of norepinephrine from adrenergic nerve endings. Dopamine also acts on specific dopaminergic receptors in the renal, mesenteric, coronary and intracerebral vascular beds to cause vasodilation. At low infusion rates (0-5 to 3 µg/kg/min), dopaminergic receptors (DA1 and DA2) are activated, leading to increases in renal plasma flow, glomerular filtration rate and Na+ excretion via vasodilation of renal vascular beds (stimulation of DA1 receptors). Stimulation of DA2 receptors inhibits noradrenaline release from the sympathetic nerve endings. At higher infusion rates (3 to 5 µg/kg/min), ß1-adrenoceptors are activated with an increase in cardiac contractility. When the infusion rate is further increased (above 10 µg/kg/min), □1- and □2- adrenoceptors are activated leading to vasoconstriction with increases in peripheral vascular resistance and arterial blood pressure (and to a decrease in diuresis).

Haemodynamic effects of dopamine in newborn animals

Hypotensive neonates treated with dopamine have poorer neurodevelopmental outcome. Therefore, the effect of dopamine on cerebral auto-regulation during hypotension was studied in newborn piglets 4-66 hrs after birth. Dopamine tended to improve cerebral auto-regulation capacity at low arterial blood pressure; however; a beneficial effect of dopamine was not confirmed by improved cerebral blood flow or cerebrovenous oxygen saturation. Thus, dopamine does not appear to impair cerebral auto-regulation in new born piglets (Eriksen et al. 2017).

Dopamine was found to be protective against the impairment of autoregulation after traumatic brain injury in the new-born (1-5 days) piglets of both sexes (Armstead et al. 2013).

In newborn piglets (1-4 days) treated with a moderate dose of dopamine, adding epinephrine or further increasing dopamine improved systemic haemodynamics similarly (Manouchehri et al. 2016).

In the newborn lamb, dopamine is an effective inotropic agent, but an inotropic : afterload mismatch exists at high infusion rates. Despite an increase in cardiac output at low rates of infusion, at higher rates of infusion dopamine impairs blood flow to the gut and kidney (Feltes et al. 1987).

Notably, in contrast to adults, in newborn piglets (Eriksen et al. 2017) and sheep (Wong et al. 2020) systemically administered dopamine crosses the blood-brain barrier.

2.6.3. Pharmacokinetics

The bioavailability of dopamine after oral administration is low (about 3%) due to its extensive first-pass metabolism in the liver and intestine. After i.v. administration, dopamine is widely distributed in the body, but does not cross the blood-brain-barrier and, therefore, does not affect the dopaminergic receptors in the brain. The apparent volume of distribution in neonates is 0.6 – 4 l/kg. Dopamine is metabolised in the liver, kidneys and plasma by catechol-O-methyltransferase (COMT), monoamine oxidase (MAO) and sulfotransferase and it is eliminated in the urine mainly as homovanillic acid. Dopamine is also metabolized to norepinephrine within adrenergic nerve terminals. The half-life of elimination in humans is about 5-10 minutes.

Non-clinical data were not provided to show whether dopamine passes the placental barrier or is excreted into breast milk.

2.6.4. Toxicology

2.6.4.1. Single /repeat-dose toxicity

In single dose and chronic toxicity studies performed in rats and dogs, dopamine had mainly effects on the cardiovascular system (electrocardiographic changes, arrhythmias, myocardial necrosis, pulmonary oedema, arteriolar damage). In humans, most of the adverse effects are related to the pharmacological profile of the substance (cardiac arrhythmias, at high doses vasoconstriction via stimulation of alfa-adrenoceptors with rises in systemic blood pressure, angina pectoris attacks, decreases in renal blood flow, impaired blood flow in the extremities). An unintentional paravenous infusion of dopamine hydrochloride can lead to local necroses and, therefore, has to be avoided. Due to the limited duration of administration of dopamine in states of shock, no chronic toxicity or carcinogenicity studies with dopamine have been performed.

2.6.4.2. Genotoxicity

Dopamine has been tested for mutagenic potential in a variety of in vitro and in vivo tests. It induces tk mutations in the mouse lymphoma assay, chromosomal aberrations in cultured hamster cells and DNA breaks in vitro. In contrast, in vivo experiments such as bone marrow micronucleus test in mice and rats gave negative results. The positive results from in vitro experiments for dopamine are typical for catecholamines and are probably related to an oxidation mechanism with generation of reactive oxygen radicals. It is highly unlikely that similar reactions would occur in vivo since effective defence mechanisms are known to be active under physiological conditions.

2.6.4.3. Carcinogenicity

N/A

2.6.4.4. Reproductive and developmental toxicity

Reproductive toxicity of dopamine was not investigated according to nowadays requirements. Some older studies are published in different journals. Dopamine did not show teratogenicity or embryotoxicity in rats and rabbits in one study whereas another study reported embryotoxicity but no teratogenicity in rats. Other sympathomimetic catecholamines (noradrenaline, adrenaline, isoproterenol) produce cardiac malformations via stimulation of ß-adrenergic receptors. Subcutaneous doses of 10 mg/kg dopamine for 10 days markedly prolonged metestrus and increased mean pituitary and ovary weights in rats. Similar doses given to pregnant rats in another study resulted in maternal toxicity and an increase in cataract formation in offspring. It was also reported that dopamine induced proliferation of FSH cells in the pituitaries, follicular development in the ovaries and estrogenic activity in the uterus via stimulation of dopamine receptors in the hypothalamus in female rats. No data are available that cover aspects of juvenile toxicity of dopamine.

2.6.4.5. Toxicokinetic data

N/A

2.6.4.6. Local tolerance

N/A

2.6.4.7. Other toxicity studies

N/A

2.6.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment for dopamine based on literature research has been provided.

The log Kow values provided by the applicant for screening on Persistence, Bioaccumulation and Toxicity are cited ones and therefore not acceptable for environmental risk assessment. According to the CHMP questions & answers document on *Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev. 1)* the log Kow should be determined experimentally.

The calculation of PECsw initial resulted in a value of 10 µg/L. The PECsw refined resulted in a value of 4.5 µg/L. Since both values are above the action limit the applicant continued with the environmental risk assessment.

The assessor agrees that the PECsw initial exceeds the trigger for a Phase II environmental risk assessment. The calculation of the PECsw refined is not acceptable. The dose of 225 mg used by the applicant is not in line with the *EMA guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 1*, June 2006)*. Moreover, it is not comprehensible why the applicant used a Fpen above the default value.

The applicant argued that no data are available in literature to calculate the PNEC and as a consequence no PEC /PNEC ratio could be provided.

The data on Phase II environmental risk assessment do not fulfil the requirements of *EMA guideline on environmental risk assessment (EMEA/CHMP/SWP/4447/00 corr 1*, June 2006)*.

Nevertheless, in this special paediatric application the assessor abstains from further requests regarding environmental risk assessment. Dopamine hydrochloride is a naturally occurring catecholamine in vertebrates and in invertebrates is therefore eliminated into the environment on the natural way. It is expected that the paediatric indication will not lead to a significant increase in the environment.

2.6.6. Discussion on non-clinical aspects

The applicant presented literature data from an open data base to cover reproductive toxicity of dopamine. It cannot be traced on which original data these quotations are based.

Some other studies are published covering different aspects of the reproductive toxicity of dopamine. However, these studies are older studies that were not performed according to GLP or any guidance documents. Embryotoxicity without an increase in malformations was seen e.g. in rats after pregnancy exposure to dopamine (Samojilik E at al. Am. J. Obstet. Gynecol. 104: 578-85, 1969). Some dopamine agonists produced morphologic abnormalities in the rat (Baldwin J, Ridings J Toxicology 42: 291-302, 1986). Dopamine was discussed to postnatally cause behavioural effects as well as neurological disorders if prenatally exposed (Middaugh LD, Zemp JW Neurobehav. Toxicol. Teratol. 7: 686-9, 1985; Baier et al. Neurotox. Res. Jul, 22(1); 16-32, 2012).

Reports about dopamine use in human pregnancy are scarce.

Prolactin release is inhibited by dopamine and dopamine may thus interfere with breast-feeding (Petraglia et al. Gynecol. Obstet. Invest. 23: 103-9, 1987). However, because of the short plasma half-life of 2 minutes, dopamine use seems to be compatible with breast-feeding.

Juvenile animal studies were not performed or discussed to cover dopamine use in infants or children. Specific juvenile animal studies were also not requested in the respective PIP discussions. Therefore, the safe use of dopamine in neonates, infants and children is not supported by respective non-clinical data but must be assessed by clinical data.

In summary, reproductive toxicity of dopamine is only insufficiently covered. However, dopamine is an endogenous substance with long-term clinical experience. Therefore, no new studies are requested. The lack of non-clinical data is reflected in the SmPC.

2.6.7. Conclusion on the non-clinical aspects

No new non-clinical studies were performed by the applicant; only literature data were submitted. Most toxicological effects of dopamine are related to its pharmacodynamics.

ERA: It can be expected that the use of the product for the paediatric indication will not pose a risk to the environment.

The application was considered approvable from nonclinical perspective.

2.7. Clinical aspects

2.7.1. Introduction

GCP aspects

The clinical trial was performed in accordance with GCP as claimed by the applicant. A GCP inspection took place and the GCP inspection report was provided (for details please, see Section 2.4 of the CHMP AR).

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Interventional RCT	EudraCT number: 2010-023988-17	To determine whether in infants born before 28 completed weeks of gestation, an observational approach to the management of hypotension compared to a standard approach using dopamine as a first line inotrope	Large pragmatic, multinational, randomised trial of two different strategies for the management of hypotension in ELGA infants (An	DOPAMINE HCI and PLACEBO-Initial dose of 5 mcg/kg/min increasing by 5mcg/kg/min every 30 minute to a maximum dose of 20mcg/kg/min; administered	111 enrolled, 58 randomized.	Less than 28 weeks gestational age	Treatment of either study drug and repeated clinical assessment will continue until the infant is no longer hypotensive and has been normotensive

		within the first 72 hrs improves: 1. Survival free from neurodevelopmental disability at 2 years corrected gestational age (GA). 2. Survival without significant brain injury at 36 weeks corrected GA.	observational approach with placebo approach versus Standard with dopamine).	by IV infusion Formulation prepared from commercially available material.			for at least 24 hours (typically about 48 hours)

2.7.2. Clinical pharmacology

2.7.2.1. Pharmacokinetics

No new pharmacokinetic studies were presented.

Bioequivalence

A BE study was considered not relevant for the aqueous parenteral solutions as supported by the "CPMP/EWP/QWP/1401/98 Rev. 1/Corr" on BE studies where it is stated: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product".

The formulation is not complex. Disposition of the API is not intended to be affected. Both formulations contain the same excipients in similar but lower quantity. Viscosity is not expected to be impacted. The content of antioxidant in intended paediatric formulation is significantly lower than in the adult formulation but this is not expected to have any impact on the PK of the API but is rather intended to improve the product`s safety profile for the intended population. The test product is ready to use formulation, no dilution prior to administration is needed. The route of administration of the test product is the same as for the reference product. The drug is administered directly into the blood stream and the dose is calculated mcg/kg/min basis, the same as for the reference adult formulation.

The justification of not conducting the BE study is acceptable.

Absorption

Orally administered dopamine is rapidly metabolised in the G.I. tract.

Dopamine infusion resulted in a dose-dependent increase in plasma concentration. In critically ill new-born infants dopamine increased from a base-line concentration of 0.5 ± 0.2 to 69.3 ±11.6 ng/ml at an infusion rate of 8 µg/kg/min; there was a significant ($r = 0.68$; $p < 0.001$) linear correlation between infusion rate and plasma dopamine concentration achieved (Padbury et al. 1990 J Pediatr 117, 472-476).

Distribution

After intravenous administration, the mean apparent volume of distribution is 0.89 L/kg in adults. In adults it does not cross the blood-brain barrier to a substantial extent. It is not known if dopamine crosses the placenta. No data are available about the distribution volumes in infants and children (Bhatt-Mehta and Nahata 1989 Pharmacotherapy 9, 303-14).

Metabolism

Dopamine itself is used as precursor in the synthesis of the neurotransmitters norepinephrine and epinephrine. Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase, with O2 and L-ascorbic acid as cofactors. Norepinephrine is converted into epinephrine by the enzyme phenylethanolamine N-methyltransferase with S-adenosyl-L-methionine as the cofactor (Musacchio 2013 in Iverson (ed.) Biochemistry of Biogenic Amines. Springer. pp. 1–35). About 25% of a dose of dopamine is metabolised to norepinephrine within the adrenergic nerve terminals.

Dopamine is broken down into inactive metabolites by a set of enzymes—monoamine oxidase (MAO), catechol-O-methyl transferase (COMT), and aldehyde dehydrogenase (ALDH), acting in sequence. Both isoforms of monoamine oxidase, MAO-A and MAO-B, effectively metabolize dopamine. Different breakdown pathways exist but the main end-product is homovanillic acid (HVA), which has no known biological activity. The two primary metabolic routes that convert dopamine into HVA are:

Dopamine → 3,4-Dihydroxyphenylacetaldehyde (DOPAL) → 3,4-Dihydroxyphenylacetic acid (DOPAC) → HVA – catalysed by MAO, ALDH, and COMT respectively;

Dopamine → 3-Methoxytyramine → HVA – catalysed by COMT and MAO+ALDH respectively,

(Musacchio 2013, Eisenhofer et al. 2004 Pharmacol Rev 56, 331–49).

Dopamine has a plasma half-life of about 2 minutes.

In patients receiving MAO inhibitors, the duration of action of dopamine may be as long as 1 hour.

Elimination

Jarnberg et al. (1981; Acta Anaesth Scand 25 328-31; citied in Bhatt-Mehta and Nahata, 1989 Pharmacotherapy 9, 303-14) studied dopamine pharmacokinetics in adults and noted an overall clearance rate of 70 to 75 ml/kg/min. Comparable results are reported in critically ill new-born infants (Bhatt-Mehta and Nahata, 1989, Pharmacotherapy 9, 303-14; Padbury et al. 1990, J Pediatr 117, 472-476; Zaritzky et al. 1988 Arch Dis Child Fetal Neonatal Ed. 81:F99-F104), however with a high interpatient variability in dopamine clearances (Zaritzky et al. 1988 Arch Dis Child Fetal Neonatal Ed. 81:F99-F104). Notterman et al. (1990 Clin Pharmacol Ther 48,. 138-147) reported a clearance nearly twice as rapid in children younger than 2 years as it was in older children (82.3 ± 27.7 ml/kg/min versus 45.9 ± 17.0 ml/kg/min). A reduced clearance was reported in children with impaired renal or hepatic function (Notterman et al. 1990 Clin Pharmacol Ther 48,. 138-147, Zaritzky et al. 1988 Arch Dis Child Fetal Neonatal Ed. 81:F99-F104).

Dopamine is excreted in urine principally as HVA and its sulphate and glucuronide conjugates and as 3, 4-dihydroxyphenylacetic acid. A very small fraction of a dose is excreted unchanged. Following administration of radio labelled dopamine, approximately 80% of the radioactivity reportedly is excreted in urine within 24 hours.

2.7.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented.

Mechanism of action

Dopamine stimulates specific dopaminergic receptors, α1-receptors, α2-receptors and β1-receptors (for receptor characteristics regarding dopamine please see the non-clinical assessment).

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.

α1-adrenergic receptor stimulation on vascular smooth muscle, leads to vasoconstriction and results in an increase in systemic vascular resistance.

Mediated through myocardial β1-adrenergic receptors, dopamine increases heart rate and force, thereby increasing cardiac output. Following IV administration, the onset of action of dopamine occurs within 5 minutes, and the drug has a duration of action of less than 10 minutes.

Primary pharmacology

Dopamine is often stated to have the following effects, which are postulated to have distinct dose-dependent pharmacologic effects. At doses of < 5 µg/kg/min, dopaminergic receptors are activated, leading to vasodilation in the renal and mesenteric beds. At doses of 5 to 10 µg/kg/min, β 1-adrenergic effects predominate, increasing cardiac contractility and heart rate. At doses of >10 µg/kg/min, α1-adrenergic effects predominate, leading to arterial vasoconstriction and an increase in BP. However this concept of certain responses of less than 5 mcg/kg/min, 5-10 µg/kg/min and greater than 10 µg/kg/min to dopamine is an oversimplification of the response to dopamine.

In adults, no effect was seen on blood pressure or heart rate at plasma concentrations of 28 ng/ml after infusions of 2 µg/kg/minute. A significant increase in heart rate was observed at 5 µg/kg/minute, when plasma concentrations reached 79 ng/ml (Jarnberg et al. 1981 *Acta Anaesth Scand* 25 328-31; citied in Bhatt-Mehta and Nahata, 1989 Pharmacotherapy 9, 303-14).

In newborn infants the thresholds of the concentrations were 14 ± 3.5 ng/ml for increase in mean blood pressure, 18 ± 4.5 ng/ml for increase in systolic blood pressure, and 35 ± 5 ng/ml for increase in heart rate. There was no correlation between thresholds for increases in blood pressure or heart rate and gestational age or birth weight (e.g, r = 0.35 mean blood pressure threshold vs birth weight). In all patients, increases in mean and systolic blood pressure occurred at lower thresholds than increases in heart rate (Padbury et al. 1987 *J Pediatr* 110 293-298).

The canine kidney has abundant α receptor at birth, and the relative density declines with increasing postnatal age. The density of β-receptors at birth is less compared to older animals, but increases with postnatal age. It is therefore possible that in human neonates the drug may produce less renal vasodilation and perhaps even vasoconstriction with dosages less than 5 µg /kg/min. In clinical studies in preterm infants renal function and urine output were not reliably increased by dopamine (Prins et al. 2001 *Intensive Care Med* 27 206-210; Dempsey and Barrington 2007 *J Perinatol* 27 469-478).

Thus, apparently a difference exists in the dose-response relationship between adult and paediatric patients, with newborns appearing to have a much lower threshold for dopamine. One must therefore be cautious when extrapolating adult dosage recommendations to newborn infants and children.

In very preterm infants dopamine induced an increase in mean arterial blood pressure at doses up to 10 µg/kg/min with little clinically relevant efficacy at higher doses up to 20 µg/kg/min (Klarr et al. 1994 *J Pediatr* 125 117-122), with almost unchanged low superior vena cava flow and right ventricular output (Osborne et al. 2002 *J Pediatr* 140 183-91).

Secondary pharmacology

Solanki et al. (2002 *Pediatr Res* 88 618-622) investigated the association between dopamine and cerebral autoregulation in preterm neonates. They found that neonates <29 weeks gestation who were exposed to dopamine during the first 96 h of life spent more time with impaired cerebral autoregulation. However, in their review Noori et al. (2003 *NeoReviews* 4;e283-e288) emphasised that the studies discussed found no evidence for a direct effect of dopamine on cerebral blood flow.

Sassano-Higgins et al. (2011 *J Perinatol* 21 647-655) even reported that dopamine administration is associated with increased cerebral blood flow. Of note, in the CAR substudy of the HIP trial (see below) dopamine as compared to placebo increased MABP but had no significant effect on cerebral oxygenation (rScO2) or cerebral autoregulation as measured by TF gain within 2 h following administration of the study drug.

Stimulation of the dopamine receptors in the carotid bodies decreases respiratory rate and depth (Seri 1995).

Dopamine regulates the release of certain hormones in the pituitary and adrenal glands and in the kidney (Seri 1995 *J Pediatr 126 333-344*). Dopamine increases plasma glucagon and insulin and supress plasma prolactin (Lorenzi at al. 1979 *J Clin Invest* 63 310-7). Dopamine also inhibits the secretion of other pituitary hormones, including thyrotropin, growth hormone, and the gonadotropins (Seri 1995 J Pediatr 126 333-344).

Dopamine, without altering leukocyte mobility or bactericidal ability, decreases superoxide anion production in these cells (Seri 1995 J Pediatr 126 333-344).

Pharmacodynamic interactions with other medicinal products or substances

Anaesthetics:

The myocardium is sensitized by the effect of dopamine, cyclopropane or halogenated hydrocarbon anaesthetics. This interaction applies both to pressor activity and cardiac β-adrenergic stimulation.

α and β blockers:

The cardiac effects of dopamine are antagonised by β-adrenergic blocking agents such as propranolol and metoprolol, and the peripheral vasoconstriction caused by high doses of dopamine is antagonised by α adrenergic blocking agents.

Phenytoin:

Administration of IV phenytoin to patients receiving dopamine has resulted in hypotension and bradycardia; some clinicians recommend that phenytoin be used with extreme caution, if at all, in patients receiving dopamine.

Diuretics:

Dopamine may increase the effect of diuretic agents.

Ergot alkaloids

The ergot alkaloids should be avoided because of the possibility of excessive vasoconstriction.

Tricyclic antidepressants and guanethidine

Tricyclic antidepressants and guanethidine may potentiate the pressor response to dopamine.

2.7.3. Discussion on clinical pharmacology

The functionality of the blood-brain barrier (BBB) in newborn infants is considered questionable. The applicant discussed different literature references concerning maturation of the BBB in humans, penetration of dopamine through the BBB in pre-term infants and parkinsonian rats and chemical

conditions needed for BBB penetration. Altogether, there are insufficient data available to assess the neurotoxic effects of dopamine when administered to neonates and children. However, publications available do not indicate obvious toxicity of dopamine when crossing the BBB.

The published literature shows a considerable heterogeneity concerning pharmacokinetics and pharmacodynamics of dopamine. At least in part this can be attributed to the different receptors affected by dopamine, developmental differences in the receptor distribution and additional effects of dopamine being a precursor of norepinephrine and epinephrine. However, there is clear evidence that in newborns, infants and children dopamine IV is an antihypotensive drug.

2.7.4. Conclusions on clinical pharmacology

The CHMP considered the application approvable from clinical pharmacology point of view.

2.7.5. Clinical efficacy

The applicant applied initially for two indications:

Treatment of hypotension in neonates including the extremely low gestational newborns.

Treatment of hypotension in infants and children

The applications as based on two lines of evidence.

a) A pivotal study was submitted in order to support an indication in extremely low gestational newborns (HIP study, with the CAR substudy).

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Interventional RCT	EudraCT number: 2010-023988-17	To determine whether in infants born before 28 completed weeks of gestation, an observational approach to the management of hypotension compared to a standard approach using dopamine as a first line inotrope within the first 72 hrs improves: 3. Survival free from neurodevelopmental disability at 2 years corrected gestational age (GA).	Large pragmatic, multinational, randomised trial of two different strategies for the management of hypotension in ELGA infants (An observational approach with placebo approach versus Standard with dopamine).	DOPAMINE HCI and PLACEBO-Initial dose of 5 mcg/kg/min increasing by 5mcg/kg/min every 30 minute to a maximum dose of 20mcg/kg/min; administered by IV infusion Formulation prepared from commercially available material.	111 enrolled, 58 randomized.	Less than 28 weeks gestational age	Treatment of either study drug and repeated clinical assessment will continue until the infant is no longer hypotensive and has been normotensive for at least 24 hours (typically about 48 hours)

		4. Survival without significant brain injury at 36 weeks corrected GA.					

In addition to support the claim a literature review on the administration of dopamine in this patient population has been submitted.

b) A comprehensive literature review was submitted to support an indication in hypotension/shock in different conditions: sepsis, shock in the context of cardiac diseases including cardiosurgery, traumatic brain injury, hypoxic ischaemic brain injury, toxicology including drug overdose.

2.7.5.1. Dose response studies

No specific dose response studies were submitted and the applicant has not provided a justification or a discussion of the dose considered appropriate in the different age groups and clinical conditions. Information on dose response can be derived from the HIP trial and the published clinical studies submitted in support of the application. These studies are discussed in detail below.

For preterm infants, the starting dose in the HIP study was 5 µg/kg/min up to a maximum dose of 20 µg/kg/min. No data have been provided in support of starting doses below 5 µg/kg/min. A concept of using lower starting doses based on the assumption that it might improve renal function is not well supported by data. In clinical studies in preterm infants renal function and urine output were not reliably increased by dopamine (Dempsey EM and Barrington KJ. J Perinatol 2007; 27: 469-478; Prins I. et al., Intensive Care Med 2001; 27: 206-210). Furthermore, some studies suggest that in preterm infants doses above 10 µg/kg/min do not mediate a relevant additional effect on MABP. In the study of Klarr JM et al., (J Pediatr 1994; 125: 117-22) 97% of the preterm children had a treatment success (based on BP criteria) at a dose of < 10 µg/kg/min, indicating that higher doses may not add much on efficacy. Similarly, in the study of Osborn D. et al., (J Pediatr 2002; 140: 183-9) little of an effect was observed when the dose of dopamine was increased from 10 to 20 µg/kg/min.

In most of the studies provided in the literature review for the whole range of paediatric patients (e.g. septic shock, toxic situations and drug overdose, cardiac conditions including cardiac surgery) higher starting doses than 2 µg/kg/min were investigated. Doses above 7.5 – 10 µg/kg/min were associated with unfavourable effects, e.g. on pulmonary haemodynamics. No studies were submitted where doses above 20 µg/kg/min were investigated or where weaning with down-titration steps below 5 µg/kg/min were assessed.

Taking these data into consideration the initially proposed posology has been amended by the applicant and clearly states that the usual dose range is 5 up to a maximum of 10 microgram/kg/min and that higher doses up to 20 microgram/kg/min should only be applied if justified in an individual patient as follows:

...

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.

Dose of dopamine hydrochloride should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indications for decreasing or temporarily suspending the dose (see section 4.4).

Specific considerations on special populations (hepatic and renal impairment, coadministration of MAO inhibitors) and weaning are included in the SmPC.

2.7.5.2. Main study

The pivotal study of this application was the HIP study that also included a sub study on cerebral oxygen saturation and autoregulatory capacity (CAR).

Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn

(short title: Hypotension in Preterm Infants (HIP) randomized trial)

Protocol number: 2010-023988-17, Sponsor: BrePco Biopharma Limited, Principal investigator: Prof. Eugene M Dempsey

Study centres: Participating: 15, enrolling 10: Ireland, Canada, Czech Republic, Belgium, UK

Study initiation date: May 2015, Study completion date: September 2017

Date of the report: 22July 2020, date signed by principal investigator: 19th Sep 2022

Publication (reference) Dempsey EM, Barrington KJ, Marlow N, et al. Arch Dis Child Fetal Neonatal Ed 2021;106:F398–F403.

Methods

It was a pragmatic, multinational, randomised trial of two different strategies for the management of hypotension in ELGAN infants (An observational approach with placebo versus standard with dopamine).

- Study Participants

Inclusion criteria

Preterm infants (male or female) admitted to the neonatal units of participating hospitals with evidence of hypotension meeting all of the following criteria:

1. GA at birth from 23 weeks to less than 28 completed weeks, i.e. up to and including 27 weeks and 6 days.

2. Postnatal age within 72 hours of birth.

3. An indwelling arterial line, suitably calibrated and zeroed, to monitor BP with the measuring dome at the level of the mid axillary line.

4. A mean BP 1 mmHg or more below a mean BP value equivalent to the GA in completed weeks, which persists over a 15 minute period.

5. A pre-trial cranial ultrasound scan free from grade III-IV IVH or cystic PVL.

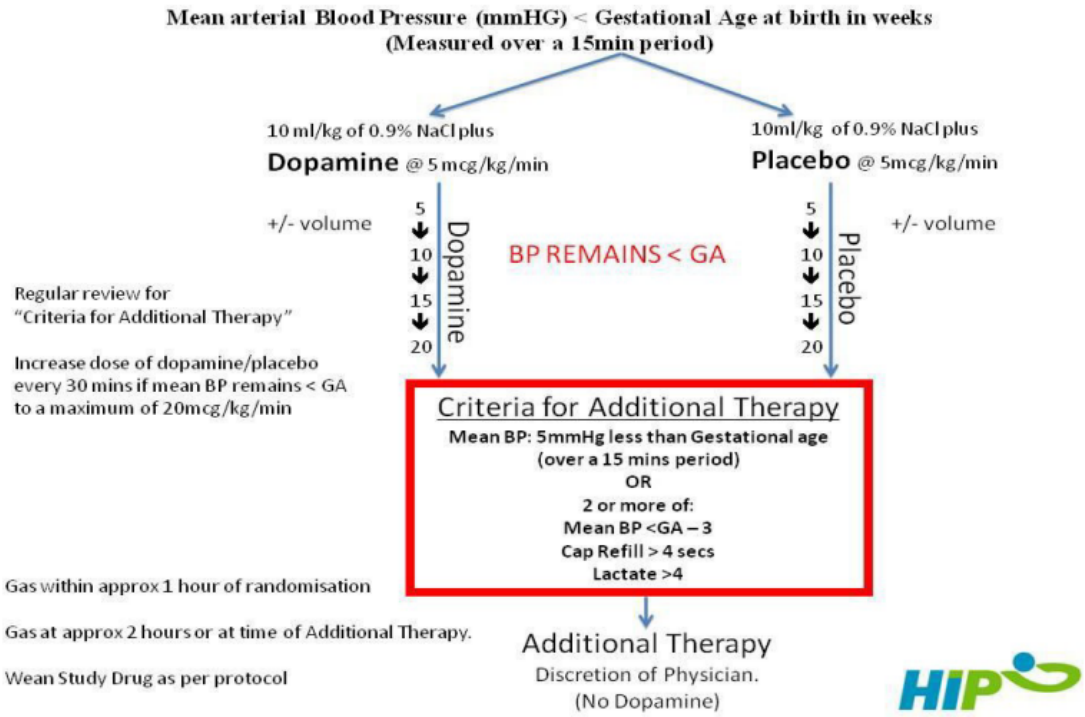
- Treatments

Standard approach: Patients received a saline infusion of 10 ml/kg administered over 20 minutes and dopamine at an initial dose of 5 µg/kg/min at the treatment goal of a MABP greater than or equal to GA. In case of insufficient response, the dose was increased by 5 µg/kg/min every 30 minutes to a maximum dose of 20 µg/kg/min.

Alternative pathway (observational “permissive” approach): Patients received a saline infusion of 10 ml/kg administered over 20 minutes and placebo infusion of dextrose 5% to be titrated upwards every 30 minutes if there was no response in mean BP to greater than or equal to GA value.

Treatment was to be continued until the infant was no longer hypotensive and was normotensive for at least 24 h. Rescue therapy: Epinephrine 0.1 µg/kg/min and titrated upwards to a dose of up to 0.4 µg/kg/min. If needed, additional treatment could be initiated in case of insufficient BP response at the discretion of the treating physician (Figure 3).

Figure 3. Treatment pathways and overall study design



IMP: Initially, commercial preparations of dopamine supplied by the hospital pharmacy at the respective clinical study site were administered. After May 2017 the study drug was Neoatricon Dopamine Hydrochloride 1.5 mg/mL Solution for infusion manufactured by CordenPharma S.p.A.

Table 2. Batch number of the study medication and the quantity supplied.

Batch No:	Study Medication	Quantity Supplied	Quantity Dispensed	Quantity Left
002C16A	Dopamine	80	1	79
In total:		80	1	79

- Objectives

Primary:

To determine whether in infants born before 28 completed weeks gestation, an observational approach to the management of hypotension compared to a standard approach using dopamine as a first line inotrope within the first 72 hrs of life improves 1. Survival free from neurodevelopmental disability at 2 years corrected gestational age and 2. Survival without significant brain injury at 36 weeks corrected gestational age.

Secondary:

To determine whether an observational approach to the management of hypotension compared to a standard approach with dopamine affects:

• All causes of mortality at 36 weeks GA

• The incidence of severe abnormality (grade III-IV intraventricular haemorrhage (IVH), periventricular cystic leukomalacia or ventricular dilatation) detected on serial cranial ultrasound examinations

• The number of adverse effects attributable to treatment

• Individual impairments at 2 years

• Developmental and behavioural scores at 2 years.

- Outcomes/endpoints

Co-primary endpoints:

- Survival free of neurodisability at 2 years corrected GA.

- Survival to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultrasound

Among the secondary endpoints were the following:

- All cause of mortality at 36 weeks corrected GA.

- Intraventricular haemorrhage grade III-IV

- Periventricular leukomalacia and/or ventriculomegaly, on cranial ultrasound

- Total duration of inotrope use

- Need for administration of rescue therapy

- Recording and reporting of any Adverse Events

In addition, a list of other endpoints relevant for the assessment of interventions and the patients´ wellbeing were predefined.

- Sample size

The initial plan was to enrol a total of 830 subjects. Following challenges related to recruiting the power was modified yielding a target sample size of 454 across both arms. The study was terminated early with less than 10 % of the initially planned number of patients were included.

- Randomisation and Blinding (masking)

Local principal Investigators performed the randomization and provided the code to the pharmacist preparing the infusion. Infants from multiple births were randomized independently. The physicians, nursing staff and parents were blinded to each of the dosing regimens.

- Statistical methods

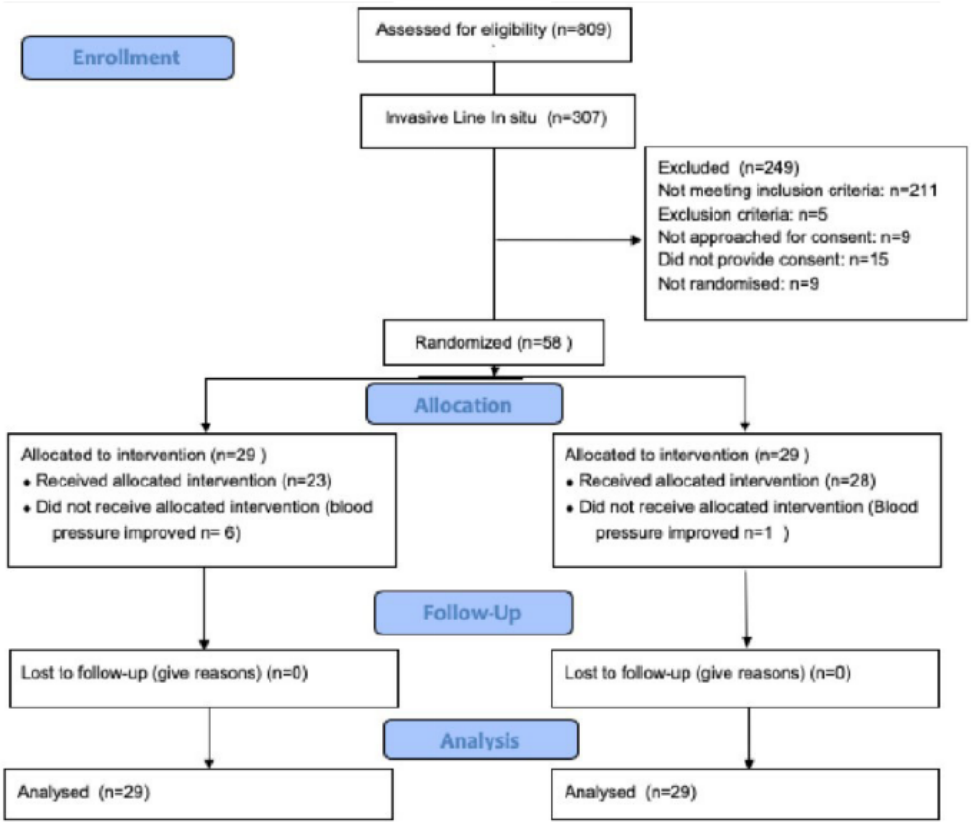
The principal analyses were performed on an intention-to-treat basis using the CONSORT guidelines. Categorical variables were described using frequency and percentage (%), and continuous variables were described using mean and SD when the variable was normally distributed or the median and IQR when the variable was not normally distributed. Logistic random- effects regression was used for comparisons of binary outcomes between the groups, and linear random- effects regression was used for comparisons of continuous outcomes between the groups. For both regression models, group was a fixed effect and centre was a random effect. All statistical analysis was performed using STATA V.15.0.

Results

- Participant flow

The disposition of patients is summarized in Figure 4.

Figure 4. CONSORT Diagram



- Recruitment

Significant recruiting difficulties were experiences during the course of the trial. The study was stopped with not more than 59 patients randomized.

- Conduct of the study

In 18 patients protocol deviations were reported by the applicant, 9 in each treatment arm. None of these deviations provided had the potential to affect the conclusion on benefit and risk. Some inconsistencies were noted in the study report.

No information on treatment compliance was provided.

- Baseline data

The median age at enrolment was 5.28 hours (IQR 3.54–12.10 hours) in the standard care group and 6.12 hours (IQR 3.93–14.34 hours) in the restrictive management group. The mean BP at the time of

enrolment was similar between the groups (21.4mm Hg vs 21.5mm Hg). The vast majority of infants were white. Numerically, a higher number of patients in the dopamine group were at the highest GA category of 27 weeks (7 vs. 2) (Table 6)

Table 3. Infant characteristics at delivery.

	Standard (n=29)	**Restrictive (n=29)**
	n (%)*	**n (%)***
GA (weeks), mean (SD)	25.3 (1.5)	25.4 (1.3)
Birth weight (g), mean (SD)	683 (146)	745 (171)
Male	21 (72)	20 (69)
Infant of multiple gestation	9 (31)	12 (41)
GA<26 weeks	19 (66)	19 (66)
Apgar at 1 min, median (IQR)†	4 (2–6)	4 (3.0–5.8)
Apgar at 5 min, median (IQR)†	7 (5.5–8.0)	7 (5.3–8.0)
Base excess on NICU admission blood gas, median (IQR)	−5.0 (−8.0 to −1.6)	−4.9 (−8.6 to −2.5)
Temperature on NICU admission (°C), median (IQR)‡	36.3 (36.0–37.0)	36.4 (35.8–37.0)
Age at enrolment (hours), median (IQR)	5.28 (3.54–12.10)	6.12 (3.93–14.34)

*Unless otherwise stated.
†n=28 in the restrictive group.
‡n=28 in the standard group.
GA, gestational age; NICU, neonatal intensive care unit.

Table 4. Maternal characteristics

	Standard (n=29)	**Restrictive (n=29)**
Maternal characteristics	n (%)*	n (%)*
Antenatal steroids (any)	28 (97)	26 (90)
Antenatal steroids (complete)	23 (82)	22 (85)
Maternal hypertension	8 (28)	7 (24)
Magnesium sulphate†	18 (75)	19 (83)
Placental abruption	2 (7)	3 (10)
PPROM	9 (31)	9 (31)
Chorioamnionitis‡		
Clinical	6 (21)	6 (21)
Histological	3 (11)	1 (3)
No	19 (68	22 (76)
Presentation‡		
Breech	9 (32)	10 (35)
Cephalic	19 (68)	19 (66)
Cord PH obtained	17 (59)	20 (69)
Venous: median (IQR)§	7.34 (7.29–7.37)	7.32 (7.30–7.38)

Arterial: median (IQR)¶	7.29 (7.23–7.35)	7.28 (7.21–7.34)
Mode of delivery		
Vaginal	11 (38)	8 (28)
Caesarean section	18 (62)	21 (72)
Cord clamping**		
Immediate	17 (61)	15 (56)
Delayed cord clamping	11 (39)	12 (44)

*Unless otherwise stated.

†n=24 in the standard group and n=23 in the restrictive group.

‡n=28 in the standard group.

§n=14 in the standard group and n=13 in the placebo group.

¶n=14 in the standard group and n=9 in the restrictive group.

**n=28 in the standard group and n=27 in the restrictive group.

PPROM, preterm premature rupture of membranes.

Table 5. Infant characteristics at enrolment

	Standard (n=29)	**Restrictive (n=29)**
	n (%)*	**n (%)***
Received respiratory support	29 (100)	29 (100)
Supplemental oxygen	25 (86)	23 (79)
CPAP	3 (10)	5 (17)
Conventional ventilation	24 (83)	23 (79)
High-frequency ventilation	2 (7)	2 (7)
Respiratory distress syndrome	25 (86)	27 (93)
Surfactant first given in the delivery room	17 (59)	19 (66)
Surfactant first given in the NICU	10 (34)	9 (31)
Not given	2 (7)	1 (3)
Pneumothorax	0 (0)	2 (7)

Inhaled nitric oxide	1 (3)	2 (7)
Patent ductus arteriosus on echo	5 (17)	6 (21)
Indomethacin for prophylaxis	0 (0)	1 (3)
Indomethacin for PDA	0 (0)	0 (0)
Ibuprofen for PDA	1 (3)	0 (0)
Pulmonary haemorrhage	1 (3)	0 (0)
Lowest recorded MABP (mm Hg), median (IQR)	21.0 (20.0–23.0)	22.0 (19.5–23.5)
Mean (SD) mm Hg BP<GA	29 (100)	29 (100)
Mean (SD) mm Hg BP<GA	3.6 (2.1)	3.5 (1.9)
Lactate (mmol/L), median (IQR)†	1.9 (1.2–3.1)	2.2 (1.6–4.6)
*Unless otherwise stated. †n=27 in the standard group. BP, blood pressure; CPAP, continuous positive airway pressure; GA, gestational age; MABP, mean arterial blood pressure; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus		

Table 6. Infant characteristics at delivery

Gestational age in the HIP trial					
	23 weeks	24 weeks	25 weeks	26 weeks	27 weeks
Dopamine	5	5	9	3	7
Placebo	5	4	10	4	2
Unknown	1	0	1	2	0

- Numbers analysed

There were 111 patients enrolled in the trial, 58 of whom became hypotensive and were randomized to receive placebo or dopamine. Short-term outcomes were collected for all 58 and long-term outcome data—survival absent neurodevelopmental disability—was collected for 55 randomized (three lost to follow-up, two from the dopamine arm, one from the placebo control). The short-term outcomes data for the other 53 patients who were enrolled but did not become hypotensive were also collected.

- Outcomes and estimation

Co-Primary endpoints

There was no statistically significant difference between the active and control arms in the co-primary end-point of survival free of neurodevelopmental disability at 2 years adjusted GA (48.1% in the dopamine group compared to 25.0% in the placebo arm, OR 2.79 (0.89-8.72, p value 0.078) (Table 7)). The mean Bayley scores all trended towards dopamine, but outside the boundary of statistical significance (Table 8 below).

Table 7. Two year primary outcome and components

Outcome	Dopamine (n=27) n (%)	Placebo (n=28) n (%)	Odds ratio (95% CI)	p-value[1]
Survival without neurodevelopmental impairment[2]	13 (48.1)	7 (25.0)	2.79 (0.89 to 8.72)	0.078
Death	6 (22.2)	8 (28.6)		
Neurodevelopmental impairment	8 (29.6)	13 (46.4)		
Severe	4	3		
Moderate	3	5		
Mild	1	5		

[1]from logistic random effects model with centre as a random effect, unless otherwise stated

[2]based on Bayleys, CP, Hearing, Speech and language and Vision

Neurodevelopmental impairment	8 (30)	13 (46)		
Worst level of any impairment[3]				
Moderate	2 (7)	8 (29)		
Severe	6 (22)	5 (18)		

[1]from logistic random effects model with centre as a random effect

[3]based on worst of: Bayleys: Cognitive, Language or Motor composite scales, Cerebral Palsy, Hearing, Speech and language or Vision

Table 8. Bayley Scores at 2 years GA

	Dopamine		Placebo		
	n	Mean (SD)	n	Mean (SD)	p-value
Cognitive	19	89.47 (18.10)	18	84.33 (19.90)	0.398
Language	17	85.24 (21.55)	18	82.33 (20.59)	0.675
Motor	19	86.47 (21.04)	18	82.89 (19.87)	0.874

The co-primary outcome of survival free of ultrasound abnormality at 36 weeks was reached by 18/29 (62%) in the dopamine standard group and by 20/29 (69%) in the restrictive management group (OR 0.74, 95% CI 0.25 to 2.18) (Table 9 below).

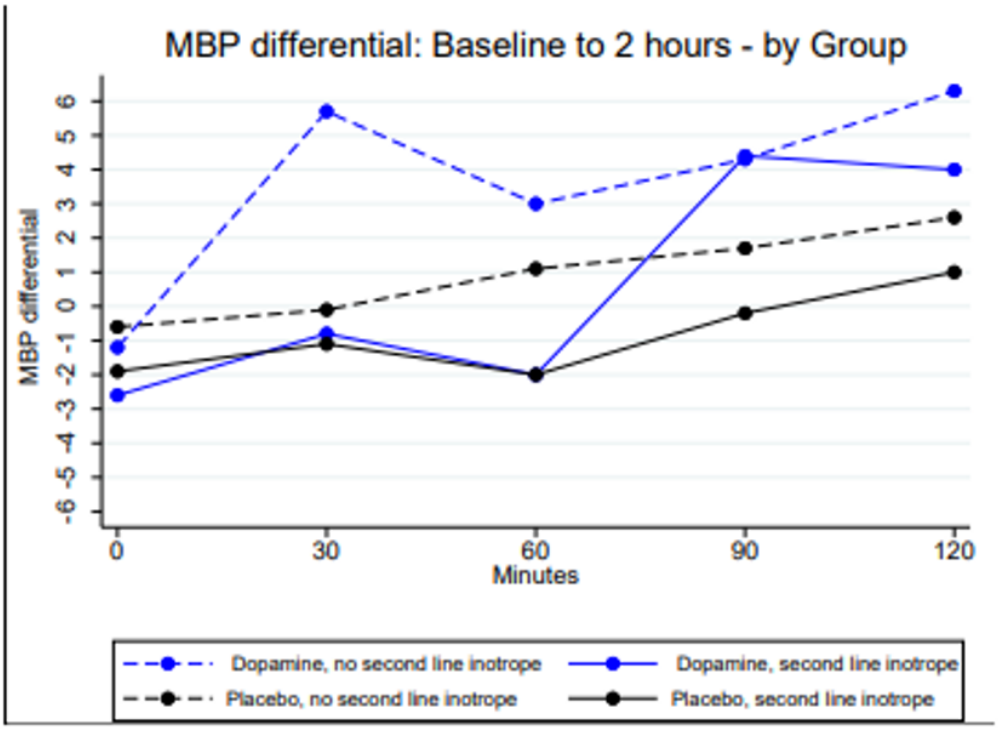
Table 9. Primary outcome survival without severe ultrasound abnormality at 36 weeks of PMA

	Standard (n=29)	**Restrictive (n=29)**		**P value***
	n (%)	n (%)	**OR (95% CI)***	
All Infants	18 (62)	20 (69)	0.74 (0.25 to 2.18)	0.58
<26 weeks (n=19 in each group)	11 (58)	10 (53)	1.24 (0.34 to 4.45)	0.74
>26 weeks (n=10 in each group)	7 (70)	10 (100)	–	0.21†
*From logistic regression analysis. †From Fisher's exact test due to being unable to perform logistic regression analysis. PMA, postmenstrual age				

Secondary endpoints

Mean arterial blood pressure over time is shown in Figure 5 below.

Figure 5. MBP differential: Baseline to 2 hours – by Group



Changes in mean BP from 0 to 2 hours differed between the placebo and dopamine groups (p=0.028 for group × time interaction). The largest difference between the two groups was at 30 min (difference in means 4.4, 95% CI 1.8 to 7.1, p=0.001).

Additional BP support was used less frequently in the standard group (11/29, 38%) compared with the restrictive group (19/29, 66%) (p=0.038). Fewer infants in the standard group received additional inotropes (28% vs 48%, p=0.11). Among infants <26 weeks of gestation, this difference was most pronounced (11% vs 63%, p=0.002). Of 22 patients who received additional inotrope, the majority, 19, received epinephrine; 5 received dobutamine; and 4 received hydrocortisone. Additional therapy was administered based on mean BP >5 mm Hg less than the equivalent GA in seven cases, and in 12 cases, the mean BP was >3 mm Hg below but with additional clinical signs or abnormal lactate values. Two infants received open-label dopamine contrary to protocol during their neonatal intensive care unit stay beyond the first 72 hours.

Results for other secondary outcomes are listed in Table 10 below.

Table 10. Secondary outcomes

	Standard (n=29)	**Restrictive (n=29)**		
	n (%)	n (%)	Odds ratio (95% CI)†	P Value†
Mortality	6 (21)	7 (24)	0.82 (0.24 to 2.83)	0.75
Severe ultrasound abnormality	5 (17)	5 (17)	1.00 (0.26 to 3.91)	1
Grade 3/4 IVH	5 (17)	2 (7)	3.06 (0.51 to 18.41)	0.22
PVL	2 (7)	2 (7)	1.04 (0.13 to 8.37)	0.97
Any ultrasound abnormality	16 (55)	13 (45)	1.51 (0.54 to 4.26)	0.43
NEC	1 (3)	4 (14)	0.22 (0.02 to 2.13)	0.19
SIP	3 (10)	3 (10)	1.00 (0.18 to 5.42)	1
BPD‡	17 (74)	14 (64)	1.87 (0.45 to 7.68)	0.39
Duration of inotrope (hours)	17.8 (7.5–30.6)§¶	13.7 (6.1–24.5)§**	1.46 (0.84 to 2.56)††	0.18
Any intervention	11 (38)	19 (66)	0.32 (0.11 to 0.94)	0.038

*Unless otherwise stated.

†From logistic regression analysis unless otherwise stated.

‡Of those who had survived to 36 weeks.

§Median (IQR).

¶n=21 in the standard group.

**n=22 in the restricted group.

††Ratio of geometric means as the duration variable was log-transformed.

BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enetrocolitis; PVL, periventricular leucomalacia; SIP, spontaneous intestinal perforation

The applicant has provided additional data differentiating between < 26 weeks and >= 26 weeks (Table 11). In the first group second line inotropes were administered more frequently in the placebo arm (numerical p value 0.001), whereas in the second group such inotropes were given at a numerically higher rate in the dopamine arm. Second line agents of any kind were more frequently administered in the placebo arm in both groups. Severe brain injury was numerically slightly higher in GA < 26 weeks at birth in the dopamine group, mortality numerically slightly higher on placebo in this lower age group.

For none of the following other secondary endpoints a difference was observed with a numerical p value of < 0.05: Mortality, Severe ultrasound abnormality, PVL, any ultrasound abnormality, NEC, SOP, and BPD. Grade 3 / 4 IVH was more frequently observed in the dopamine group (5 vs. 2 cases). Considering the low number of events it is hardly possible to draw conclusions in this regard. For further discussions see below (safety).

Table 11. Secondary outcomes: <26 weeks vs 26+ weeks subgroup

		Dopamine	Placebo	p-value (from chi sq test)
Survival absent neurodevelopment disability at 2 years GA	< 26 weeks	42.1% (8/19)	47.4% (9/19)	.744
	>=26 weeks	30% (3/10)	0% (0/10)	0.211
Mortality	< 26 weeks	21.1% (4/19)	36.8 (7/19)	0.283
	>=26 weeks	20% (2/20)	10% (1/10)	1.000
Severe brain injury (check data may be injury of any severity)	< 26 weeks	73.3% (14/19)	52.6% (10/19)	0.179
	>=26 weeks	20% (2/10)	30% (3/10)	0.850
Second line inotrope	< 26 weeks	10.5% (2/19)	12/19 (63.2%)	0.001
	>=26 weeks	60% (6/10)	20% (2/10)	0.170
NEC or Spontaneous intestinal perforation	< 26 weeks	15.8% (3/19)	33.3% (6/18)	0.269
	>=26 weeks	10% (1/10)	10% (1/10)	1.000
NEC or Spontaneous intestinal perforation or death	< 26 weeks	31.6% (6/19)	52.6 (10/19)	0.189
	>=26 weeks	20% (2/10)	20% (2/10)	1.000
Second line agent used	< 26 weeks	21.1% (4/19)	68.4% (13/19)	0.003
	>=26 weeks	30% (3/10)	70% (7/10)	0.0754
Neonatal chronic lung disease	< 26 weeks	64.7% (11/17)	47.1% (8/17)	0.300
	>=26 weeks	60% (6/10)	60% (6/10)	1.000

- Ancillary analyses

CAR substudy

Study of cerebral oxygen saturation and autoregulatory capacity (CAR)

Publication: Thewissen L. et al., Pediatric Research 2021; 90: 373–380; https://doi.org/10.1038/s41390-021-01483-w

As part of HIP, a prospective cohort study of blinded cerebral regional oxygen saturation values (rScO2), was conducted.

Methods

Values of rScO2, mean arterial blood pressure (MABP), duration of cerebral hypoxia and transfer function (TF) gain inversely proportional to CAR were compared between hypotensive infants randomized to receive dopamine or placebo and between hypotensive and non-hypotensive infants, and related to early intraventricular haemorrhage or death. The study was conducted at 8 different study centres.

Statistical Methods for CAR Substudy

For hypotensive infants receiving the study drug, mean values of rScO2, MABP and TF gain were calculated in 2-hour epochs before, after start and after stop of the study drug. Furthermore, percentage of time with rScO2 below 63% (% time rScO2 < 63%) was calculated as a measure for cerebral hypoxia in the same time frames. Identical parameters were calculated for each infant, for day 1, 2 and 3 and the first 3 days after birth overall to compare between hypotensive and non-hypotensive infants. The relation of the parameters with the composite outcome of occurrence of IVH by day 7 or death before discharge from the hospital was assessed. An exploratory analysis focussed on the relation between multiple pairs of median MABP with TF gain and median rScO2, respectively, per day and in all available 20-min pressure-passive epochs per patient, to investigate whether these relations would permit identification of adverse outcome.

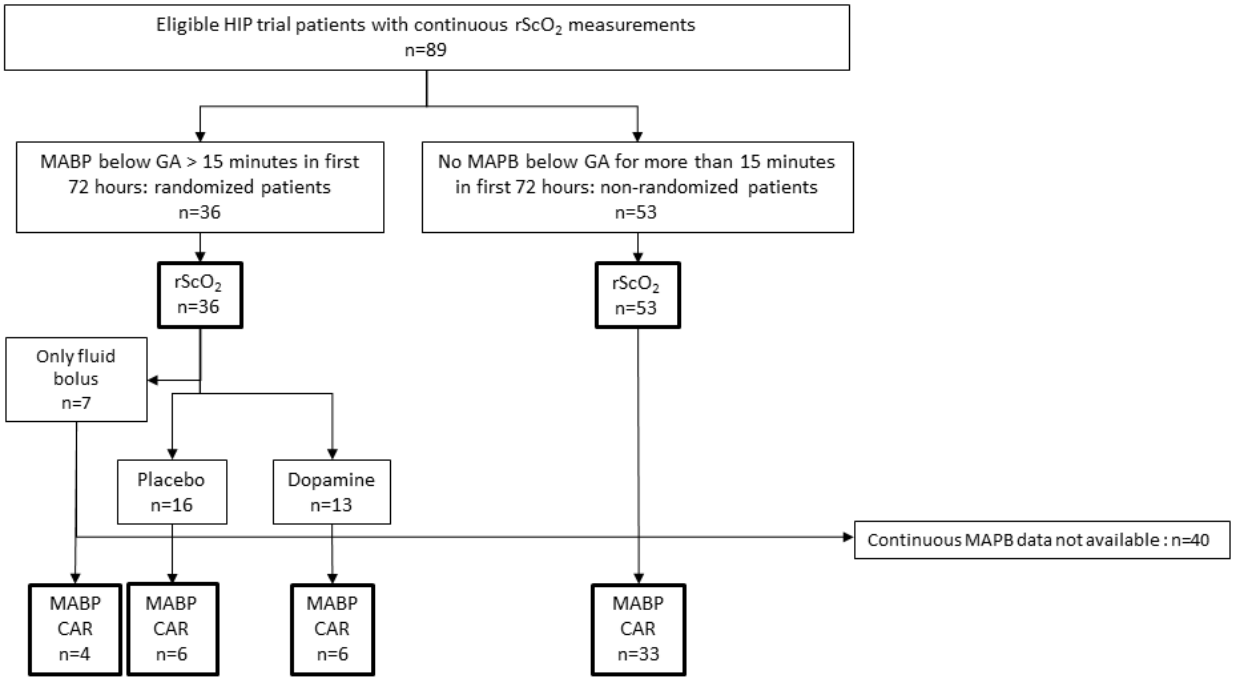
To identify a difference of 10 % (SD 12%) in rScO2 after dopamine therapy in comparison with placebo, with a type 1 error of 0.05 and type 2 error of 0.2, 23 participants in each group were needed.

A multivariate linear model for longitudinal measures with an unstructured covariance matrix was used to compare the evolution of study parameters between groups over time. A direct likelihood approach was adopted such that cases with missing information were still included in the analysis. Least-squares means (and their 95% confidence interval (CI)) are reported. P values are given after Bonferroni Holm correction for multiple testing. Relation with outcome was assessed using univariable and bivariate logistic regression models. To characterize the relation between TF gain-MABP and rScO2-MABP, spearman correlations were performed per day for all infants. Furthermore, using all available individual 20-min epoch data for each infant, linear mixed models with (correlated) random intercepts and slopes on (log-transformed) TF gain and rScO2 values were used comparing the relation TF gain-MABP and rScO2-MABP as a function of outcome. Restricted cubic splines with four knots were used to allow a nonlinear relation between the pairs. The model contained terms for the spline basis (2 extra terms on top of the intercept and the linear slope), the main effect of group (i.e. the levels of the outcome) and additional terms referring to the interaction between group and MABP. The result is given of an overall test for any difference between both levels in the relation. Predicted mean outcomes were plotted with pointwise 95% confidence intervals. Empirical standard errors were used to correct for misspecification of the covariance structure. Analyses were performed on the information from the first day. Gestational age was added as a continuous covariate in the model. A P value < .05 was considered statistically significant. All reported P values are two-sided. Analyses have been performed using SAS software, version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC) and SPSS Statistics for Windows version 24.0 (IBM corp, Armonk, NY).

Disposition of patients and participant flow

Using near-infrared spectroscopy NIRS, rScO2 measurements were obtained in 89 potentially eligible infants. 53 infants were normotensive and 36 hypotensive who were randomized to either placebo or dopamine. Of those, 13 received dopamine and 16 received placebo. (Figure. 6)

Figure 6. Recruitment and participants flow



Results

In total, 3 patients were lost to follow up.

Baseline characteristics

Baseline characteristics are described in Table 12 below. When comparing hypotensive vs. non-hypotensive patients, hypotensive patients were more likely to be male, had a lower GA, and birth weight. There was a trend towards a higher mortality and a numerical imbalance for IVH favouring non-hypotensive patients.

Table 12. Baseline characteristics for a.) hypotensive, normotensive and b.) hypotensive infants treated with either dopamine or placebo

a.)

Infant characteristics	Hypotensive	Non-hypotensive	Total	p-value
Male n (%)	25 (69)	26 (49)	51 (57)	0.056
GA in weeks Median (IQR)	25.3 (24.7 - 26.5)	25.9 (25.1-26.9)	25.7 (24.9-26.6)	0.036
Birth weight in g median (IQR)	755 (607-860)	800 (670-950)	770 (650-829)	0.037
Apgar 1 min, median (IQR)	4 (2-6) (n=35)	5 (2-7) (n=48)	4 (2-6) (n=83)	0.237
Apgar 1 min, median (IQR)	7 (5-8) (n=35)	6.5 (5-8.75) (n=48)	7 (5-8) (n=83)	0.826
CRIB Score, median (IQR)	11 (7-13) (n=35)	10 (7-12) (n=48)	11 (7-12) (n=83)	0.381
Study drug received n (%)	29 (81)	0 (0)	29 (33)	
Additional treatment n (%)	11 (31)	0 (0)	11 (12)	
IVH by day 7 n (5)	13 (36)	12 (23)	25 (28)	0.165
Survival to discharge, n (%)	28 (78)	49 (93)	77 (87)	0.061

b.)

	Dopamine (n=13)	Placebo (n=16)	Total (n=29)	P-value
Male n (%)	9 (69)	11 (69)	20 (69)	1.000
GA in weeks Median (IQR)	25.1 (24.9-26.4)	25.6 (25-26.6)	25.4 (24.9-26.4)	0.449
Birth weight in g median (IQR)	760 (639-815)	705 (613-938)	750 (639-860)	0.779
Apgar 1 min, median (IQR)	3 (2-5.5)	4 (3-6) (n=15)	4 (2-6) (n=28)	0.340
Apgar 1 min, median (IQR)	7 (6-8)	7 (5-8) (n=15)	7 (6-8) (n=28)	0.524
CRIB Score, median (IQR)	8 (4.5-13)	12 (10-13) (n=15)	11 (5.5-13) (n=28)	0.317
Study drug received n (%)	13 (100)	16 (100)	29 (100)	1.000
Additional treatment n (%)	4 (31)	7 (44)	11 (38)	0.702
IVH by day 7 n (5)	6 946)	5 (31)	11 (38)	0.466
Survival to discharge, n (%)	12 (92)	12 (75)	28 (83)	0.343
Additional treatment was adrenaline; IVH defined as grade 1-IV (15) and assessed at day 7 after birth				

Table 13 summarizes the association between duration of cerebral hypoxia (defined as rScO2 < 63%1) and of MABP at days 1, 2, and 3, respectively, with IVH or Mortality at day 7 in the entire group of patients including those with and without MABP below GA in the first 72 hours. For NIRS below 63% the p value for a difference between the groups was below 0.05 at all three days, for MABP it was below 0.05 at day 1. GA at birth was also associated with IVH or Mortality at day 7. Analyses for IVH at day 7 or mortality at discharge are summarized in Table 14. The applicant states that duration of cerebral hypoxia (defined as rScO2 < 63%1) was predictive of early intraventricular haemorrhage or death, odds ratio 1.036 (95% CI 1.004 to 1.069) P=.026.

Table 13. Differences in MABP and Cerebral perfusion between IVH/Mortality+/-

	IVH or Mortality on Day 7		
	No (n=57)	Yes (n=32)	P-Value
Percent of time NIRS below 63% day 1	6.27	13.98	0.011
Percent of time NIRS below 63% day 2	5.16	9.42	0.008
Percent of time NIRS below 63% day 3	7.65	19.83	0.027
Mean arterial blood pressure day 1	34.56	31.88	0.048
Mean arterial blood pressure day 2	36.51	34.33	0.162
Mean arterial blood pressure day 3	37.43	35.57	0.213
GA in weeks (continuous variable)	26.11	25.03	<0.001

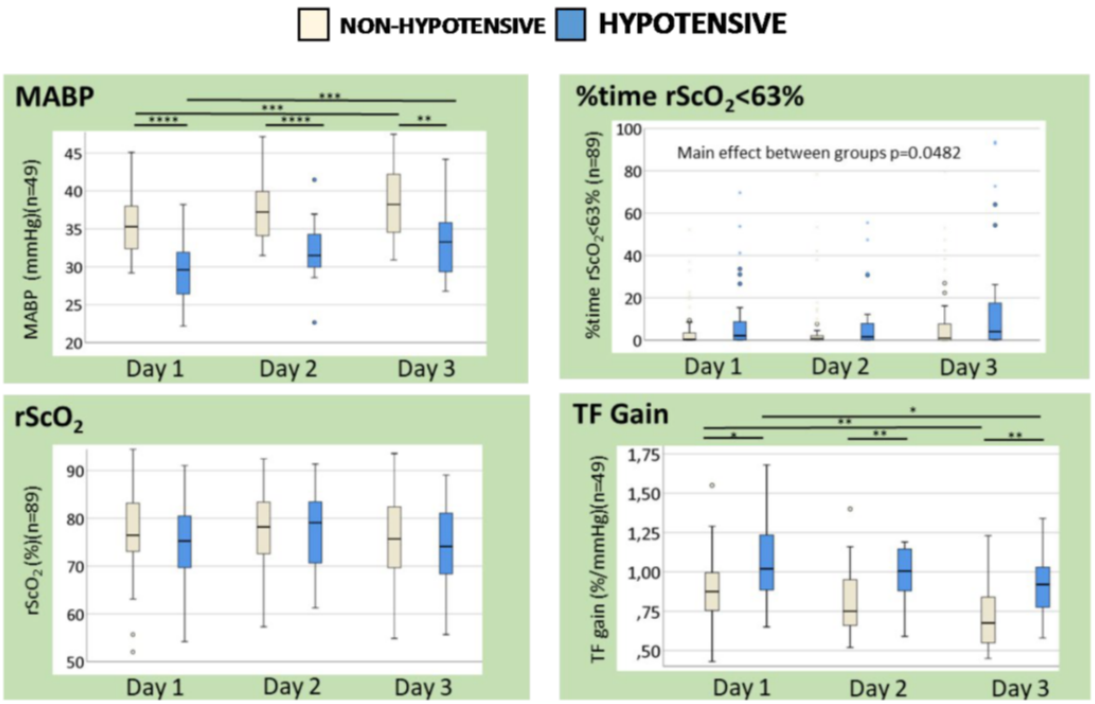
Table 14. Any IVH or death before discharge

Any IVH by day 7, death before discharge		
	Odds ratio	P-value
% time rScO2<63% day 1	1.025	0.133
% time rScO2<63% day 2	1.020	0.204
% time rScO2<63% day 3	1.027	0.023
MABP day 1	0.853	0.029
MABP day 2	0.899	0.124
MABP day 3	0.930	0.231
TF Gain day 1	3.376	0.276
TF Gain day 2	6.251	0.194
TF Gain day 3	3.792	0.332
Gestational age	0.441	0.0003
CRIB score (not complete)	1.439	0.025

Boxplot analyses for MABP, % time rScO2<63%, rScO2 and TF gain are shown in Figure 7 below for hypotensive vs. non hypotensive (at entry) infants and in Figure 8 for dopamine vs. placebo in hypotensive (at entry) children.

The duration of cerebral hypoxia was significantly higher in 36 hypotensive patients (3.2 %; 95% CI 1.9 to 5.2) compared to 53 non-hypotensive infants (1.6%;1 to 2.5) P=.048. Mean TF gain was significantly higher in 16 hypotensive infants (0.97 %/mmHg; 95% CI 0.82 to 1.12) compared to 33 non-hypotensive infants (0.79; 0.66 to 0.92). According to the applicant this suggests that hypotension defined as a mean BP less than gestational age is associated with impaired cerebral autoregulation.

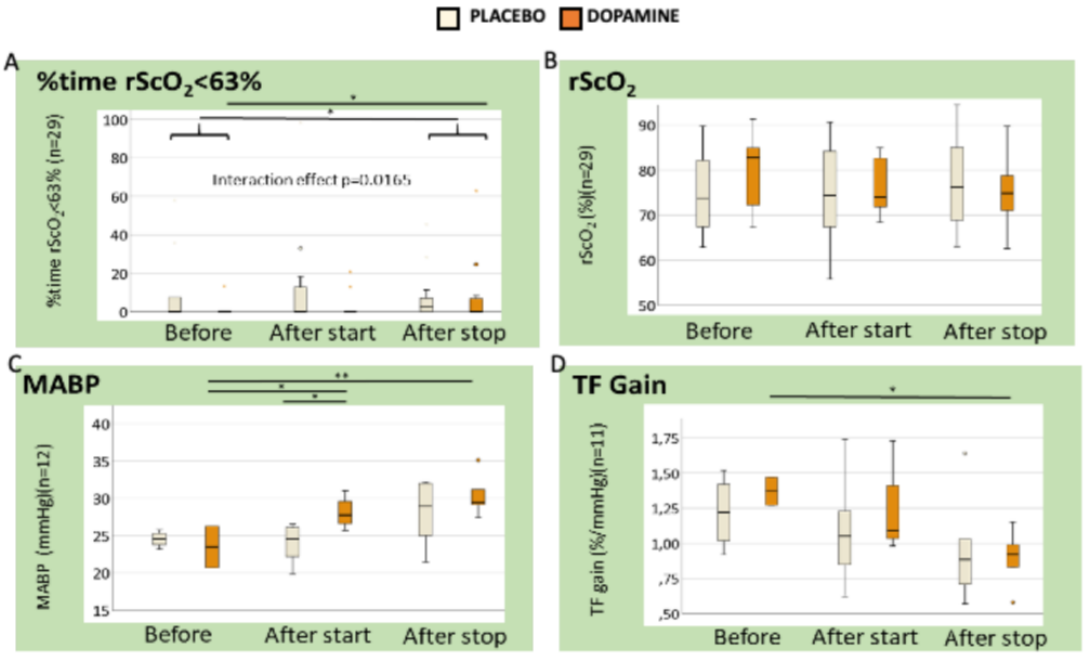
Figure 7. Box plots hypotensive versus non-hypotensive : A, MABP over first 3 days, %time rScO2 below 63%, C. rScO2, and TF Gain



No significant difference in mean rScO2 was observed after dopamine (n=13) (77.7 %; 95% CI 71.2 to 84.1) compared to placebo (n=16) (75.8; 69.8 to 81.7) P>.99. TF Gain improved over the first three days, but the sample size consisted of only 6 observations per arm.

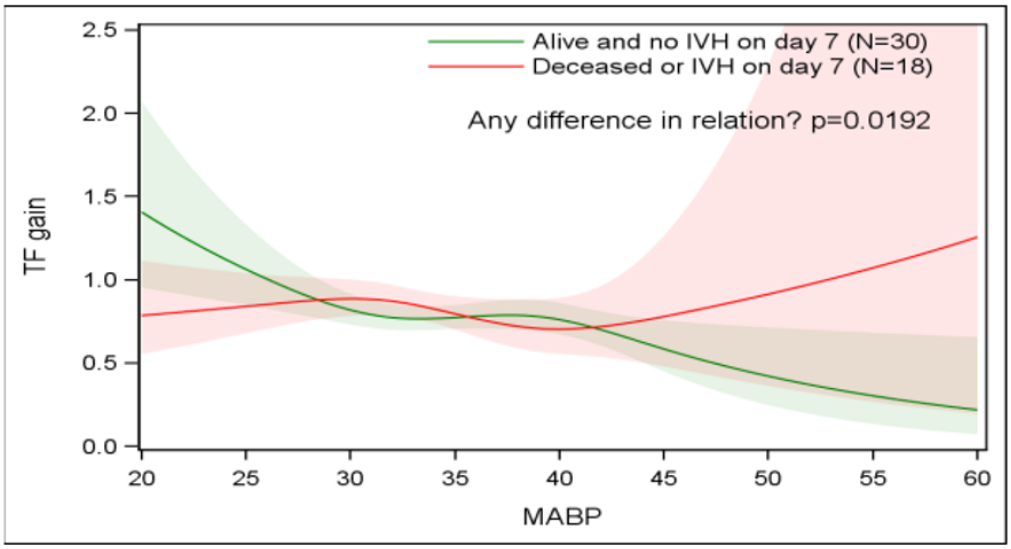
MABP increased significantly over time in both randomised (i.e. hypotensive) and non-randomized groups but was — as expected— significantly lower in the randomized group (p<0.0001). Autoregulatory capacity as measured by TF Gain was lower with lower blood pressure (higher TF Gain values indicate diminished autoregulatory capacity). TF gain significantly decreased over time in both groups and was significantly higher in the randomised group (p=0.0009). TF gain increased with decreasing MABP on each day (D1: r=-0,31; D2: r=-0,37; D3: r=-0,40; all p<0.05).

Figure 8. Boxplots (middle: median; end of boxes: 25th and 75th percentiles; whiskers: 11/2 IQR) indicating evolution of rScO2 (A), percentage of time with rScO2 below 63% (B), MABP (C) and TF gain (D) over the first 3 days after birth in hypotensive versus non-hypotensive infants. *P<.05



Autoregulatory capacity was estimated to have generally remained intact within a range of about 30 to 40 mmHg. For uninjured babies, BP below 30 coincided with a reduced autoregulation (Figure 9) as indicated by an increase in TF-Gain. For injured babies their TF-Gain appeared to improve at lower blood pressure levels.

Figure 9. TF Gain versus MABP



The main findings are: dopamine increased MABP but had no significant effect on rScO2 or TF gain compared to placebo in a time frame of 2 h. Hypotension and cerebral hypoxia were associated with early intraventricular haemorrhage or death.

- Summary of main efficacy results

The following tables summarise the efficacy results from the HIP trial supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

<table>
<tr><td colspan="4">Title: Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn</td></tr>
<tr><td>Study identifier</td><td colspan="3">Protocol number: 2010-023988-17</td></tr>
<tr><td rowspan="4">Design</td><td colspan="3">It was a pragmatic, multinational, randomised trial of two different strategies for the management of hypotension in ELGAN infants (An observational approach with placebo approach versus Standard with dopamine). <free text></td></tr>
<tr><td colspan="2">Duration of main phase:

Duration of Run-in phase:

Duration of Extension phase:</td><td>Treatment duration 72 hours, assessment up to 2 years
not applicable

not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority (observational approach vs. standard approach using dopamine)</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Observational (Placebo)</td><td>Placebo 5 → 10 → 15→ 20 µg/kg/min if needed, up to 72 h, n =29
>. <duration>, <number randomized></td></tr>
<tr><td colspan="2">Dopamine</td><td>Dopamine. 5 → 10 → 15→ 20 µg/kg/min if needed, up to 72 h, n =29</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td>Co-Primary endpoint</td><td>- 2 yrs outcome

- 36 wks GA outcome</td><td>- Survival free of neurodisability at 2 years corrected GA.

- Survival to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultra-sound</td></tr>
<tr><td>Secondary</td><td>- All cause of mortality at 36 weeks corrected GA.</td><td></td></tr>
<tr><td>Secondary</td><td>- Grade 3 / 4 IVH</td><td></td></tr>
<tr><td>Database lock</td><td colspan="3">Study completion date: September 2017</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Intent to treat 2 years and 36 weeks GA</td></tr>
</table>

Title: *Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn*				
Study identifier	Protocol number: 2010-023988-17			
Descriptive statistics and estimate variability	Treatment group	Dopamine	Observational (Placebo)	
	Number of subject	29	29	
	- Survival free of neurodisability at 2 years	13 (48.1%)	7 (25.0%)	
	- Survival to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultra-sound	18 (62%)	20 (69%)	
	- All cause of mortality at 36 weeks corrected GA.	6 (21%)	7 (24%)	
	- Grade 3 / 4 IVH	5 (17%)	2 (7%)	

Effect estimate per comparison	<Co->Primary endpoint	Comparison groups	
		Odds ratio	
		(95% CI)	
		P-value Logistic random-effects regression	
	- Survival to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultra-sound	Comparison groups	2.79
		variability statistic	0.89 – 8.72
		P-value	0.078
	- Survival to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultra-sound	Comparison groups	0.74
		variability statistic	0.25 – 2.18
		P-value	0.58
	- All cause of	Comparison groups	0.82

Title: *Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn*			
Study identifier	Protocol number: 2010-023988-17		
	mortality at 36 weeks corrected GA.	variability statistic	0.24 – 2.83
		P-value	0.75
	- Grade 3 / 4 IVH	Comparison groups	3.06
		variability statistic	0.51 – 18.41
		P-value	0.22

Published trials in hypotensive preterm infants

The available literature contains conflicting results regarding the hypotension and its treatment in extremely preterm infants. For extremely pre-term (GA ≤ 28 weeks) infants who have adequate perfusion, it remains unclear whether the interventions have a clinically meaningful impact, and if so, whether they are beneficial or harmful. There are numerous studies indicating potential harm of interventions and hypotension treatment. Key literature is summarized below:

In a study by Faust et al., (Arch Dis Child Fetal Neonatal Ed 2015;0:F1–F5) hypotension during the first 24 h of life was associated with adverse outcomes in very-low-birthweight infants. Hypotensive infants had a higher rate of intraventricular haemorrhage (IVH, 20.3% vs 15.9%, p<0.001), bronchopulmonary dysplasia (BPD, 19.2% vs 15.1%, p<0.001) and death (5.2% vs 3.0%, p<0.001).

In a retrospective cohort study with 118 extremely low birth weight infants (Dempsey et al., 2009 Arch Dis Child Fetal Neonatal Ed 2009;94:F241–F244.) hypotensive infants (BP<GA) with clinical evidence of good perfusion had as good of an outcome as normotensive patients, however, treatment of low blood pressure (inotrope or/and fluid boluses administration) was associated with adverse outcome (increased mortality, severe IVH, cystic PVL, surgical NEC or GI perforation). The study however failed to correct for hypotension as a factor for adverse outcome, confounding by indication is an issue.

The few studies reporting an association between hypotension and developmental delay were small and do not appear to be adequately controlled for potential confounders. In the study of (B. Batton et al., 2009 J Pediatr 2009;154:351-7) 3 cohorts of extremely preterm infants were compared: untreated with normal blood pressure (BP) (67 infants), untreated with low BP (31 infants), and treated with low BP (70 infants). Untreated infants with low BP had similar survival rates, but more cerebral palsy, deafness, or any ND (neurodevelopmental) impairment when compared with infants with normal BP. Treated infants with low BP had more mortality, worse ND, and less survival without ND impairment compared with infants who had normal BP.

In the study of B. Batton et al., (Pediatrics 2013 Jun;131(6):e1865-73) extremely preterm infants who received antihypotensive therapy had worse outcomes than untreated infants. Treated infants were more likely than untreated infants to develop severe retinopathy of prematurity (15% vs 8%, P = .03) or severe intraventricular haemorrhage (22% vs 11%, P < .01) and less likely to survive (67% vs 78%, P = .02). However, these differences were no longer significant after controlling for study centre, gestational age (GA), severity of illness, and the number of low BP values.

In a subsequent report of 331 infants (90 percent of the original cohort), the risk of death or neurodevelopmental impairment at age 18 to 22 months was higher among infants who received one of these interventions (fluid bolus, dopamine, dobutamine, epinephrine, hydrocortisone, vasopressin, or any blood product) in the initial 24 hours compared with untreated infants after controlling for confounding factors (odds ratio 1.84; 95% CI 1.09-3.09) (B. Batton et al., Arch Dis Child Fetal

Neonatal Ed 2016;101:F201–F206). There were significant differences in the incidence of NIDD (neurodevelopmental impairment or developmental delay) or the composite outcome of death/NIDD from random-effects logistic regression models. For each one week increase in GA at birth, both the likelihood of NIDD or death/NIDD decreased. The presence of any marker of severity of illness increased the odds of both NIDD and death/ NIDD as did the cumulative number of severity of illness markers. When incorporating these variables and changes in BP into regression models, treatment with any anti-hypotensive therapy was a significant predictor of death/NIDD, but not NIDD alone. In similar regression models incorporating anti-hypotensive treatment, the rise in BP (at the expected rate versus less than the expected rate) was not significantly associated with either outcome. However, the study authors failed to correct for hypotension and thus making it unsure if the degree of hypotension is an important independent factor of adverse outcomes. Thus, confounding by indication cannot be ruled out.

A Canadian study comparing inotrope use in neonatal intensive care units (Wong et al., Am J Perinatol 2015 Jan;32(1):9-14) concluded that risk of mortality and major morbidities (severe retinopathy of prematurity, severe neurological injury, bronchopulmonary dysplasia, and necrotising enterocolitis) were significantly higher in neonates who received inotropes. Rates of inotrope use varied significantly between participating sites (0-36% infants). However, the study authors highlighted that other factors including unmeasured confounders and the severity of illness in these patients may significantly contribute to the associations found in their study, rather than their exposure to inotropes alone. It is possible that their findings are at least in part, a reflection of the overall critical condition of their study population and confounding by indication cannot be ruled out.

A case-controlled study presented data that were obtained from anonymised regional case notes of Project 27/28, a national case-controlled study run by the Confidential Enquiry into Stillbirths and Deaths in Infancy (Ewer et al, Paediatr Perinat Epidemiol 2003 Apr;17(2):180-6). All deaths in the first year of the study in the West Midlands (cases, n = 22) and matched regional controls (survivors, n = 29) were included. The primary outcome was death within 28 days. Sixteen of the 22 deaths were considered 'not inevitable' on the basis of the neonates' condition at birth. These newborns received on average more than twice the volume expansion compared with controls in the first 48 h of life (38.2 vs. 18.2 mL/kg, P = 0.007). Newborns who received >or= 30 mL/kg volume expansion in the first 48 h of life were more likely to die than those who received <30 mL/kg (OR 4.5 [95% CI 1.2, 17.2]). The newborns who received >or= 30 mL/kg volume expansion had lower birthweight, were more hypothermic, had greater maximum oxygen requirements in the first 12 h, were more likely to receive more than two doses of surfactant and had higher CRIB (clinical risk index for babies) scores. Although the babies who died were more likely to have received inotropes than survivors (75% vs. 26%), this treatment was always given after volume expansion had already been administered. Of the 16 ‘not inevitable’ deaths, 12 (75%) resulted from causes potentially associated with cardiovascular compromise, which could have been affected by postnatal derangement of fluid dynamics. However, they did not have significantly different lowest mean blood pressure or maximum base deficit. The authors concluded that administration of >or= 30 mL/kg volume expansion is associated with increased mortality in neonates of 27-28 weeks' gestation. The authors stressed that unless there is clear evidence of hypovolaemia, clinicians should exercise caution when prescribing volume expansion. It could be argued that this study is a hypothesis generator. The study also was strictly evaluating effects of volume expansion; however, it could be considered that inotropes may also be implicated in volume expansion, thus the results may also be applicable for dopamine. Newborns who received a higher amount of volume expansion therapy were more critically ill, thus confounding by disease cannot be ruled out. However, administration of an inappropriate amount of volume expansion remains a sound possibility with respect to adverse outcomes, and thus a contributary role of dopamine cannot be entirely ruled out.

In a prospectively recorded study collected from two level IV neonatal intensive care units (NICUs; St. Louis Children's Hospital, University of Virginia Children's Hospital) over a 5-year period (2012–2017) the authors demonstrated that infants who develop severe IVH have substantially more unstable BPs in the first week of life, in which infants with severe IVH have a consistent pattern of low BP initially followed by an "overshoot" and instability (Vesoulis et al, Pediatr Res. 2020 January ; 87(1): 69–73). It remains unclear as to where in this pattern severe IVH occurs. The authors state that clinical interventions such as the administration of intravenous fluids, inotropic agents, and postnatal corticosteroids introduce additional instability to the BP, creating the potential for therapeutic overshoot and possibly contributing to IVH risk. However, they also discuss that infants with good outcomes spend time outside of this narrow window, nearly 8% of the recording (approximately 14 h in the first week) on average. In a secondary analysis of this cohort, infants without exposure to inotropes spent an average of 4% of the recording (nearly 7 h) with an MABP ≥ 46 h mm Hg, suggesting that MABP values this high routinely occur as a part of the natural progression of the BP rather than from over-treatment. The authors conclude that persistent and prolonged hypotension or hypertension should be a warning sign prompting further investigation and possibly intervention. Follow-up studies with close attention to the discrete timing of IVH may offer the possibility of a therapeutic BP target. The role of inotropes in this phenomenon remains uncertain.

Another chart review study of all 156 ELBW infants admitted to their level III NICU in 1998 –1999 found a significant association between treated hypotension and grade III-IV IVH ($P < .016$), a longer hospital stay ($P < .002$), and death ($P < .013$) (Fanaroff et al Semin Fetal Neonatal Med 2006 Jun;11(3):174-81). Treated hypotension was significantly associated with a lower Bayley motor score at a corrected age of 20 months (69.9 < 15.3 vs 77.1 < 16.7; $P < .035$) and hearing loss (10.3% vs 1.3%; $P < .045$). Treated hypotension was not, however, associated with either Bayley mental scores at a corrected age of 20 months ($P < .220$) or cerebral palsy ($P < .565$). Controlling for maternal socioeconomic status and coexisting neonatal morbidity was performed. The authors also found that the smallest, least mature infants were most likely to have treated hypotension. In addition, the study did not control for degree of hypotension itself. Therefore, confounding by indication is also problematic in this study.

Review of published literature provided by the applicant

The applicant has identified 11 randomly controlled trials involving dopamine, two meta-analysis and 2 critical systematic reviews relevant to the use of dopamine to treat hypotension in premature neonates.

Published active controlled trials in hypotensive preterm infants

Reviews based on controlled trials

Cochrane review

Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242. DOI: 10.1002/14651858.CD001242

Dopamine was more effective than dobutamine in the short term treatment of systemic hypotension in preterm infants. All-cause mortality was numerically slightly higher with dopamine but no reliable conclusions were possible. There was no robust evidence for a differential effect on the incidence of adverse neuroradiological sequelae (severe periventricular haemorrhage and/or periventricular leucomalacia), or on the incidence of tachycardia. The authors concluded that in the absence of data

confirming long-term benefit and safety of dopamine compared to dobutamine, no firm recommendations can be made regarding the choice of drug to treat hypotension.

Dempsey EM and Barrington KJ Journal of Perinatology 2007; 27: 469 – 478 (49)

Conclusion of the authors:

The authors conclude that there is very little evidence to define an acceptable BP or that intervention in hypotensive infants is associated with improved long-term outcome and that even the contrary may be true.

Sassano-Higgins S. et al., Journal of Perinatology 2011; 31, 647–655 (50)

Meta-Analysis: dopamine

Dopamine increases BP (robust result), more so than dobutamine (less robust) and may be similar effective as epinephrine, CBF is increased in hypotensive (less robust) but not in normotensive infants and no difference in neurological outcome events could be detected between dopamine and other agents administered.

Individual controlled studies

Gill AB and Weindling AM, Archives of Disease in Childhood 1993; 69: 284-287

Comparator: Plasma protein fraction, N=39. Inclusion criterion for preterm infants: <1501g

There was a superior effect of dopamine vs. plasma protein fraction on BP in hypotensive preterm infants at a median dose. There was no significant difference in clinical outcome between the groups. The option for a cross over between the drugs investigated blurred the interpretation of the outcome data.

Greenough A , Emery EF (Eur J Pediatr. 1993 Nov;152(11):925-7)(32)

Comparator: Dobutamine N=40. 23 to 27 weeks GA.

Dopamine increased the BP more than dobutamine, no data on clinical outcome were provided

Roze JC et al., Archives of Disease in Childhood 1993; 69: 59-63(33)

Comparator: Dobutamine N=20. N = 20, < 32 weeks GA

Dopamine increased MABP and SVR, and decreased LVO. Dopamine increased MABP more than dobutamine. Dobutamine treatment was associated with an increase in LVO

Klarr JM et al., J Pediatr 1994;125:117-22)(34)

Comparator: Dobutamine. N=63 (out of 72 enrolled and randomized), ≤34 weeks with respiratory distress syndrome.

Dopamine was more effective than dobutamine in increasing MABP. No significant difference was found for adverse clinical outcome events.

Hentschel R et al., Biol Neonate. 1995;68(5):318-24 (35, only abstract available)

Comparator: Dobutamine N=20.

Dopamine and dobutamine were similar effective in raising MABP, both drugs raised intestinal perfusion.

Phillipos EZU et al., Pediatric research (1996; 39: 238A, published as abstract only) (36)

Comparator: Epinephrine N=20 “sick infants” >1750g.

Dopamine and epinephrine treatment were associated with a similar significant increase in MABP and a concomitant increase in mean pulmonary pressure.

Bourchier D, Weston PJ Archives of Disease in Childhood 1997; 76:F174 – F 178 37

Comparator: Hydrocortisone, N=40 < 34 weeks.

MABP increased in both groups, with a significantly higher increase in the hydrocortisone group.

Lundstrom K et al., Early Human Development 57 (2000) 157–16 (38)
Comparator: Volume N=36 < 33 weeks, MABP between 29 and 40 mmHg.

Dopamine was more effective than volume-expansion in increasing blood pressure; volume expansion and dopamine infusion increased left ventricular output equally; no effect on global cerebral blood flow could be demonstrated by either treatment

Ruelas-Orozco, G. and Vargas-Origel A. AMERICAN JOURNAL OF PERINATOLOGY; VOLUME 17: 2000 (39)

Comparator: Dobutamine N=66 1000g to 1500g. MAP < 30 mmHg

At a dose of 5 µg/kg/min numerically dopamine tended to have a better response on MABP than dobutamine.

Osborn D. et al., (J Pediatr 2002;140:183-9 (40)

Comparator: Dobutamine N=42. <30 weeks,

Dopamine and dobutamine had a differential effect on SVC flow. The increase in BP was more pronounced with dopamine, whereas SVC flow increased with dobutamine but not much with dopamine. No difference was observed for clinical outcome but due to low numbers of patients included and an cross over option, the data are to interpreted with caution.

Pellicer A et al Pediatrics 2005;115;1501 (41)

Comparator: Epinephrine N=60, <32 weeks or less than 1.5kg.

MBP, heart rate, CBV, and cerebral intravascular oxygenation increased from baseline throughout the study period, with no differences between groups except for a higher heart rate with epinephrine. Overall mortality rate was 15% (3 deaths in the dopamine group and 6 deaths in the epinephrine group)

Pellicer A., et al., PEDIATRICS 2009; 123: 1369 – 1376 (45)

Epinephrine N=60. <32 weeks or less than 1.5kg.

Long term follow-up study to Pellicer 2005. No difference in outcome was observed between dopamine and epinephrine. Severe IVH or PVHI was statistically more frequent only in infants who failed to normalize blood pressure according to protocol and needed rescue treatment. Some of these children had pressor-resistant hypotension. However, infants who normalized blood pressure with the initial study drug (i.e., dopamine or epinephrine) had outcomes comparable with those of controls when the most severe CUS diagnoses were considered. A multivariate analysis did not detect an association between final cranial ultrasound findings and the use of vasopressors/inotropes.

Valverde E. et al., PEDIATRICS 2006; 117: e1213 (42)

Comparator: Epinephrine N=60 <32 weeks or less than 1.5kg.

No difference was observed between dopamine and epinephrine regarding effects on MABP. Epinephrine infusion was associated with a greater chronotropic effect.

Filippi L. et al., Arch Dis Child Fetal Neonatal Ed 2007;92:367–371. (43)

Comparator: Dobutamine N=35 <1500g.

The necessary cumulative and mean administered dose, and the maximum infusion rate required to normalise MABP were significantly higher for the dobutamine group than the dopamine group ($p < 0.01$ for all).

Osborn A., et al., Pediatrics (2007) 120: 372–380 (only abstract available, 44)

Comparator: Dobutamine N=42. <30 weeks GA,

For infants treated with inotropes, no significant differences were found in clinical outcomes, except for reduced rates of late severe periventricular/intraventricular haemorrhage in the dobutamine group. At the 3-year follow-up there was a numerically lower rate of late severe periventricular/intraventricular haemorrhage in the dobutamine group. Infants in the dopamine group had significantly more disability and a lower Griffiths General Quotient. At the latest time measured, however, combined rates of death or disability were similar.

Rios DR. et al. J Pediatr. 2015; 166: 850–855 (46)

Comparator: Vasopressin N=20, GA of ≤30 weeks

The increase in BP was similar in both groups.

Studies supporting an indication for the Treatment of hypotension in haemodynamically unstable neonates, infants and children < 18 years

Systematic literature review on the administration of dopamine in cardiovascular instability over the whole paediatric age range

Dopamine for the treatment of Cardiovascular Instability in Paediatric Patients

The applicant provided a systematic literature review of the use of dopamine for the treatment of cardiovascular instability in paediatric patients, conducted in 2014 and updated 2022 with by repeating the search methods employed originally by 4 additional publications, two RCT's and two systematic reviews. A meta-analysis was not conducted due to the significant heterogeneity of the studies.

Sepsis

In the updated review (2014 – 2022), two double blind controlled trials comparing dopamine and epinephrine in patients with septic shock and one meta-analysis over three controlled trials were identified. The third study included in the Meta Analysis is analysed separately in addition. In the search up to 2014 a total of 75 articles were retrieved from the combined search with 29 articles presenting data on the use of dopamine in the paediatric population in the setting of hypotension or shock. These were predominantly retrospective series from single or multiple institutions, and all included patients in an ICU setting.

Traumatic Brain Injury

120 abstracts were identified, 3 Publications were considered in the Application, two in adult patients only, one retrospective cohort study.

Hypoxic Ischaemic Brain Injury

79 abstracts were identified, 4 were considered in this application and one review that essentially refers to one of the submitted studies only. One randomised placebo controlled double blind trial, on report of 4 cases, and one report on 22 newborn children.

Cardiac diseases

A total of 222 abstracts were identified of which 19 publications were included in the submission. Among these were 3 randomized controlled trials, and in addition observational studies supplemented by surveys on the use of inotropes in paediatric cardiosurgery.

Toxic effects and treatment after drug overdose

125 Abstracts were identified, of these 20 publications were submitted in the Application. There were no systematic reviews or randomised control trials. The majority are case reports, and case series, which describe dopamine administration in various different doses settings following ingestion of various different agents. A large number have occurred following clonidine ingestion, others including tricyclic antidepressant ingestion and some related to envenomation.

Summary of results of published key studies

Septic shock

Controlled randomized trials vs. Epinephrine

Ventura AM. Et al., Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock Critical Care Medicine 2015; 43: 2292-2302.

It was a Double-Blind Prospective Randomized Controlled single centre trial conducted in Brazil February 1, 2009, to July 31, 2013.

120 patients were evaluable, 63 on dopamine, 57 on epinephrine. Baseline characteristics and therapeutic interventions were largely similar. Small numerical imbalances were seen for age (Dopamine vs. Epinephrine): 39.6 (46.3) vs. 56.9 (58.2) months, and Pediatric Risk of Mortality (15.7 (10.4) vs. 13.3 (9.9)).

There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and 4 (7%) in the epinephrine group ($p = 0.033$). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1-37.8; $p = 0.037$) and healthcare-associated infection (HAI) (odds ratio, 67.7; 95% CI, 5.0-910.8; $p = 0.001$). Patients in the dopamine group also died significantly earlier during the course of the disease than those in the epinephrine group ($p = 0.047$). HAI occurred in 18 of 63 patients in the dopamine group (28.5%) and four of 57 patients in the epinephrine group (2.3%). Ventilator-associated pneumonia was the main site of infection and was diagnosed in 11 of 18 patients in the dopamine group and two of four patients in the epinephrine group.

Ramaswamy KN et al., Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock, (Pediatr Crit Care Med 2016; 17:e502–e512)

29 children were randomized to the epinephrine group and 31 to the dopamine group (all completers). Baseline characteristics were largely balanced including SOFA and PRISM III scores, with the exception of a numerical imbalance in age (Epinephrine vs. Dopamine) mean age 7 (1 – 11) vs. 4 (0.8 – 8) years.

Resolution of shock was achieved in 16 children (26.6%) within the first hour of resuscitation; 12 (41.4%) had received epinephrine and four (12.9%) dopamine as the first-line vasoactive therapy (p = 0.019). Resolution of shock in the first hour was more likely with epinephrine as compared to dopamine (OR, 4.8; 95% CI, 1.3–17.2). Achievement of normal systolic blood pressure, heart rate normal for age, and urine output was similar between both the groups.

The proportion of children who achieved resolution of shock within 6 hours of resuscitation was numerically higher in children who received epinephrine (48.3%) than dopamine (29%), (OR, 2.01; 0.7–5.7; p = 0.18). The day-28 all-cause mortality in the study cohort was 53.3% (32/60): 48.3% in epinephrine group and 58.1% in dopamine groups (RR, 0.83; 95% CI, 0.51–1.34; p = 0.605). No significant difference was observed between the two groups on survival analysis (log-rank p = 0.27).

Baske K et al., Epinephrine versus dopamine in neonatal septic shock: a double-blind randomized controlled trial. European Journal of Pediatrics 2018; 177: 1335–1342 (not included in the review as submitted by the applicant)

Patient characteristics were largely balanced: mean gestational age (epinephrine vs. Dopamine) 30.3 ± 3.4 vs. 30.7 ± 2.9 wks., Birth weight (g) 1100 (926, 1400) vs. 1181 (892, 1540). There were some imbalances in different outcome measures numerically favouring one or the other treatment. Mortality was numerically slightly in favour of epinephrine (n = 14 (70%) vs. n = 16 (80%).

Brain Injury Traumatic Brain Injury (TBI): T79.4 Traumatic Shock and T79.9 Unspecified early complication of trauma

Only one study with paediatric patients was identified

Retrospective cohort study of children 0-17 years old admitted to a level 1 trauma centre (between 2002 and 2007 with moderate-to-severe TBI who received a vasopressor to increase blood pressure. Eighty-two patients contributed data to the entire dataset. The most common initial medication was phenylephrine (57%) followed by dopamine (29%). Dopamine was administered in 24 patients aged 0-17 years and was associated with an increase in MAP and an increase in CPP. Vasopressor use varied by age. While there was no statistically significant difference in MAP or CPP between vasopressor groups, norepinephrine was associated with a numerical higher CPP and lower intracranial pressure at 3 h after start of vasopressor therapy compared to the other vasopressors examined.

Hypoxic Ischaemic Brain Injury

Diessa TG et al., The Journal of Paediatrics 1981; 99: 772-776 (51)

Fourteen severely asphyxiated infants were entered into a double-blind study designed to compare the effects of dopamine (2.5 /µg/kg/ minute) or placebo (dextrose in water). Systolic BP of at least 50mmHg was an inclusion criterion. Mean weight (kg) 2.96 ± 0.49 vs. 3.46 ± 0.34, Gestational age (wk) 41.1 ± 1.5 vs. 39.8 ± 0.89, 1-minute Apgar 1.7 ± 2 vs. 2.4 ± 3; 5-minute Apgar 3.1 ± 2.1 vs. 4.0 ± 2,2.

Echocardiographically determined shortening fraction and mean velocity of circumferential fibre shortening increased when compared to pre-infusion values (p < 0.05). There was no significant

change in these echo indices of cardiac function in the placebo-treated group. Systolic blood pressure rose in the dopamine group when compared to pre-dopamine infusion values and to the post infusion values of the placebo group (P less than 0.001 and 0.025, respectively). Diastolic blood pressure increased to a small degree in the dopamine group. There was no significant change in heart rate or echocardiographically measured systolic time intervals.

Walther FJ, et al., The Journal of Paediatrics 1985; 107: 781 – 785 (53)

In 22 newborn infants with left ventricular myocardial dysfunction diagnosed by M-mode echocardiography cardiac output was measured by pulsed Doppler echocardiography. 8 patients were hypotensive; cardiac output and stroke volume were low in 20. The abnormalities were more pronounced in infants with asphyxia. Six infants were given various doses of dopamine (4 to 10 µg/kg/min). Within 1 hour of therapy arterial blood pressure increased from 38 ± 9 mm Hg to 57 ± 7 mm Hg (P <0.001), cardiac output from 114 ± 26 ml/min/kg to 201 ± 39 ml/min/kg (P <0.001), and stroke volume from 0.80 ± 0.19 ml/kg to 1.26 ± 0.14 mi/kg (P <0.001). Heart rate rose slightly from 144 ± 6 to 159 ± 21 bpm (P <0.05). Myocardial contractility normalized within 1 hour; the other echocardiographic abnormalities normalized over 24 to 48 hours.

Cardiac disease

Three randomised trials were identified:

Laitinen P. et al., Amrinone Versus Dopamine-Nitroglycerin After Reconstructive Surgery for Complete Atrioventricular Septal Defect. Journal of Cardiothoracic and Vascular Anesthesia, 1997; 11: 1997: 870-874

Thirty-two infants with complete atrioventricular septal defect were included. Amrinone loading dose, 2 mg/kg, followed by a maintenance infusion, 7.5 µg/kg/min, was given to 17 infants before separation from cardiopulmonary bypass. The remaining 15 patients received a combination of dopamine, 5 µg/kg/min, and nitroglycerin, 1 microgram/kg/min. The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass.

Amrinone provided a higher cardiac output, more favourable oxygen dynamics, and lower pulmonary vascular resistance than a combination of dopamine and nitroglycerin.

Laitinen P. et al., Amrinone Versus Dopamine and Nitroglycerin in Neonates After Arterial Switch Operation for Transposition of the Great Arteries. Journal of Cardiothoracic and Vascular Anesthesia, Vo113, No 2 (April), 1999: pp 186-190. (63)

Thirty-five neonates with transposition of the great arteries participated. A loading dose of amrinone, 2 mg/kg, followed by a maintenance infusion of 7.5 µg/kg/min, was administered to 16 neonates before separation from cardiopulmonary bypass. The remaining 19 patients were administered a combination of dopamine, 5 µg/kg/min, and nitroglycerin, 1 µg/kg/min. The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass. Open-label epinephrine infusion was administered in both groups as required.

With the dosage regimen used, supplemented with epinephrine, amrinone provided a higher cardiac output and more favourable oxygen dynamics than a combination of dopamine and nitroglycerin.

Booke PD et al., Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. British Journal of Anaesthesia 1995; 74: 419-42

Blinded, three-period, two-treatment, crossover design study in 19 children, aged 2-54 months, requiring high-dose inotropic support after cardiac surgery, given either dopamine or dobutamine at a dose of 7.5-20 ug/kg/min, respectively.

Dobutamine and dopamine were equipotent inotropes. In five children given neither enoximone nor phenoxybenzamine, dopamine, in a dose of 7.5 ug/kg/min or more, produced significant mean increases in PAP and PVRI (P = 0.04), compared with the same dose of dobutamine. The investigators decided not to continue with this dose regimen due to this observation.

Toxicology and administration after overdose of drugs

The following studies were provided:

Clonidine overdose

Articles by Connor, Artmann, Deutsch, Fiser and Gitter are only provided as abstracts by the applicant. In the Article by Anderson, no paediatric patient was treated with dopamine.

Olsson reported one 25-month-old girl, where administration of dopamine at a rate of 5 to 7 ug/kg/min was associated with a prompt increase and stabilization of blood pressure. Another 44 month old boy was successfully treated with norepinephrine.

Caravati described a successful administration of dopamine at 5 µg/kg/min with weaning over 6 hours in a 9 month old boy.

Calcium channel inhibitor overdose

Passal et al (Pediatrics Vol. 73 No. 4 April 1984 543 – 545) described a patient with verapamil overdose that after administration of phenobarbital and other drugs became hypotensive. Neither Isoproterenol nor dopamine (13µg/kg/min) alone, but a combination thereof stabilized blood pressure.

Ramoska et al (Ann Emerg Med February 1993;22:196-200) described that dopamine was effective in increasing the BP in 10 patients with no effect on conduction or heart rate. It is unclear, how many paediatric patients were among these 10 and which doses were administered.

Hydroxychloroquine overdose

The article by de Jong-Strakova (Ned Tijdschr Geneeskd; 1990 Dec 15;134(50):2445-6) is provided as abstract by the applicant. It is not clear, whether paediatric patients treated with dopamine are described in the article.

Scorpion stings

Administration of dopamine (standard dose 5 – 10 µg/kg/min) + insulin was described as being successful in stabilising blood pressure in 3 cases, dopamine was not successful in 1 case. The time course of BP stabilization is not specified in the article, in one case stabilization within 10 hours was mentioned. (Murthy et al., Annals of Tropical Medicine & Parasitology 1991, 85:6, 651-657).

No details were provided on the circumstances of administration of dopamine in paediatric patients, two of which died in the publication by Bawaskar et al. (Indian Pediatrics 2003; 40:1072-1081).

Prophylactic administration in patients on barbiturate therapy

No conclusions can be drawn from the publication provided (Oda et al., No Shinkei Geka 1992 Dec;20(12):1241-6)

Cyclobenzaprine (CBP) overdose

In a chart review of 402 pure CBP ingestions no patients < 10 years had hypotension, of those > 10 years 5 had hypotension, 2 were treated with dopamine. Age range and doses are not reported. (Spiller et al.; The Journal of Emergency Medicine 1995, Vol 13 No 6; 781-785)

Tiagabine overdose

Reference was made to 1 out of 2 patients being treated with dopamine (4% of 57 patients identified). No information is available on age, dose, and success of treatment (Spiller et al., Clinical Toxicology 2005, 43:7, 855-859).

Bupropione overdose

A case report is presented (Shenoi et al. Pediatr Emer Care 2011;27: 43Y45) where dopamine up to 15 µg/kg/min was administered in concert with norepinephrine and epinephrine in an 11 month old boy. Only after initiation of ECMO the clinical status improved. No conclusions can be drawn on efficacy from this study.

2.7.5.3. In vitro biomarker test for patient selection for efficacy

N/A

2.7.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

For pooled analyses and meta-analyses see discussion above in the context of the different clinical entities.

2.7.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Rationale to provide an age appropriate standardized formulation.

The applicant outlined several inherent problems with using the adult formulation to be diluted for the paediatric use as a reason for the development of a ready-to-use paediatric formulation. The applicant has provided an overview over literature indicating that a standardized age appropriate ready to use solution of dopamine could provide a contribution to reduce mistakes, medication errors and issues associated with non-sterile preparation of solution in the intensive care unit. While all these issues are acknowledged formulation/dilution related issues were not reported in the HIP study when using the adult formulation in the investigational group.

Posology

A dose range of 5 to 20 µg/kg/min IV has been proposed for neonates including preterm infants. The recommended dose range in the SmPC is 5 – 10 µg/kg/min with a proposed starting dose of 5 µg/kg/min. Doses above 10 µg/kg/min up to a maximum of 20 microgram/kg/min may be administered if considered justified. Information relevant for dose selection can be derived from PD considerations, the pivotal HIP trial and from the literature submitted, including randomized clinical trials, observational studies, meta-analyses and case reports.

Therapeutic indications

The application concerns the treatment of hypotension/shock in the paediatric population covering the whole age range from term newborn infants and children and adolescents up to 17 years of age.

The study report of a pivotal study (HIP trial) including a substudy (CAR) was provided to support a claim for the treatment of preterm infants, accompanied by a literature search on published studies available.

In order to provide additional data on B/R, the applicant proposed a post authorization efficacy study (PAES) to be conducted after approval. A synopsis of the study protocol was submitted for review.

Hypotension in preterm infants

HIP trial, Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn

It was a pragmatic, multinational, randomised trial of two different strategies for the management of hypotension in ELGAN infants (An observational approach with placebo approach versus Standard with dopamine) in preterm infants GA at birth from 23 – 28 weeks with evidence of hypotension defined as MABP at lese 1 mmHg below GA.

Two treatment approaches were compared, that included a comparison of dopamine 5µg/kg/min to a maximum dose of 20µg/kg/min vs. dextrose 5% (placebo) by allowing different levels of MABP with epinephrine 0.1 µg/kg/min up to a dose of 0.4 µg/kg/min as rescue therapy per protocol.

Co-primary endpoints:

- Survival free of neurodisability at 2 years corrected GA.

- Survival to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultrasound.

Initially a sample size of 830 infants in total to ensure 385 evaluable infants per group was planned. Following challenges in recruitment the planned sample size was downscaled to overall 454 infants. The study was stopped prematurely after 58 infants were randomized due to recruitment difficulties. The observation that not randomized normo- compared to randomized hypotensive patients did not show a difference in IVH added to concerns that the entry criterion of hypotension and its treatment may not be a main factor determining outcome in the study population as selected. This added to the decision to stop the trial.

CAR substudy

As part of HIP, a prospective cohort study of blinded cerebral regional oxygen saturation values (rScO2), was conducted.

53 infants were normotensive and 36 hypotensive who were randomized to either placebo or dopamine. Of those, 13 received dopamine and 16 received placebo.

Review of published literature

The applicant has identified 11 randomly controlled trials involving dopamine, two meta-analyses and 2 critical systematic reviews relevant to the use of dopamine to treat hypotension in premature neonates.

Overall, the design of the studies as planned was appropriate. For the published literature BP thresholds and target BP values were not in line with criteria generally applied today. Probably a

relevant number of patients included in these studies would not have received catecholamines or even fluids today in order to increase BP.

Dopamine for the treatment of Cardiovascular Instability in Paediatric Patients

The applicant provided a systematic literature review of the use of dopamine for the treatment of cardiovascular instability in paediatric patients, conducted in 2014 and updated 2022 by 4 additional publications, two RCT's and two systematic reviews. A meta-analysis was not conducted due to significant heterogeneity of the studies.

Sepsis

In the updated review (2014 – 2022), two double blind controlled trials comparing dopamine and epinephrine in patients with septic shock and one meta-analysis over three controlled trials were identified. The third study included in the Meta Analysis is analysed separately in addition. In the search up to 2014 a total of 75 articles were retrieved from the combined search with 29 articles presenting data on the use of dopamine in the paediatric population in the setting of hypotension or shock. These were predominantly retrospective series from single or multiple institutions, and all included patients in an ICU setting. Additional observational studies published after the initial submission were provided during the ongoing procedure.

Traumatic Brain Injury

120 abstracts were identified, 3 Publications were considered in the Application, two in adult patients only, one retrospective cohort study.

Hypoxic Ischaemic Brain Injury

79 abstracts were identified, 4 were considered in this application and one review that essentially refers to one of the submitted studies only. One randomized placebo controlled double blind trial, one report of 4 cases, and one report on 22 new-born children.

Cardiac diseases

A total of 222 abstracts were identified of which 19 publications were included in the submission. Among these were 3 randomized controlled trials, and in addition observational studies supplemented by surveys on the use of inotropes in paediatric cardiosurgery.

Toxic effects and treatment after drug overdose

125 Abstracts were identified, of these 20 publications were submitted in the Application. There were no systematic reviews or randomised control trials. The majority are case reports and case series, which describe dopamine administration in various different doses settings following ingestion of various agents. A large number have occurred following clonidine ingestion, others including tricyclic antidepressant ingestion and some related to envenomation.

Overall, the methodology to identify and select publications was appropriate.

Current clinical practice

In the EMA scientific advice in 2019 the applicant was advised to provide an overview and discussion about the common clinical practice in most relevant EU centres, including several countries covering EU heterogeneity. Such an overview was not included in the provided documentation. The applicant claims that a large number of observational studies highlight that dopamine has been and continues to be the first line agent used, but this cannot be considered sufficient. A thorough overview was not provided upon request. A feasibility assessment initiated by the EMA revealed that a study in the DARWIN EU associated databases would not reveal reliable results.

GCP issues

HIP trial

A request for a routine GCP inspection has been adopted for the HIP study and two study cites and the sponsor site were inspected (Management of Hypotension In the Preterm: A multi-centre randomised, controlled trial of hypotension management in the extremely low gestational age newborn, Protocol number: 2010-023988-17). An integrated inspection report has been provided (EMA/IN/0000123873) dated 09-06-2023 the revealed major deficiencies at the two study cites but no critical issue. Several critical issues were however identified at the sponsor site.

Ultimately, considering also that the HiP trial was inconclusive for the primary endpoints, the applicant decided to not pursue the authorisation specifically for the population of ELGANs and therefore, since there were no other studies included in this dossier and conducted by the same sponsor, the inspection findings do not have an impact on the benefit-risk balance.

Published literature

An in depth assessment of GCP compliance for the publications submitted is not possible. In newer publications usually approval by the respective ethics committees or adherence to the respective standards was mentioned.

Proposed Post–approval efficacy study (PAES)

The applicant has provided during the assessment a revised protocol for the proposed PAES in order to address some of the concerns raised. Since an application for ELGANs was no longer pursued, a PAES in this group of patients is no requirement.

Efficacy data and additional analyses

Posology

A justification has been provided for the proposed dose range of 5 – 20 µg/kg/min (preterm/neonates) and for the dose range of 5 – 20 µg/kg/min in the overall population.

For preterm infants, the starting dose in the HIP study was 5 µg/kg/min up to a maximum dose of 20 µg/kg/min. No data have been provided for starting doses below 5 µg/kg/min. A concept of using lower starting doses based on the assumption that it might improve renal function is not well supported by data. In clinical studies in preterm infants renal function and urine output were not reliably increased by dopamine (Dempsey EM and Barrington KJ. J Perinatol 2007; 27: 469-478; Prins I. et al., Intensive Care Med 2001; 27: 206-210). Furthermore, some studies suggest that in preterm infants doses above 10 µg/kg/min do not mediate a relevant additional effect on MABP. In the study of Klarr JM et al., (J Pediatr 1994; 125: 117-22) 97% of the preterm children had a treatment success (based on BP criteria) at a dose of < 10 µg/kg/min, indicating that higher doses may not add much on efficacy. Similarly, in the study of Osborn D. et al., (J Pediatr 2002; 140: 183-9) little of an effect was observed when the dose of dopamine was increased from 10 to 20 µg/kg/min. For this reason, in some studies, the maximal dose investigated was 10µg/kg/min (e.g. Ruelas-Orozco, G. and Vargas-Origel A. American Journal of perinatology, 2000; 17).

Similarly, in most of the studies provided in the literature review for the whole range of paediatric patients (e.g. septic shock, toxic situations and drug overdose, cardiac conditions including cardiac surgery) higher starting doses than 0.5 µg/kg/min were investigated. Although in a number of the studies doses up to 20 µg/kg/min were used, administration of doses higher than 10 µg/kg/min have been challenged. Booke et al., (British Journal of Anaesthesia 1995; 74: 419-42) described

unfavourable effects of dopamine (doses from 7.5 µg/kg/min) vs. Dobutamine on pulmonary haemodynamics in paediatric patients in the context of cardiac surgery. E.g. in the review by Irazuzta J., (J Pediatr (Rio J). 2007;83(2 Suppl):S36-45) cited by the applicant that refers to variable responses and adverse events it is recommended to initiate dopamine at 5 µg/kg/min and not to exceed 10 µg/kg/min.

The applicant has modified the proposed dose range in as such that 5 – 10 µg/kg/min is the standard target dose and higher doses up to 20 µg/kg/min can be administered if justified in an individual patient.

Hypotension in preterm infants

HIP study (main results)

29 patients were analysed in each group, the patient characteristics were overall balanced.

There was no statistically significant difference between the active and control arms in the co-primary end-point of survival free of neurodevelopmental disability at 2 years adjusted GA (48.1% in the dopamine group compared to 25.0% in the placebo arm, OR 2.79 (0.89-1.71, p value 8.72). The mean Bayley scores all trended towards dopamine, but outside the boundary of statistical significance (Cognitive, Language, Motor Bayley scores at age 2 years dopamine vs. placebo, n =17 – 19, mean (SD): 89.47 (18.10) vs. 84.33 (19.90) p = 0.398; 85.24 (21.55) vs. 82.33 (20.59) p = 0.675; 86.47 (21.04) vs. 82.89 (19.87), p = 0.874)

The co-primary outcome of survival free of ultrasound abnormality at 36 weeks was reached by 18/29 (62%) in the dopamine group and by 20/29 (69%) in the placebo group (OR 0.74, 95% CI 0.25 to 2.18).

Changes in mean BP from 0 to 2hours differed between the placebo and dopamine groups (p=0.028 for group × time interaction). The largest difference between the two groups was at 30 min (difference in means 4.4, 95% CI 1.8 to 7.1, p=0.001). Additional BP support was used less frequently in the standard group (11/29, 38%) compared with the restrictive group (19/29, 66%) (p=0.038).

In the study report (p 63), it is stated that "*Among infants <26 weeks of gestation, this [administration of additional inotropes] difference was most marked (11% vs 63%, p=0.002)*". The corresponding data, however, seem not to have been provided.

No significant difference was observed for secondary outcome measures (Dopamine vs. Placebo, n (%), Odds ratio (95%CI, p value): Mortality: 6 (21) vs. 7 (24) OR 0.82 (0.24 to 2.83) p= 0.75, Severe ultrasound abnormality: 5 (17) vs. 5 (17) OR 1.00 (0.26 to 3.91) p = 1, Grade 3/4 IVH: 5 (17) vs. 2 (7) OR 3.06 (0.51 to 18.41) p = 0.22, PVL: 2 (7) vs.2 (7)OR 1.04 (0.13 to 8.37) p = 0.97; Any ultrasound abnormality: 16 (55) vs. 13 (45) OR 1.51 (0.54 to 4.26) p = 0.43; NEC: 1 (3) vs. 4 (14) OR 0.22 (0.02 to 2.13) p = 0.19; SIP 3: (10) vs. 3 (10) OR 1.00 (0.18 to 5.42) p = 1; BPD*: 17 (74) vs.14 (64) OR 1.87 (0.45 to 7.68) p = 0.39; Duration of inotrope (hours) (n = 21 and 22): 17.8 (7.5–30.6) vs. 13.7 (6.1–24.5) OR 1.46 (0.84 to 2.56) p = 0.18; Any intervention: 11 (38) vs.19 (66) OR 0.32 (0.11 to 0.94) p = 0.038 *Of those who had survived to 36 weeks

BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leucomalacia; SIP, spontaneous intestinal perforation

The time points of the assessment of secondary endpoints is provided for mortality and ultrasound abnormality (36 wks GA) and for BPD (those that survived 36 wks GA) in the study report but the time points of the assessment of some other secondary endpoints are not entirely clear. Upon request, the applicant has specified the assessment time for some but not for all secondary endpoints. Considering

that the HIP study has not provided robust evidence of efficacy or lack thereof, the issue is not further pursued.

The applicant has clarified that SNAP-II/SNAPPE-II scores as predictors of mortality and morbidity were not used in the HIP trial due to practicability reasons.

The results of the pivotal HIP study are inconclusive and do not support the administration of dopamine. Neither of the two co-primary endpoints showed a statistically significant effect in favour of one or the other treatment strategy and it is neither possible to conclude on superiority nor on non-inferiority. The applicant has removed reference to preterm infants in the indication and reference in the posology to infants below a body weight of 2.0 kg.

CAR substudy

25 hypotensive (study drug received) and 26 non-hypotensive (no study drug) patients were included. The respective associations between duration of cerebral hypoxia (defined as rScO2 < 63%1) and of MABP at days 1, 2, and 3, with IVH or Mortality at day 7 in the entire group of patients including those with and without MABP below GA in the first 72 hours was investigated. NIRS below 63% at day 1, 2, and 3 was significantly associated with IVH or mortality. For MABP such an association was only found for day 1. GA at birth was also associated with IVH or Mortality at day 7.

Duration of cerebral hypoxia (defined as rScO2 < 63%1) was predictive of early intraventricular haemorrhage or death with an odds ratio of 1.036 (95% CI 1.004 to 1.069) P=.026 if calculated with a univariate logistic regression analysis. Both, the robustness and the relevance of the result is unclear. An OR of 1.036 is close to 1.00. In addition, no statistically significant result was found with a bivariate logistic regression corrected for GA. The time range of measurement of cerebral hypoxia is not stated in the study report.

The analyses for the association between cerebral hypoxia, MABP and other factors with clinical endpoints are based on a composite endpoint of mortality and IVH. Exploratory analyses differentiating between IVH and mortality were provided upon request and indicated consistent results.

Autoregulatory capacity was estimated to have generally remained intact within a range of about 30 to 40 mmHg. For uninjured babies, BP below 30 coincided with a reduced autoregulation as indicated by an increase in TF-Gain. For injured babies their TF-Gain appeared to improve at lower blood pressure levels.

In hypotensive extremely preterm infants, dopamine increased MABP but had no significant effect on rScO2 or TF gain compared to placebo in a time frame of 2 h following administration of the study drug.

Upon request the applicant explained that the threshold for rScO2 of < 63% is generally excepted and inherent to the method used.

In summary, the data indicate that dopamine had no effect on rScO2 compared to placebo in hypotensive infants. Hypotension and cerebral hypoxia were associated with early intraventricular haemorrhage or death.

Only high level results and conclusions from controlled trials and of single selected uncontrolled studies are summarized here. For a more detailed assessment of all key studies submitted see above.

Published active controlled trials in hypotensive preterm infants

Reviews based on controlled trials

Cochrane review

Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD001242. DOI: 10.1002/14651858.CD001242

Dopamine was more effective than dobutamine in the short term treatment of systemic hypotension in preterm infants. All-cause mortality was numerically slightly higher with dopamine but no reliable conclusions were possible. There was no robust evidence for a differential effect on the incidence of adverse neuroradiological sequelae (severe periventricular haemorrhage and/or periventricular leucomalacia), or on the incidence of tachycardia. The authors concluded that in the absence of data confirming long-term benefit and safety of dopamine compared to dobutamine, no firm recommendations can be made regarding the choice of drug to treat hypotension.

Dempsey EM and Barrington KJ Journal of Perinatology 2007; 27: 469 – 478 (49)

Conclusion of the authors:

Based on their review of literature the authors conclude that there is very little evidence to define an acceptable BP or that intervention in hypotensive infants is associated with improved long-term outcome and that even the contrary may be true.

Sassano-Higgins S. et al., Journal of Perinatology 2011; 31, 647–655 (50)

The key results of the Meta-Analysis were: Dopamine increases BP (robust result), more so than dobutamine (less robust) and may be similar effective as epinephrine. CBF is increased in hypotensive (less robust) but not in normotensive infants and no difference in neurological outcome events could be detected between dopamine and other agents administered.

Individual controlled studies

Gill AB and Weindling AM, Archives of Disease in Childhood 1993; 69: 284-287

Comparator: Plasma protein fraction, N=39. Inclusion criterion for preterm infants: <1501g

There was a superior effect of dopamine vs. plasma protein fraction on BP in hypotensive preterm infants at a median dose. There was no significant difference in clinical outcome between the groups. The option for a cross over between the drugs investigated blurred the interpretation of the outcome data.

Greenough A , Emery EF (Eur J Pediatr. 1993 Nov;152(11):925-7)(32)

Comparator: Dobutamine N=40. 23 to 27 weeks GA.

Dopamine increased the BP more than dobutamine, no data on clinical outcome were provided.

Roze JC et al., Archives of Disease in Childhood 1993; 69: 59-63(33)

Comparator: Dobutamine N=20. N = 20, < 32 weeks GA

Dopamine increased MABP and SVR, and decreased LVO. Dopamine increased MABP more than dobutamine. Dobutamine treatment was associated with an increase in LVO

Klarr JM et al., J Pediatr 1994;125:117-22)(34)

Comparator: Dobutamine. N=63 (out of 72 enrolled and randomized), ≤34 weeks with respiratory distress syndrome.

Dopamine was more effective than dobutamine in increasing MABP. No significant difference was found for adverse clinical outcome events.

Hentschel R et al., Biol Neonate. 1995;68(5):318-24 (35, only abstract available)

Comparator: Dobutamine N=20.

Dopamine and doputamine were similar effective in raising MABP, both drugs raised intestinal perfusion.

Phillipos EZU et al., Pediatric research (1996; 39: 238A, published as abstract only) (36)

Comparator: Epinephrine N=20 “sick infants” >1750g.

Dopamine and epinephrine treatment were associated with a similar significant increase in MABP and a concomitant increase in mean pulmonary pressure.

Bourchier D, Weston PJ Archives of Disease in Childhood 1997; 76:F174 – F 178 37

Comparator: Hydrocortisone, N=40 < 34 weeks.

MABP increased in both groups, with a significantly higher increase in the hydrocortisone group.

Lundstrom K et al., Early Human Development 57 (2000) 157–16 (38)
Comparator: Volume N=36 < 33 weeks, MABP between 29 and 40 mmHg.

Dopamine was more effective than volume-expansion in increasing blood pressure; volume expansion and dopamine infusion increased left ventricular output equally; no effect on global cerebral blood flow could be demonstrated by either treatment.

Ruelas-Orozco, G. and Vargas-Origel A. AMERICAN JOURNAL OF PERINATOLOGY; VOLUME 17: 2000 (39)

Comparator: Dobutamine N=66 1000g to 1500g. MAP < 30 mmHg

At a dose of 5 µg/kg/min numerically dopamine tended to have a better response on MABP than dobutamine.

Osborn D. et al., (J Pediatr 2002;140:183-9 (40)

Comparator: Dobutamine N=42. <30 weeks,

Dopamine and dobutamine had a differential effect on SVC flow. The increase in BP was more pronounced with dopamine, whereas SVC flow increased with dobutamine but not much with dopamine. No difference was observed for clinical outcome but due to low numbers of patients included and an cross over option, the data are to interpreted with caution.

Pellicer A et al Pediatrics 2005;115;1501 (41)

Comparator: Epinephrine N=60, <32 weeks or less than 1.5kg.

MBP, heart rate, CBV, and cerebral intravascular oxygenation increased from baseline throughout the study period, with no differences between groups except for a higher heart rate with epinephrine. Overall mortality rate was 15% (3 deaths in the dopamine group and 6 deaths in the epinephrine group)

Pellicer A., et al., PEDIATRICS 2009; 123: 1369 – 1376 (45)

Epinephrine N=60. <32 weeks or less than 1.5kg.

Long term follow-up study to Pellicer 2005. No difference in outcome was observed between dopamine and epinephrine. Severe IVH or PVHI was statistically more frequent only in infants who failed to normalize blood pressure according to protocol and needed rescue treatment. Some of these children had pressor-resistant hypotension. However, infants who normalized blood pressure with the initial study drug (i.e., dopamine or epinephrine) had outcomes comparable with those of controls when the most severe CUS diagnoses were considered. A multivariate analysis did not detect an association between final cranial ultrasound findings and the use of vasopressors/inotropes.

Valverde E. et al., PEDIATRICS 2006; 117: e1213 (42)

Comparator: Epinephrine N=60 <32 weeks or less than 1.5kg.

No difference was observed between dopamine and epinephrine regarding effects on MABP. Epinephrine infusion was associated with a greater chronotropic effect.

Filippi L. et al., Arch Dis Child Fetal Neonatal Ed 2007;92:367–371. (43)

Comparator: Dobutamine N=35 <1500g.

The necessary cumulative and mean administered dose, and the maximum infusion rate required to normalise MABP were significantly higher for the dobutamine group than the dopamine group ($p < 0.01$ for all).

Osborn A., et al., Pediatrics (2007) 120: 372–380 (only abstract available, 44)

Comparator: Dobutamine N=42. <30 weeks GA,

For infants treated with inotropes, no significant differences were found in clinical outcomes, except for reduced rates of late severe periventricular/intraventricular haemorrhage in the dobutamine group. At the 3-year follow-up there was a numerically lower rate of late severe periventricular/intraventricular haemorrhage in the dobutamine group. Infants in the dopamine group had significantly more disability and a lower Griffiths General Quotient. At the latest time measured, however, combined rates of death or disability were similar.

Rios DR. et al. J Pediatr. 2015; 166: 850–855 (46)

Comparator: Vasopressin N=20, GA of ≤30 weeks

The increase in BP was similar in both groups.

The results of the published studies can be summarized as follows: No robust comparative data on short term and long term clinical outcome are available in the published literature. BP thresholds and target values often were not line with values applied today. Many of the children may not have received catecholamine treatment today or even treatment with fluids. This does not generally invalidate the observation of an increase in BP but adds to the uncertainties of how to define the appropriate patient population to be treated with catecholamines, how to guide treatment and which vasoactive drug to select.

Systematic literature review on the administration of dopamine in cardiovascular instability over the whole paediatric age range

Septic shock

Controlled randomized trials vs. epinephrine

Ventura AM. Et al., Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock Critical Care Medicine 2015; 43: 2292-2302.

It was a Double-Blind Prospective Randomized Controlled single centre trial conducted in Brazil February 1, 2009, to July 31, 2013.

120 patients were evaluable, 63 on dopamine, 57 on epinephrine. Baseline characteristics and therapeutic interventions were largely similar. Small numerical imbalances were seen for age (Dopamine vs. Epinephrine): 39.6 (46.3) vs. 56.9 (58.2) months, and Pediatric Risk of Mortality (15.7 (10.4) vs. 13.3 (9.9)).

There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and 4 (7%) in the epinephrine group (p = 0.033). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1-37.8; p = 0.037) and healthcare-associated infection (HAI) (odds ratio, 67.7; 95% CI, 5.0-910.8; p = 0.001). Patients in the dopamine group also died significantly earlier during the course of the disease than those in the epinephrine group (p = 0.047). HAI occurred in 18 of 63 patients in the dopamine group (28.5%) and four of 57 patients in the epinephrine group (2.3%). Ventilator-associated pneumonia was the main site of infection and was diagnosed in 11 of 18 patients in the dopamine group and 2 of 4 patients in the epinephrine group.

Ramaswamy KN et al., Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock, (Pediatr Crit Care Med 2016; 17:e502–e512)

29 children were randomized to the epinephrine group and 31 to the dopamine group (all completers). Baseline characteristics were largely balanced including SOFA and PRISM III scores, with the exception of a numerical imbalance in age (Epinephrine vs. Dopamine) mean age 7 (1 – 11) vs. 4 (0.8 – 8) years.

Resolution of shock was achieved in 16 children (26.6%) within the first hour of resuscitation; 12 (41.4%) had received epinephrine and four (12.9%) dopamine as the first-line vasoactive therapy (p = 0.019). Resolution of shock in the first hour was more likely with epinephrine as compared to dopamine (OR, 4.8; 95% CI, 1.3–17.2). Achievement of normal systolic blood pressure, heart rate normal for age, and urine output was similar between both the groups.

The proportion of children who achieved resolution of shock within 6 hours of resuscitation was numerically higher in children who received epinephrine (48.3%) than dopamine (29%), (OR, 2.01; 0.7–5.7; p = 0.18). The day-28 all-cause mortality in the study cohort was 53.3% (32/60): 48.3% (14/29) in the epinephrine group and 58.1% (18/31) in dopamine group (RR, 0.83; 95% CI, 0.51–1.34; p = 0.605). No significant difference was observed between the two groups on survival analysis (log-rank p = 0.27).

Baske K et al., Epinephrine versus dopamine in neonatal septic shock: a double-blind randomized controlled trial. European Journal of Pediatrics 2018; 177: 1335–1342 (not included in the review as submitted by the applicant)

Patient characteristics were largely balanced: mean gestational age (epinephrine vs. Dopamine) 30.3 ± 3.4 vs. 30.7 ± 2.9 wks., Birth weight (g) 1100 (926, 1400) vs. 1181 (892, 1540). There were some imbalances in different outcome measures numerically favouring one or the other treatment. Mortality was numerically slightly in favour of epinephrine (n = 14 (70%) vs. n = 16 (80%).

In response to the MO an additional study was cited in septic shock in preterm infants.

Nissimov S et al., European Journal of Pediatrics 2023; 182:1029–1038.

It was a retrospective cohort study over 10 years at two tertiary neonatal units. Preterm infants born < 35 weeks post-menstrual age (PMA), who received DA or NE as primary therapy for hypotension during sepsis, defined as culture-positive or culture-negative infections or necrotising enterocolitis (NEC), were included. Episode-related mortality (< 7 days from treatment), pre-discharge mortality, and major morbidities among survivors were compared between two groups. Analyses were adjusted using the inverse probability of treatment weighting estimated by propensity score.

A total of 156 infants were included, 113 received DA and 43 NE. The mean ± SD PMA at birth and at treatment for the DA and NE groups were 25.8 ± 2.3 vs. 25.2 ± 2.0 weeks and 27.7 ± 3.0 vs. 27.1 ± 2.6 weeks, respectively (p > 0.05). Pre-treatment, the NE group had higher mean airway pressure (14 ± 4 vs. 12 ± 4 cmH2O), heart rate (185 ± 17 vs. 175 ± 17 beats per minute), and median (IQR) fraction of inspired oxygen [0.67 (0.42, 1.0) vs. 0.52 (0.32, 0.82)] (p < 0.05 for all).

After propensity score adjustment, NE was associated with lower episode-related mortality [adjusted odds ratio (95% CI) 0.55 (0.33, 0.92)], pre-discharge mortality [0.60 (0.37, 0.97)], post-illness new diagnosis of significant neurologic injury [0.32 (0.13, 0.82)], and subsequent occurrence of NEC/sepsis among the survivors [0.34, (0.18, 0.65)].

Kohn-Loncarica et al., 2020, Revista Brasileira de Terapia Intensiva 32(4):551-556.

Objective: To analyse the clinical outcome of children with fluid-refractory septic shock initially treated with dopamine or epinephrine.

Methods: A retrospective cohort study was conducted at a paediatric emergency department of a tertiary hospital.

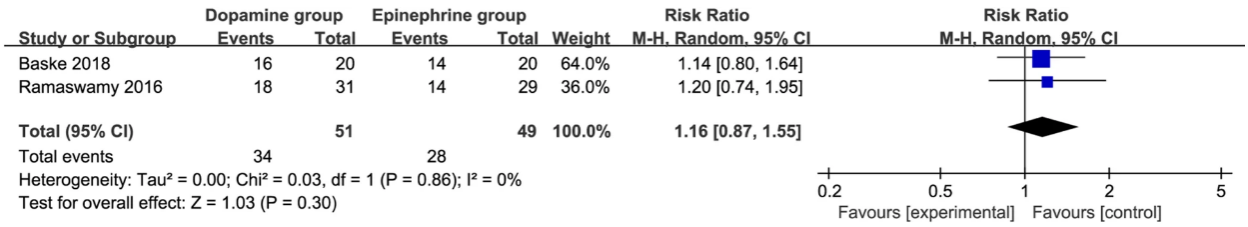
Population: children admitted because of fluid-refractory septic shock. Clinical outcome was compared between two groups: Dopamine and Epinephrine.

Results: 118 patients were included. The groups were not well balanced. The group that received dopamine more often had underlying disease (p = 0.032) or oncological disease (p = 0.007), treatment with immunosuppressants (p = 0.003), and positive blood cultures (p = 0.04).

A total of 58.5% received dopamine and 41.5% received epinephrine. The rate of invasive mechanical ventilation was 38.8% for epinephrine versus 40.6% for dopamine (p = 0.84), with a median of 4 days for the Epinephrine Group and 5.5 for the Dopamine Group (p = 0.104). Median time of inotropic therapy was 2 days for both groups (p = 0.714). Median hospital stay was 11 and 13 days for the Epinephrine and Dopamine groups, respectively (p = 0.554), and median stay in intensive care was 4 days (0 - 81 days) in both groups (p = 0.748). Mortality was 5% for the Epinephrine Group versus 9% for the Dopamine Group (p = 0.64). After exclusion of patients with oncological diseases, the negative imbalance favouring epinephrine with respect to mortality disappeared.

Despite of the numerically higher mortality in the dopamine treated patients it is concluded that due to the retrospective design and the differences in patient characteristics at baseline, the study does not allow drawing robust conclusions, neither on the presence or the absence of a signal of concern regarding mortality and clinical outcome when comparing dopamine and epinephrine.

A Meta analysis of Wen et al 2020 (Italian Journal of Pediatrics (2020) 46:6) refers to the studies discussed above. For mortality the following analysis is provided with a numerical imbalance in favour of epinephrine over dopamine:



Forest plot for the meta-analysis of mortality

Numerically, the imbalance favouring epinephrine in paediatric patients is well in line with the HR of 1.12 for a significantly increased mortality with dopamine vs. noradrenaline in adult patients with sepsis as shown in the meta-analyses based on randomized trials by DeBaker et al 2012 (Crit Care Med 2012; 40: 725-730).

On the contrary, a very recent additional multicentre cohort study (Foote HP et al., Journal of Perinatology (2023) 43:1274–1280) of infants in the neonatal intensive care unit with an episode of septic shock did not raise a concern of dopamine as compared to epinephrine but rather indicated a worse outcome with epinephrine. Inborn infants less than 120 days old with an episode of septic shock who were discharged from NICUs managed by the Pediatrix Medical group from 2010 to 2018. The median (IQV) gestational age was 25 weeks (24, 28) and the median birth weight was 760 g (605 g, 1174 g). Five hundred infants (31%) had early onset sepsis, defined as onset on postnatal days 0–2. Overall mortality was 50%. Vasopressor was most commonly started on the same day that positive blood culture was drawn (55% of cases). Gram-negative organisms (52% of cases) were most commonly identified. Dopamine was the most used vasopressor (92% of episodes) with epinephrine (28%) and dobutamine (24%) also frequently used. Hydrocortisone was co-administered with a vasopressor in 38% of episodes. Medication usage did not vary significantly across gestational age groups.

Compared to infants who were treated with dopamine alone, adjusted odds of mortality were higher for those who received epinephrine alone (aOR 4.7 [95% CI: 2.3–9.2]) or the combinations of dobutamine and dopamine (aOR 2.3 [1.5–3.6]); epinephrine and dopamine (aOR 6.2 [3.8–10.2]); or epinephrine, dobutamine, and dopamine together (aOR 15.6 [7.6–32.2]). Compared to infants who received the combination of dopamine and dobutamine, adjusted odds for mortality were higher for those who received a combination of dopamine and epinephrine (p = 0.001). No difference in adjusted odds for mortality was seen between infants who received epinephrine alone and those who received the combination of epinephrine and dopamine (p = 0.48). Adjuvant hydrocortisone was associated with lower adjusted odds of mortality (aOR 0.60 [0.42–0.86]) compared to infants to did not receive hydrocortisone.

The most significant limitation of the study arises from the observational design of the cohort. Of note, in the publication baseline characteristics of infants were only provided for the overall group of patients without differentiation between the different treatment groups. Therefore, it cannot be assessed, to which degree differences in baseline disease states were relevant for treatment decisions as to whether administer epinephrine or dopamine. The observation that combined administration of vasoactive drugs was associated with a worse outcome clearly indicates worse disease state and does not indicate a negative impact of the combined administration. On this line, the authors considered that divergent observed outcomes between infants that received dopamine compared to epinephrine may be due to the cohort of infants who received epinephrine representing a baseline sicker population. This is acknowledged, no conclusions on comparative efficacy and safety can be drawn.

In all of the 3 of the randomized controlled trials investigating the administration of dopamine vs. epinephrine in paediatric patients with septic shock mortality was either significantly or numerically

higher in the dopamine group. A higher mortality was also observed in an additional retrospective cohort study in preterm infants. This goes in line with results from a study in adults also indicating that administration of dopamine, as compared with norepinephrine, may be associated with higher rates of death among patients with septic shock (De Backer et al., Crit Care Med 2012; 40: 725-730). In the study by Ventura a higher rate of in hospital acquired infections was observed in patients treated with dopamine. The issue of infections associated with the administration with dopamine is discussed in more detail below (safety). Despite of the highly relevant methodological drawbacks, the observational study of Foote et al 2023 does not appear to be in line with the otherwise consistent pattern of a statistically or numerically increased mortality of dopamine as compared to epinephrine/norepinephrine in paediatric and adult patients with septic shock. Similar methodological concerns may to some degree also apply to the study of Nissimov et al., (European Journal of Pediatrics 2023; 182:1029–1038). Taken all of the information together, the totality of evidence currently may not be robust enough to finally conclude on a detrimental effect of dopamine and to justify a contraindication for a first line treatment in paediatric patients with septic shock. A warning statement was added to section 4.4 regarding septic shock and reflecting the concerns and the uncertainty regarding clinical outcome and stating that based on signals of an increased mortality with the first line use of dopamine in paediatric and adult patients with septic shock, first line administration of dopamine in paediatric patients with sepsis is not recommended.

Brain Injury Traumatic Brain Injury (TBI): T79.4 Traumatic Shock and T79.9 Unspecified early complication of trauma

Only one study with paediatric patients was identified

Di Gennaro, J. L., et al. (2010). Dev Neurosci 32(5-6): 420-430

It was a retrospective cohort study of children 0-17 years old admitted to a level 1 trauma centre (between 2002 and 2007 with moderate-to-severe TBI who received a vasopressor to increase blood pressure. Eighty-two patients contributed data to the entire dataset. The most common initial medication was phenylephrine (57%) followed by dopamine (29%). Dopamine was administered in 24 patients aged 0-17 years and was associated with an increase in MAP and an increase in CPP. Vasopressor use varied by age. While there was no statistically significant difference in MAP or CPP between vasopressor groups, norepinephrine was associated with a numerical higher CPP and lower intracranial pressure at 3 h after start of vasopressor therapy compared to the other vasopressors examined.

Hypoxic Ischaemic Brain Injury

The search terms were chosen to identify studies with ischaemic brain injury, but due to different underlying causes, there is overlap with studies presented for cardiac reasons for hypotension.

Diessa TG et al., The Journal of Paediatrics 1981; 99: 772-776 (51)

Fourteen severely asphyxiated infants were entered into a double-blind study designed to compare the effects of dopamine (2.5 /µg/kg/ minute) or placebo (dextrose in water). Systolic BP of at least 50mmHg was an inclusion criterion. Mean weight (kg) 2.96 ± 0.49 vs. 3.46 ± 0.34, Gestational age (wk) 41.1 ± 1.5 vs. 39.8 ± 0.89, 1-minute Apgar 1.7 ± 2 vs. 2.4 ± 3; 5-minute Apgar 3.1 ± 2.1 vs. 4.0 ± 2,2.

Echocardiographically determined shortening fraction and mean velocity of circumferential fibre shortening increased when compared to pre-infusion values ($p < 0.05$). There was no significant

change in these echo indices of cardiac function in the placebo-treated group. Systolic blood pressure rose in the dopamine group when compared to pre-dopamine infusion values and to the post infusion values of the placebo group (P less than 0.001 and 0.025, respectively). Diastolic blood pressure increased to a small degree in the dopamine group. There was no significant change in heart rate or echocardiographically measured systolic time intervals.

Walther FJ, et al., The Journal of Paediatrics 1985; 107: 781 – 785 (53)

In 22 newborn infants with left ventricular myocardial dysfunction diagnosed by M-mode echocardiography cardiac output was measured by pulsed Doppler echocardiography. 8 patients were hypotensive; cardiac output and stroke volume were low in 20. The abnormalities were more pronounced in infants with asphyxia. Six infants were given various doses of dopamine (4 to 10 µg/kg/min). Within 1 hour of therapy arterial blood pressure increased from 38 ± 9 mm Hg to 57 ± 7 mm Hg (P <0.001), cardiac output from 114 ± 26 ml/min/kg to 201 ± 39 ml/min/kg (P <0.001), and stroke volume from 0.80 ± 0.19 ml/kg to 1.26 ± 0.14 mi/kg (P <0.001). Heart rate rose slightly from 144 ± 6 to 159 ± 21 bpm (P <0.05). Myocardial contractility normalized within 1 hour; the other echocardiographic abnormalities normalized over 24 to 48 hours.

Cardiac disease

Three randomised trials were identified:

Laitinen P. et al., Amrinone Versus Dopamine-Nitroglycerin After Reconstructive Surgery for Complete Atrioventricular Septal Defect. Journal of Cardiothoracic and Vascular Anesthesia, 1997; 11: 1997: 870-874

Thirty-two infants with complete atrioventricular septal defect were included. Amrinone loading dose, 2 mg/kg, followed by a maintenance infusion, 7.5 µg/kg/min, was given to 17 infants before separation from cardiopulmonary bypass. The remaining 15 patients received a combination of dopamine, 5 µg/kg/min, and nitroglycerin, 1 microgram/kg/min. The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass.

Amrinone provided a higher cardiac output, more favourable oxygen dynamics, and lower pulmonary vascular resistance than a combination of dopamine and nitroglycerin.

Laitinen P. et al., Amrinone Versus Dopamine and Nitroglycerin in Neonates After Arterial Switch Operation for Transposition of the Great Arteries. Journal of Cardiothoracic and Vascular Anesthesia, Vo113, No 2 (April), 1999: pp 186-190. (63)

Thirty-five neonates with transposition of the great arteries participated. A loading dose of amrinone, 2 mg/kg, followed by a maintenance infusion of 7.5 µg/kg/min, was administered to 16 neonates before separation from cardiopulmonary bypass. The remaining 19 patients were administered a combination of dopamine, 5 µg/kg/min, and nitroglycerin, 1 µg/kg/min. The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass. Open-label epinephrine infusion was administered in both groups as required.

With the dosage regimen used, supplemented with epinephrine, amrinone provided a higher cardiac output and more favourable oxygen dynamics than a combination of dopamine and nitroglycerin.

Booke PD et al., Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. British Journal of Anaesthesia 1995; 74: 419-42

Blinded, three-period, two-treatment, crossover design study in 19 children, aged 2-54 months, requiring high-dose inotropic support after cardiac surgery, given either dopamine or dobutamine at a dose of 7.5-20 ug/kg/min, respectively.

Dobutamine and dopamine were equipotent inotropes. In five children given neither enoximone nor phenoxybenzamine, dopamine, in a dose of 7.5 ug/kg/min or more, produced significant mean increases in PAP and PVRI (P = 0.04), compared with the same dose of dobutamine. The investigators decided not to continue with this dose regimen due to this observation.

No conclusions can be drawn on B/R of the administration of dopamine in paediatric patients with traumatic brain injury and with cardiac shock beyond a characterization of haemodynamic effects.

Cardiogenic shock

When considering the totality of data available for cardiogenic shock, data generated in the adult population have some relevance even if they cannot be directly translated to the paediatric population. In the adult population dopamine controlled trials have not consistently shown a protective effect on renal function (e.g. Bellomo R et al., Lancet 2000;356:2139-2143). Dopamine induced more arrhythmias and was associated with an increased 28-day rate of death among patients with cardiogenic shock (De Backer D N Engl J Med 2010;362:779-789; Rui et al., Medicine (Baltimore). 2017 Oct;96(43):e8402). Despite of differences between adult and paediatric patients with cardiogenic shock, the data should have some relevance at least for the older adolescent patients but raises concerns irrespectively of age. In the absence of robust outcome data in the paediatric population in cardiogenic shock it is not possible to conclude on a positive benefit risk balance of the administration of dopamine in a first line setting. No information was provided on the benefit risk balance of the administration of dopamine in a second line add-on setting.

According to a survey by Vogt et al.(Pediatric Anesthesia 21 (2011) 1176–1184) dopamine is only used (among other drugs) in patients with LCOS with low systemic vascular resistance (SVR) but not in patients with elevated SVR of with elevated pulmonary vascular resistance. Considering the effect of dopamine on SVR and PVR, the differentiation appears more than reasonable. The applicant has provided a proposal how to reflect it in the SmPC but a broader wording should be discussed. Booke et al., described unfavourable effects of dopamine (doses from 7.5 µg/kg/min) vs. Dobutamine on pulmonary haemodynamics in paediatric patients in the context of cardiac surgery. Such an effect was also described by Outwater KM et al., J Clin Anesth 1990; 2: 253 – 257, Harrison DC Br J Pharmacol 1969; 37: 618; Holloway EL Br Heart J 1975; 37: 482. Mentzer RM Jr J Thorac Cardiovasc Surg 1976; 71: 807. Loeb HS Circulation 1977; 55: 375. The applicant has provided a proposal to reflect a respective wording in the context of cardiac surgery. The applicant has discussed the issue of acute pulmonary hypertension and proposed to include a statement that dopamine should not be administered in this instance in the context of cardiosurgery. Warnings were added to section 4.4 of the SMPC regarding situations of cardiac surgery and instances of increased pulmonary arterial pressure.

In cardiac surgery dopamine hydrochloride is selectively used in paediatric patients with low cardiac output syndrome (LCOS) and low systemic vascular resistance (SVR) to improve cardiac output. Its use in patients with elevated SVR or elevated pulmonary vascular resistance (PVR) is generally limited due to the potential to worsen vascular resistance abnormalities. The decision to administer dopamine hydrochloride in cardiac surgery should always be made based on the patient's specific clinical condition.

In instances of increased pulmonary arterial pressure, Dopamine hydrochloride can increase pulmonary vascular resistance, particularly at higher doses. When administering dopamine hydrochloride in patients with increased pulmonary arterial pressure, close haemodynamic monitoring is recommended

and doses above 10 µg/kg/min should be avoided. In acute pulmonary hypertension dopamine hydrochloride should only be administered if considered necessary based on an individual assessment of the haemodynamic and clinical state of the patient.

Toxicology and administration after overdose of drugs

No reports on controlled studies were provided. The publications mainly summarize uncontrolled observations and case reports providing evidence for the administration of dopamine in these conditions and with some reference to BP stabilising efficacy in the following conditions:

Clonidine overdose

Calcium channel inhibitor overdose

Hydroxychloroquine overdose

Scorpion stings

Prophylactic administration in patients on barbiturate therapy

Cyclobenzaprine (CBP) overdose

Tiagabine overdose

Bupropione overdose

The literature submitted provides evidence for the use of dopamine in cases of drug overdose and poisoning. However, little information can be derived from the publications on doses administered, representation of age groups, and success of treatment in the different conditions discussed. Some articles (clonidine- or hydroxychloroquine overdosage) are submitted as abstract only.

Since the benefit-risk balance currently cannot be assessed for dopamine in the treatment of hypotension associated with overdose of clonidine or other drugs in the paediatric population based on the data submitted the full articles and a more detailed tabular summary of the number of paediatric patients treated in these conditions is needed, including patient characteristics, dopamine doses used and treatment success as assessed by haemodynamics as well as clinical outcome, as far as available. Upon request the applicant has provided a discussion of the data available documenting the use up to 2011. The data do not allow a conclusion on the benefit risk balance. No further data can be expected in this regard.

Additional expert consultation

Scientific Advisory Group CV was convened on 12 January 2024 to address questions raised by the CHMP. The following points were discussed.

1. Extremely low gestational age newborn (<28 weeks) (ELGANs):

a). Please share your opinion and experience regarding the current place and clinical use of dopamine in ELGANs with impaired circulatory function in the context of measures and medicinal products available to stabilise haemodynamics.

Dopamine is used off label in ELGANs. Dopamine use in this patient population decreased in recent years, according to experts neonatologists participating in the meeting. Some centres abandoned the use of dopamine several years ago and prefer using other vasopressor agents. The main concern with the use of dopamine is its effect on pulmonary vascular resistance, and on increasing the systemic afterload, but its effect on prolactin and thereby immunology are also of importance.

The use of dopamine varies depending on experience and preferences of prescribers in specific centres, patient profile and the underlying pathophysiological mechanism of the disease.

The evidence to support the use of dopamine in ELGANs but also in children in general is not strong. Furthermore, the literature evidence is confusing and contradictory but this is also true for other vasoactive agents. There seems to be no evidence supporting the use of dopamine in preference to other vasopressors, and even some arguments against the use of dopamine as the first line treatment (pending clinical conditions).

The opinion of experts was not totally uniform regarding the current place and use of dopamine in ELGANs. Some participants of the SAG meeting expressed that they would not use dopamine even in second or third line of treatment. Others stated that they would use dopamine, although not as preferred or first line agent. One expert stated that blood pressure (BP) is the key driver for brain and organ perfusion and the most important parameter to be considered when treating ELGANs with hypotension is organ perfusion (not cardiac output). If the main problem is low BP, dopamine and epinephrine could be considered. Tachycardia as side effect occurs more often with epinephrine compared to dopamine according to previous randomised clinical trial. Careful titration of any vasopressor including dopamine is important and used. Another expert supported the use of dopamine when critical drop of BP is observed and when no other vasoactive agents are available although it was admitted that in most centres several vasoactive agents are available. The majority of the experts stated, that considering the BP is the starting point, for optimal treatment in these patients the detailed analysis of the deterioration of haemodynamics has to be taken into account. After this analysis often more specific vasoactive agent can be used. It is optimal to have a haemodynamic assessment before deciding on the strategy taken.

One expert explained that dopamine has an unpredictable effect in ELGANS due to widely varying receptor configuration and density. Also, in ELGANs the myocardium is immature as compared to the myocardium in full term babies (circulatory maladaptation). This immature myocardium can handle afterload very poorly. Challenged with higher afterload produced by dopamine this can lead to an important decrease of cardiac function and output, despite a raise in BP. Therefore, it is difficult to use any medicine that increases the afterload in ELGANs regardless of the pathophysiology that explains the circulatory failure in a specific patient.

Experts indicated that one should preferably treat a condition rather than a symptom (BP). In sepsis or cardiogenic shock dopamine is not often used in ELGANs as there are only few randomised trials assessing the outcomes and they are underpowered. The experts discussed if there is anything specific about dopamine compared to other catecholamines to take into account. It was indicated that cardiac output is lower with dopamine compared with epinephrine use. Also, it was indicated that dobutamine increases blood flow compared to dopamine while dopamine increased BP compared to dobutamine.

The permissive approach to the hypotension treatment was discussed. In many situations the permissive approach was considered preferable. However, with prolonged hypotension, it seems to be important to start the intervention to increase the BP at one point.

In current clinical practice a change is observed in the way ELGANs and generally children are treated with more widespread consideration for the pathophysiological mechanism of the disease using functional echocardiography. However, this practice is relatively new, having been more and more appreciated in the last 5 to 10 years. Older studies were not taking this into account.

The dilution of dopamine for use in children in hospitals can lead to problems due to lack of stability and the value of the stabiliser developed by the company in the current application was noted. In addition, septicaemia could potentially be avoided if a ready to use formulation was available. However, this was not a problem noted in the HIP study. It will still be necessary to manipulate the

new formulation and the risk of medication errors when several concentration formulations are available on a ward was flagged. It was not clear during the discussion if the lower concentration is to be advantageous, because fluid management is an important issue in the very small ELGANS. Opinion was expressed that the use of a concentrated product in children may be preferable to avoid volume overexposure. One expert stated that it is better to have a single dopamine concentration on the unit (NICU/PICU) to avoid medication errors. The contraindications and warnings in the product information may likely not solve the above problem entirely, with incorrect or off label use remaining to be an issue.

The existence of paediatric clinical practice guidelines was acknowledged. However, they permit to use different inotropic agents based on individual clinical situations. Recent guidelines acknowledge that functional echocardiography is more commonly available. Parameters other than echocardiography could help to guide clinicians regarding the most probable pathophysiology. It was noted that guidelines do not place dopamine as the preferred vasoactive agent.

In children receptors mature at different speeds with dopaminergic receptors maturing earlier than alfa receptors. The increase of mortality observed in some studies when dopamine was compared to norepinephrine or epinephrine may come from the stimulation of dopamine receptors by dopamine in addition to alfa and beta-receptors as opposed to more selective stimulation of alfa and beta receptors by norepinephrine and/or epinephrine.

From a statistical point of view, the HIP study raises many concerns. Even though centre effects have been taken into account, the fact that a small sample is distributed in an uneven fashion over centres raises concerns about potentially spurious findings due to accidental lack of balance within centres. Also, the violations of GCP guidelines and the low recruitment were critically discussed. The same holds true for the fact that the statistician analysing the trial data was unblinded.

b). Can you please comment on the criteria as to when circulatory support is to be provided and how to assess treatment success?

The value of BP measurement as a clinical sign was underlined by some experts in view of the urgency of the clinical decision. Following this initial judgment a more in-depth clinical assessment is often made and a more adequate decision follows regarding the choice/continuation of the vasoactive agent. If an in-depth analysis of the haemodynamic situation is not possible, some experts felt that dopamine in patients with low BP might be a reasonable tool.

In ELGANs, obtaining invasive measures is complicated and functional echocardiography may not always be available. Optimally, functional echocardiography should be however used to assess the indication and the effect of the treatment. It is not the only additive to BP measurement to guide the treatment. Assessment of the treatment effect on: the haemodynamic situation, clinical context, organ hypoperfusion, saturation of the brain, cardiac output, renal function/urinary output, existence of the right to left shunting in cases with open PDA (patent ductus arteriosus), oxygenation of the brain and measurement of blood gases, should contribute to the choice of the treatment.

2. General paediatric population from 0 - < 18 years of age:

a). Please share your opinion and experience regarding the current place and clinical use of dopamine in the following conditions:

i. Septic shock

ii. Cardiogenic shock

iii. Cardiosurgery

Dopamine is used off label in the paediatric population from 0 - < 18 years of age.

Concern was expressed that approval of this new formulation based on the weak evidence, for the treatment of children with hypotension, could foster a more widespread use of dopamine in paediatrics over other vasopressor agents.

i. Regarding the use of dopamine in septic shock divergent views were expressed. Some experts informed that in septic shock dopamine should not be used, whilst others indicated that there is a possibility to use it in some situations. One expert stated that they would consider dopamine doses targeting alfa receptors. Overall the use of dopamine in patients with pulmonary hypertension was seen as contraindicated (see below).

The majority of experts believe that dopamine would be very rarely used as a first choice agent in septic shock (if ever).

Mortality concern observed in studies with adults should not be simply extrapolated to paediatrics settings was stated by some experts, but was generally noted as concerning. It was furthermore observed in studies with children.

ii. Regarding the use of dopamine in cardiogenic shock, divergent views were also expressed. Some experts stated that dopamine should not be used as first line drug but it should be available as second line treatment. Second-line treatment should be considered when the use of other catecholamines do not increase the BP or when side effects [i.e. tachycardia] were observed with other catecholamines.

It was noted that in cardiogenic shock contrary to septic shock, no evidence of increased mortality was reported as compared to the use of other vasopressors in adults. However, the value of this was not clear.

iii. Most experts stated that dopamine should not be used as the first line drug after cardiac surgery but it should be available to be used in second line. In paediatric cardiac surgery in recent years dopamine is used in some EU centres while in some other it is not used at all in this setting.

Experts flagged the danger of occurrence of side effects of dopamine (like rhythm disturbances and tachycardia), in particular, in patients likely receiving haemodynamic support with more than one drug (with similar side effects profile) after cardiac surgery.

b). Please share your opinion and experience regarding the impact of the haemodynamic profile of dopamine including pulmonary vascular effects on the selection of patients and treatment algorithms.

Dopamine increases BP in the systemic and pulmonary circulation. A warning included in the draft product information, as proposed by the Rapporteur regarding the instances of increased pulmonary arterial pressure, was noted.

There are several patient populations with low BP: sepsis patients, heart failure patients, pulmonary arterial hypertension patients, low afterload, volume depletion patients. It would be preferrable to consider using different and more specific vasopressor agents according to the haemodynamic situation.

Given that dopamine increases both pulmonary vascular and systemic vascular resistance, it may lead to harm in some clinical situations. When the risk of pulmonary hypertension exists, most experts would be reluctant to use dopamine in children. Ultrasound examination could help to determine this. The group of patients with pulmonary hypertension encompasses a broad group of patients (for example patients with congenital malformations, intra-uterine growth restriction or prolonged

oligohydramnios) and the effect of using dopamine can vary in each condition. Also, higher doses of dopamine should be avoided.

2.7.7. Conclusions on the clinical efficacy

It is acknowledged that an age-appropriate formulation for the paediatric population is an advantage over preparing solutions from formulations provided for adult patients. It may help to reduce well known risks for dosing mistakes in the NICU and PICU and a possible risk for contaminations when preparing solutions. Concerns were raised by the SAG on the availability of several concentrations on the ward as a possible reason for dosing mistakes, as even the high concentration currently available may be needed in some infants to avoid fluid overload.

Currently the data submitted are not sufficient to allow concluding on a demonstrated clinically relevant efficacy of the administration of dopamine in preterm hypotensive infants and the applicant does no longer apply for an indication in this age group.

Posology

The proposed recommended dose range of 5 µg/kg/min up to 10 µg/kg/min with the possibility to increase the dose up to 20 µg/kg/min if justified appears to be acceptable.

There is ample data showing a dose related effect on arterial blood pressure at least in the range of 5 µg/kg/min – 10 µg/kg/min in the different settings applied for but the clinical relevance of this effect on BP is currently unclear.

Hypotension in Preterm Infants

The HIP study failed to show a relevant difference on short term (wk 35 GA) and long term (2 year) outcome, when comparing a dopamine based approach to treat hypotension as defined by MABP below GA vs. a permissive approach (placebo infusion) allowing for lower BP values that depended on signs of hypoperfusion before additional inotropic drugs were administered. The study does not allow robust conclusions on the impact of the different BP values for decision making nor whether dopamine itself has a beneficial or negative effect in these infants. As outlined by the applicant other parameters like cerebral oxygenation or cerebral vascular regulation are in use to guide treatment decisions but the predictive value in the context of drug development is currently unknown. Analyses from the CAR study showed in a limited number of infants that despite of an increase in MABP dopamine had no effect on rScO2 compared to placebo in hypotensive infants.

The reliability of the data of the HiP study is in question. A routine GCP inspection of the EMA has revealed major deficiencies at the two study cites but no critical issue but several critical issues at the sponsor site.

However, since the results from the HiP study were inconclusive and not suitable to support the conclusion of a positive benefit risk balance, the HIP study being GCP-noncompliant was considered less of importance. The applicant agreed not to pursue the indication: treatment of the hypotension in ELGANs.

Shock across the whole paediatric patient population

Little information is provided on outcome for most of the conditions.

In septic shock two randomized controlled studies available showed a significantly or numerically higher mortality in paediatric patients when treated with dopamine as compared to epinephrine. This is paralleled by a randomized study in adults showing also a higher day 28 mortality in the dopamine group. In preterm infants with septic shock a retrospective cohort study also indicated a higher episode

related and pre-discharge mortality as compared to norepinephrine. One additional observational study showed a higher mortality in paediatric patients on dopamine treatment but the results were inconclusive due to relevant baseline differences, another observational study in preterm infants with sepsis that revealed a lower mortality with dopamine than with epinephrine, was also inconclusive since baseline characteristics of the infants were not presented separately for the two groups.

These findings raise concerns in the treatment of septic shock in paediatric patients. Taken all of the information together, the totality of evidence is not robust enough to conclude on a detrimental effect of dopamine and to justify a contraindication for a first line treatment in paediatric patients with septic shock.
A warning statement reflecting the concerns and the uncertainty regarding clinical outcome and stating that first line treatment with dopamine is not recommended in paediatric patients with sepsis, was considered appropriate by the CHMP.

No controlled outcome data are available for paediatric patients with cardiogenic shock. One study in adults indicated that dopamine induced more arrhythmias and was associated with an increased 28-day rate of death. This was supported by a meta-analysis over randomized studies that came to the same conclusion. There are heterogeneous expert statements as to whether dopamine administration should be discouraged or can be left as an option. Information on a second line administration has not been discussed by the applicant. The overall evidence is weak in this instance and data from the adult population, although raising concerns, cannot be easily transferred to the paediatric patients with cardiogenic shock.

Similarly, in the other conditions discussed (brain injury, drug overdose, toxicology) no robust outcome data are provided. In case of drug overdose and toxicology it is acknowledged that controlled trials may not be a feasible option.

There is ample evidence of the administration of dopamine in different conditions in the past. In the context of cardiac surgery surveys revealed that PDE inhibitors are among the most frequently administered drugs with dopamine among others far behind. Information on current use is not readily available. Based on the data provided it is not clear, whether dopamine is mainly used as an add-on drug if other drugs fail or if it is administered first line in some patients. However, since many of the publications do not represent current use, the role of dopamine in current clinical practice cannot directly be derived from the data submitted. Information coming from the SAG indicated heterogeneity in this regard with some centres using dopamine whereas others having abandoned its use in this context.

2.7.8. Clinical safety

The safety data described in this Overview are derived from the following sources:

1. The clinical Trial Report of the “Management of Hypotension in the Preterm” trial (HiP trial) (EudraCT Number 2010-023988-17)
2. Literature sources

2.7.8.1. Patient exposure

HiP Trial:

According to the clinical trial report, dopamine was administered acutely at a dose between 5 and 20 µg/kg/minute. Titration occurred in 5 µg/kg increments every 30 minutes up to the maximum dose. The average duration of dopamine administration was 17.2 h (95% CI: 9.1 – 32.7). According to the information provided in the synopsis of the study report, the median duration (IQR) of dopamine therapy was 17.8 hours (IQR: 7.5–30.6), while in the control arm, dextrose was administered for a median duration of 13.7 hours (IQR: 6.1–24.5).

Detailed data on dosing steps were reported for the patients with SAEs in appendix 16.2.7 (Individual adverse event listing). In case of some subjects, no increments between doses are provided, e.g., "5 ☐ 20 µg/kg/min" and dosing information is missing for two subjects.

2.7.8.2. Adverse events

HiP Trial:

Due to the low number of participants, interpretation of the reported AEs is rather difficult. Table 15 below lists the 121 serious adverse events (SAEs) reported during the HIP study (taken from table 21 in the clinical trial report). The table in the clinical study report contained some AEs that had been assigned to the wrong SOCs. These errors were corrected by the rapporteur in Table 15 below. In addition, the applicant has reported 26 non-serious AEs (Table 16 below).

Of the 121 SAEs (Table 15), 2 were reported as "possibly IMP related" (1.7%), 24 as "unlikely to be IMP related" (19.8 %), and 95 as "not IMP related" (78.5%). Per the definition used by the applicant, all documented AEs occurred after dopamine administration. The 121 SAEs were reported in 40 patients (placebo: n=20; dopamine: n=20). The 26 non-serious AEs were reported in 17 patients (placebo: n=9 dopamine: n=8). Of the 26 non-serious AEs (Table 16), 5 (19.2%) were reported as "unlikely related", the rest (21; 80.8%) as "not related". In Table 15, the total number of reported AEs is numerically higher with dopamine (D) as compared to placebo (P) (65 *vs.* 56), which is mainly driven by the SOCs "Surgical and medical procedures" (D: n=7; P: n=4) and "Vascular Disorders" (D: n=8; P: n=5). In the SOC "Vascular Disorders", the difference is mainly driven by different kinds of haemorrhages (intraventricular haemorrhages of various grade, including right subependymal bleed [D: n=6, P: n=4]; pulmonary haemorrhage [D: n=2, P: n=0]). The AEs of intraventricular haemorrhage are shown in red font in Table 15 below. The numerically higher incidence of IVH with dopamine as compared to placebo (6 *vs.* 4, including subependymal bleed) may be related to blood pressure fluctuations following commencement of dopamine therapy. A relationship between IVH and inotropes administration is supported by a prospective cohort study (Abdul Aziz AN et al., 2020) with 497 preterm infants, 97 of which (19.5%) received inotropes during the first 72 hours. Early use of inotropes was associated with increased risk of death and/or severe brain injury (AOR [adjusted odds ratio] 4.5; 95%CI: 2.4–8.5), severe brain injury (AOR 4.2; 95% CI: 1.9–8.9), and IVH of any grade (AOR 2.9; 95%CI: 1.7–4.9) (Abdul Aziz AN et al., 2020). The information provided by the HiP trial cannot clearly exclude this risk. Regarding IVH, see also section on "Adverse events reported in the literature" below.

Furthermore, at the level of individual AEs ("Verbatim"), a numerical difference was observed with regard to various AEs related to bronchiolitis (D: n=9: P: n=6; in blue font in Table 15). Moreover, when the instances possibly associated with infections (highlighted in yellow in Table 15) are summed up across SOCs, there seems to be a major imbalance suggesting more infections with dopamine as compared to placebo (D: n=18; P: n=12). For a detailed discussion of a potential relationship between dopamine use and infection risk, please see discussion of literature sources in the next section below.

Numerically more AEs in the dopamine as compared to the placebo group (Δ>1 AE) were also observed for *patent ductus arteriosus (including PDA coil occlusion)* (D: n=3; P: n=1) as well as for *inguinal hernia bilateral* (D: n=2; P: n=0). Minor numerical imbalances, for which the literature (see literature discussion below) seems to support a potential relationship with dopamine, were observed for various cases of *"Retinopathy of prematurity"* (DA: n=5; P: n=4) and for *(Suspected) necrotizing enterocolitis, necrosis of intestinal wall (*DA: n=3; P: n=2). An additional case of *"Retinopathy of prematurity"* was reported as non-serious AE in a dopamine-treated subject (see Table 16 below).

Table 15. Serious adverse events from the HIP trial as reported in Table 21 of the clinical trial report (wrong assignment of some AEs to SOCs was corrected by assessor). The sums across SOCs were calculated by the rapporteur. The "verbatim" AEs in red font represent incidences of intraventricular haemorrhages; AEs in blue font are related to bronchiolitis. AEs highlighted in yellow might be associated with infections.

System Organ Class (SOC)	Verbatim	Dopamine (DA)	Placebo (Plc)
Blood and lymphatic system disorders	*Anaemia*	1	0
	Sickle cell crisis	1	0
	Sum	2	0
Cardiac disorders	*Heart failure*	1	0
	Patent ductus arteriosus	2	1
	Persistent tachycardia	0	1
	Profound prolonged bradycardia	1	0
	PDA coil occlusion	1	0
	Sum	5	3
Eye disorders	*Bilateral Retinopathy of Prematurity*	1	0
	Retinopathy of Prematurity	3	2
	Retinopathy of Prematurity stage II bilateral	0	1
	Sum	4	3
Gastrointestinal disorders	*Bilateral inguinal hernia repair*	0	1
	Blood in stool	1	0
	Meconium Ileus	1	0
	Ileus and necrotizing enterocolitis	1	0
	Ileus and surgery of GIT with bowel adhesions causing ileus found	1	0
	Inguinal hernia bilateral	2	0
	Intestinal perforation	2	3
	Left inguinal hernia repair	0	1
	Necrosis of intestinal wall	0	1
	Pneumoperitoneum spontaneous intestinal perforation	0	1
	Postrepair intestinal obstruction	0	1
	Pyloric stenosis	0	1
	Suspected necrotizing enterocolitis	1	0
	Vomiting	0	1
	Sum	9	10
General disorders and administration site conditions	*Death*	0	1
	Multiorgan failure	1	0
	Multi organ failure secondary to gram negative sepsis	1	0
	Sum	2	1
Infections and infestations	*Acute upper respiratory tract infection/acute tonsillitis*	1	0
	Chicken pox	1	0
	Culture negative sepsis, pulmonary hypertension secondary to the sepsis	0	1
	Late onset sepsis	1	0
	Lower respiratory tract infection	0	1
	Meningitis	1	0
	Respiratory tract infection	0	1
	Staphylococcus aureus sepsis	0	1
	Systemic candida	0	1
	Viral illness	1	0
	Sum	5	5
Injury, poisoning and	*Admitted for observation post head injury*	1	0

procedural complications	*Postoperative ileus*	1	0
	Sum	2	0
Investigations	*Increased stoma output*	0	1
	Sum	0	1
Metabolism and nutrition disorders	*Failure to thrive*	1	0
	Hyperglycaemia	0	2
	Hyperkalaemia	0	1
	Hypernatraemia	0	1
	Reduced feeding	1	0
	Sum	2	4
Nervous system disorders	*Periventricular leukomalacia*	0	1
	Sum	0	1
Pregnancy, puerperium and perinatal conditions	*Cystic periventricular leukomalacia grade II bilateral*	1	0
	Cystic periventricular leukomalacia grade III bilateral	0	1
	Cystic periventricular leukomalacia grade III right side	1	0
	Death	0	1
	Necrotising enterocolitis	1	1
	Sum	3	3
Respiratory, thoracic and mediastinal disorders	*Bronchiolitis*	3	3
	Bronchiolitis – RSV positive	1	1
	Coughing	1	0
	Death – Respiratory Failure	0	1
	Hospitalisation for Bronchiolitis	1	0
	Hospitalisation for Bronchiolitis due to Bocca virus	1	0
	Hospitalisation for Bronchiolitis due to RSV Bronchiolitis	1	0
	Bronchiolitis – haemophilus influenza	1	0
	Irreversible CLD with pulmonary hypertension	0	1
	Lower respiratory tract infection and bronchiolitis	0	1
	Lung apoplexy	0	1
	Mild bronchiolitis	1	0
	Pneumothorax (left)	1	0
	Pneumothorax (right)	0	1
	Pulmonary hypertension	0	1
	Respiratory failure	0	2
	Respiratory failure secondary to bronchiolitis	0	1
	Respiratory insufficiency	0	1
	Right lower lobe pneumonia	0	1
	Right middle lobe pneumonia	1	0
	Tachypnoea	1	0
	Tension pneumothorax (left)	1	0
	Viral illness	0	2
	Viral upper respiratory tract infection	1	0
	Viral URTI/LRTI	1	0
	Sum	16	17
Surgical and medical procedures	*ASD surgical repair*	0	1
	Bilateral inguinal hernia repair	1	1
	Elective hospitalisation for hunger provocation	1	0
	Elective hospitalisation for placement of gastrostomy	1	0
	Hernia repair	1	0
	Right sided inguinal hernia repair	0	1
	ROP Requiring laser surgery	1	1
	Surgical repair of hypospadias	1	0
	Surgical repair of left inguinal hernia	1	0
	Sum	7	4
Vascular disorders	*Bilateral intraventricular haemorrhage (grade 3)*	1	0
	IVH	2	1
	IVH (grade 3-4)	0	1
	IVH (grade 3)	0	1
	IVH (grade 3) right side	1	0
	IVH (grade 2)	0	1
	IVH (grade 3) left sided	1	0
	Pulmonary haemorrhage	2	0
	Refractory hypotension	0	1
	Right subependymal bleed	1	0

	Sum	8	5
Overall sum of reported AEs		65	56
IVH: intraventricular haemorrhage; ROP: Retinopathy of Prematurity			

Table 16. Non-serious adverse events from the HIP trial as reported in the applicant's D121 response. The sums across SOCs were calculated by the rapporteur.

System Organ Class (SOC)	Verbatim	Dopamine (DA)	Placebo (Plc)
Eye disorders	*Retinopathy of prematurity Grade III*	1	0
	Sum	1	0
Gastrointestinal disorders	*Hernia inguinalis bilat*	1	0
	Sum	1	0
Infections and infestations	*Sepsis - Staphylococcus capitis*	0	1
	Sepsis	1	0
	Pneumonia	1	0
	Sum	2	1
Metabolism and nutrition disorders	*Hyperglycaemia*	7	8
	Hypernatraemia	1	1
	Hyponatremia	1	0
	Sum	9	9
Respiratory, thoracic and mediastinal disorders	*Bilateral pneumonia*	0	1
	Respiratory illness - requiring hospitalisation	0	1
	Sum	0	2
Vascular disorders	*Ischemia right foot and leg*	0	1
	Sum	0	1
Overall sum of reported AEs		13	13

Adverse events reported in the literature

In the following, specific adverse events are discussed that are considered potentially related to dopamine based on literature reports. The literature regarding well-known adverse events that are already listed in the SmPCs of most dopamine products, e.g., supraventricular or ventricular tachycardia or nausea, etc. is not discussed anymore.

Incidence of IVH/subependymal bleed in dopamine-treated patients

The numbers and the differences between the groups in the HiP trial are too small to draw any conclusions on a causal relationship between intracerebroventricular haemorrhage and use of dopamine in preterm neonates.

However, dopamine-induced fluctuations in blood pressure may lead to the occurrence of IVH/subependymal bleed by the following mechanisms:

(1) Blood Pressure Instability: rapid changes in blood pressure may impact cerebral blood flow and perfusion in the vulnerable brain of premature infants.

(2) Increased Cerebral Perfusion Pressure: increase in systemic blood pressure and concomitantly in cerebral perfusion pressure (the latter was not observed in HiP) may strain the delicate blood vessels in the premature brain.

(3) Disruption of Cerebral Vessels: increase of norepinephrine release, resulting in vasoconstrictive effects on blood vessels, which may contribute to the disruption of cerebral blood vessels.

Rapid fluctuations in mean arterial pressure have specifically been observed during infusion changeover. Kirupakaran et al (Arch Dis Child 2020 Apr;105(4):390-394) report that, by preparing the dopamine solution 30 min prior to infusion and limiting the infusion duration to 12 h, rapid fluctuations

during infusion changeover are minimised. Presumably, instability of dopamine leads to a decrease of exposure during infusion, and a sudden increase in the exposure to active substance occurs, when the old infusion is replaced by a new one.

Effects on splanchnic oxygen metabolism and perfusion

In hypotensive preterm neonates, dopamine led to a reduction of cardiac output in association with blood pressure increase and reduced bowel perfusion (Zhang et al., Arch Dis Child Fetal Neonatal Ed 1999;81:F99–F104). Jakob et al. (Shock 2002 Jul;18(1):8-13) report that dopamine appears to reduce splanchnic oxygen consumption in septic and cardiac surgery patients, despite an increase in regional perfusion. Dopamine-induced vasoconstriction and reduction in bowel perfusion may favour gastrointestinal AEs, specifically necrotising enterocolitis. In the HIP study, only a minor numerical imbalance occurred with regard to necrotising enterocolitis. However, it has been reported in the literature that in preterm infants, necrotising enterocolitis (NEC)-associated sepsis was associated with dopamine administration ($p<0.0001$) among other factors (Garg PM et al., Pediatr Res 2022 Dec;92(6):1705-1715).

Recently, Jozwiak M et al (Front Med (Lausanne) 2022 May 23:9:82644) reported on an analysis of 24 million reports in the WHO VigiBase® database. The analysis revealed 104 events of acute mesenteric ischaemia (AMI), and disproportionality analyses yielded significant association with all vasopressors (including dopamine), except for selepressin. The Odd's Ratios (ORs) demonstrate that dopamine might increase the risk for mesenteric ischaemia, although the OR of dopamine is at the lower end of the scale compared to other vasopressors.

Retinopathy of Prematurity (ROP)

In the HiP trial, ROP occurred in 5 instances in the dopamine group and four times in the placebo group. In the literature, the role of dopamine in ROP is discussed controversially. Mizoguchi MB et al. (Br J Ophthalmol. 1999 Apr;83(4):425-8) see an association between dopamine use and the development of ROP. Liu PM, et al (Am J Perinatol 2005 Feb;22(2):115-20) also report that birthweight ≤ 1000 g, intraventricular haemorrhage, sepsis, and use of glucocorticoid or dopamine were risk factors associated with higher incidence of ROP. In addition, Garg R et al (J Perinatol. 2003 Apr-May;23(3):186-94) describe an association between dopamine and retinopathy of prematurity. However, Allegaert K et al. (Br J Ophthalmol. 2004 Feb;88(2):309-10) are of the opinion that dopamine is an indicator but not an independent risk factor for grade 3 ROP in extreme low birthweight infants. Moreover, Catenacci et al. (J Pediatr 2013;163:400-5) have found that severity of neonatal hypotension (dopamine-resistant hypotension) is associated with the development of ROP.

In summary, the current literature is scarce and controversial; however, it seems likely that the occurrence of ROP is connected to underlying conditions like immature gestational age, severe neonatal hypotension etc. rather than to the use of dopamine itself. Thus, it is not considered necessary to modify the PI in this regard.

Endocrine effects

Suppression of pituitary function by dopamine

Dopamine influences the endocrine system by activating D2 receptors in the anterior medium eminence of the hypothalamus and the pituitary. This causes cessation of prolactin production, of growth hormone impulses as well as inhibition of thyrotropin-releasing hormone production. The latter results in a reduction in thyroxine (T_4) and triiodothyronine (T_3). Filippi et al (Eur J Ped 2004, 163: 7 – 13; Pediatr Crit Care Med 2006; Vol 7 No 3: 249 - 251) reported reduced levels of thyroid hormones in preterm infants treated with dopamine.

It is noted that there are reports on negative long-term effects of reduced thyroid hormone levels in preterm neonates. Data from a longitudinal study with 280 preterm infants (birth weight <1850 g) suggest a major association between low plasma T3 in preterm neonates and later developmental outcome at 18 months' corrected age, specifically with regard to Bayley mental and motor scales and the Academic scale of Developmental Profile II (Lucas A et al., Arch Dis Child 1988 Oct;63(10):1201-6). A retrospective cohort study published by Coquelet et al (Front Pediatr. 2020 May 5:8:224) has identified a free thyroxine level ≤10 pmol/L in infants as a threshold, below which the risk for neonatal clinical impairment and poor outcome at an age of three years is increased. It remains unclear, whether short-term application of dopamine in preterm neonates may also result in impaired long-term development, an effect, which might have been overlooked due to the low number of subjects participating in the HiP trial. Moreover, it is currently unclear, whether acute complications may result from reduced thyroid function. Finally, reduction of thyroid hormones by dopamine may impair early diagnosis of congenital hypothyroidism, which is based on the detection of high TSH in association with low T4. It may be useful to test all new-borns simultaneously for TSH and T4 values at primary screening and to re-evaluate thyroid hormones after dopamine discontinuation.

Rebound effects after dopamine withdrawal

Van den Berghe (Crit Care Med, 1994; 22:1747 – 1753) reported on the pituitary effects of dopamine infusion in critically ill infants and children recovering from cardiovascular surgery. In newborns, dopamine suppressed the release of prolactin, growth hormone and thyrotropin. However, 20 minutes after dopamine withdrawal, a rebound effect started, and one day later, prolactin was ten times higher, pulsatile growth hormone secretion was augmented, thyrotropin was unchanged, T_3 was increased by 30% and the T_3/reverseT_3 ratio was inverted. In the children, dopamine suppressed only prolactin and thyrotropin, but not growth hormone. Rebound also started 20 min after dopamine withdrawal, and one day later, prolactin was at least twice as high, thyrotropin was increased by 10-fold, T_4 was augmented by 14%, T_3 by 30% and the T_3/reverseT_3 ratio doubled. The data indicate that dopamine infusion induces or aggravates partial hypopituitarism and the euthyroid sick syndrome in critically ill infants and children.

Den Brinker et al (Intensive Care Med (2005) 31:970–976) found also evidence of a suppressive effect of dopamine on TSH in critically ill children, which, after dopamine withdrawal, was followed by an increase of more than four times in TSH at a median of 14 h, clearly indicating a rebound effect.

No data on T_3/reverse T_3 and T_4 levels of the preterm neonates were provided by the applicant, which prohibits any conclusion on the effects of dopamine on thyroid hormones in the HIP study.

Inhibition of immune function and increased risk of infections

The above-mentioned endocrine effects of dopamine may also affect immune functions, e.g. via inhibition of prolactin release. Prolactin receptors occur on T- and B-lymphocytes, and in animal experiments, reduced prolactin levels have been associated with impaired cellular immune function and increased likelihood of infection (Bernton et al., Science 1988 Jan 22;239(4838):401-4). At a dose of >5µg/kg/min, dopamine reduced serum prolactin by 90%, which was associated with a temporarily impaired T cell response and reduced lymphocyte count (Devins et al., Crit Care Med. 1992 Dec;20(12):1644-9). Given this mechanistic background, it is conceivable that an increased risk of infections may occur in dopamine-treated paediatric patients, as it was also suggested by the AEs reported in the HiP trial (see above). An increased risk of death and healthcare-associated infection has also been observed in children with septic shock treated with dopamine (Ventura AMC et al., Septic Shock Critical Care Medicine 2015; 43: 2292-2302). According to another study, dopamine use was, among other factors, associated with healthcare-associated infections after paediatric cardiac surgery

(Hatachi T et al, Pediatr Crit Care Med 2018; 19:237–244). This association seems to hold true for extremely preterm infants, where the use of a large amount of dopamine was associated with various types of infections (Hotta M et al., European Journal of Pediatrics (2020) 179:1797–1803).

Gangrene

Gangrene may occur at relatively low doses and in children and neonates without pre-existing vascular disease. Koerber et al (Clin Pediatr (Phila) 1984 Feb;23(2):106-7) describes peripheral gangrene in a child that received a low to medium dose of dopamine (4.1 to 8.3 µg/kg/min during the majority of the postoperative course; terminally, the infusion was increased to 15 µg/kg/min) after surgery in the context of pentalogy of Fallot. This patient's clinical course was complicated by congestive heart failure, respiratory distress, oliguria, and mild disseminated intravascular coagulation.

Maggi et al (J Pediatr 1982 Feb;100(2):323-5) reports on sustained ischaemia of a lower extremity followed by dry gangrene of the toes after administration of dopamine at a maximum dose of 7 µg/kg/min in a 2-week-old, previously well infant female patient. The infant was treated in the context of sepsis and paroxysmal atrial tachycardia. The author concludes: *"We strongly recommend that any child receiving a peripheral infusion of dopamine should have careful serial examinations of the extremities throughout the period of dopamine administration."*

Adverse effects on respiratory function and oxygenation

According to van de Borne et al (Circulation 1998 Jul 14;98(2):126-31), low-dose dopamine (5 µg/kg/min) is able to decrease chemoreflex sensitivity to hypoxia. Dopamine inhibited the chemoreflex responses during hypoxic breathing in normal humans, preferentially affecting the ventilatory response more than the sympathetic response. Dopamine also depressed ventilation in normoxic heart failure patients breathing room air. Bhatt-Mehta V and Nahata MC (1989 Pharmacotherapy 9, 303-14) explain the following with regard to neonates: Dopamine *"has a direct inhibitory effect on the activity of carotid body adrenergic receptors, leading to reduced hypoxic ventilatory drive. While adults are able to respond to hypoxia by increasing tidal volume and minute ventilation, infants respond in a different manner. Their response is biphasic so that after a brief period of hyperventilation (increased tidal volume and minute ventilation), they are unable to maintain increased minute ventilation. Apparently, the central depressant effects of hypoxia override the peripheral chemoreceptor-stimulant mechanism. Peripheral chemoreceptors take 3 weeks and 1 week to mature in preterm and full-term neonates, respectively. Preterm infants often have a low resting arterial oxygen saturation and may require supplemental oxygen to avoid respiratory problems such as apnea. Since dopamine administration in a spontaneously breathing neonate may depress peripheral chemoreceptor activity, the need for oxygen may increase due to persistent hypoxia and subsequently cause cardiovascular problems such as hypotension. Although never demonstrated scientifically, it appears possible on theoretical grounds, to induce persistent hypoxia and an increased oxygen need in neonates."* In addition, it has been reported that dopamine reduces arterial oxygen saturation by impairing regional ventilation/perfusion matching in the lung (Shoemaker WC, Chest 1989 Jul;96(1):120-6).

Johnson RL (Circulation. 1998 Jul 14;98(2):97-9) summarised this as follows: *"In summary, available data from multiple sources now indicate that dopamine infusions in critically ill patients can interfere with 2 important protective mechanisms against a fall in arterial O_2 saturation in the presence of uneven distribution of alveolar ventilation: it can (1) depress local vasoconstriction in response to alveolar hypoxia, which normally keeps perfusion appropriately matched to ventilation in the lung, and (2) depress the chemoreceptor drive to ventilation normally induced by arterial hypoxemia and probably hypercapnia."*

Another aspect regarding oxygenation was reported by Li et al (J Am Coll Cardiol 2006;48:1859–64), who evaluated the effects of dopamine on haemodynamic status and oxygen transport in neonates after the Norwood procedure (cardiopulmonary bypass). Although dopamine increases tissue oxygen delivery (DO2) by augmenting cardiac performance, it might also increase systemic oxygen consumption (VO2), e.g., by stimulating cell metabolism via adrenergic receptors or by action on the central and the sympathetic nervous system. Specifically in neonates with limited myocardial functional reserve and with significantly elevated VO2, e.g., after the Norwood procedure (cardiopulmonary bypass), as reported by Li et al (J Am Coll Cardiol 2006;48:1859–64), dopamine may adversely affect VO2-DO2 balance. Li et al (J Am Coll Cardiol 2006;48:1859–64) report that early termination of dopamine in these patients was associated with a significant decrease in VO2 leading to an improved VO2-DO2 balance. They assume that these counterintuitive effects of dopamine largely reflect the stimulation of non-cardiac tissue metabolism. The authors conclude that dopamine should be used with caution in neonates after cardiopulmonary bypass.

Increase in pulmonary artery pressure

Driscoll et al (J Thorac Cardiovasc Surg 78:765-768, 1979) studied the effects of dopamine in 10 patients who were undergoing diagnostic cardiac catheterization for investigation of congenital heart disease (age: 0.4 to 16.3 years). In one patient who had pulmonary vascular obstructive disease, infusion of 7.75 µg/kg/min of dopamine increased the right ventricular pressure to a supra-systemic level and the mean pulmonary arterial blood pressure was increased in comparison to the mean systemic arterial blood pressure. The authors state that there *"is evidence that dopamine increases pulmonary artery pressure, and the use of dopamine may be contraindicated in patients with elevated pulmonary vascular resistance."*

This was confirmed by Outwater et al (J Clin Anesthesiology; 1990: 253), who described the renal and haemodynamic effects of dopamine during the immediate postoperative period in six infants following repair of congenital cardiac defects. Dopamine was infused at rates of 5, 10, and 15 mcg/kg/min. Pulmonary artery pressure increased significantly in one of these patients. However, it is noted that a tendency towards increased pulmonary arterial pressure (PAP) as compared to baseline was observed across all 6 patients, specifically at dopamine doses of 10 and 15 µg/kg/min.

Booker et al (British Journal of Anaesthesia 1995; 74: 419-423) found that in young children undergoing cardiac surgery *"dopamine in doses >7 µg/kg^{-1}min^{-1}, caused pulmonary vasoconstriction, an effect mediated by α-adrenergic receptors."* Specifically, *"in five children given neither enoximone nor phenoxybenzamine, it was observed that dopamine, in a dose of 7.5 µg/ kg^{-1}min^{-1} or more, produced significant mean increases in PAP and PVRI (P = 0.04), compared with the same dose of dobutamine. These last results were so striking and clinically undesirable, even in patients with normal pulmonary vascular tone, that we felt it would be unethical to continue with that portion of the study in patients in whom increases in pulmonary vascular tone would be detrimental."*

Similarly, Liet JM (J Pediatr 2002;140:373-5), who investigated the effects of dopamine on pulmonary artery pressure in 18 ventilated hypotensive preterm neonates by using the flow characteristics of the ductal shunt. They found that dopamine has variable effects on pulmonary/systemic mean arterial pressure ratio with half the neonates showing an increase in pulmonary pressure relative to systemic pressure.

Use of dopamine in patients with hypovolaemia and hypokalaemia

The current version of the SmPC states in section 4.4 that *"Hypovolaemia should be corrected where necessary prior to dopamine infusion."* This is supported, because fluid administration is essential for a proper haemodynamic response and supports the effects of inotropes and vasoconstrictors. In

the HiP study, volume was also given first, followed by dopamine administration. However, it is noted that the SmPCs of other dopamine products contain hypovolaemia as a contraindication in section 4.3. Section 4.4 of the current SmPC furthermore states that *"Excess administration of potassium-free solutions may result in significant hypokalaemia."* This is possibly due to dilution effects. However, it is also noted that Animal experiments with anaesthetised dogs also showed that dopamine was able to induce hypokalaemia (Blevins RD et al., J Cardiovasc Pharmacol 1989 Apr;13(4):662-6).

2.7.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)in the HiP Trial

Please see Table 15 and corresponding discussion in the preceding section.

Deaths:

According to the clinical trial report, the overall mortality for the entire cohort was 24% (21% in the dopamine arm *vs* 28% in the observational arm). Table 17 shows the 14 fatalities (6 in the dopamine group [IMP received: n=4], and 8 in the placebo group [IMP received: n=7]) at or prior to 36 weeks as reported in the applicant's D121 response.

Table 17. Fatalities in context of the HiP trial, at or prior to 36 weeks.

Subj ID	Adverse Event	Cause of Death	IMP received?	Trial arm
0010003	Intestinal Perforation	Multi-organ dysfunction secondary to culture negative sepsis	Yes	Dopamine
0010021	No IMP	Refractory Hypotension & acidosis. Possible intra-abdominal haemorrhage	No	Dopamine
0010056	Profound prolonged bradycardia	Profound prolonged bradycardia	Yes	Dopamine
0010059	Intestinal Perforation	Intestinal Perforation	Yes	Placebo
0010072	Irreversible CLD with Pulmonary Hypertension	Irreversible CLD with Pulmonary Hypertension	Yes	Placebo
0020004	Respiratory Insufficiency	Respiratory Insufficiency	Yes	Placebo
0020070	No IMP	Respiratory Insufficiency/Abdominal Aspergillus	No	Dopamine
0030041	Persistent Pulmonary Hypertension	Persistent Pulmonary Hypertension	Yes	Dopamine
0070009	No IMP	NEC with Intestinal Perforation	No	Placebo
0070118	Grade III IVH, Hyperglycaemia, Refractory Hypotension, Respiratory Failure	Respiratory Failure, Refractory Hypotension & Extreme Prematurity	Yes	Placebo
0080022	Grade IV IVH	Grade IV IVH	Yes	Placebo
0080043	Grade II IVH with hydrocephalus, Respiratory Failure with prolonged hypoxia secondary to pneumothorax & RDS	Respiratory Failure with prolonged hypoxia secondary to pneumothorax & RDS	Yes	Placebo

0120002	Necrosis of Intestinal Wall	Necrosis of Intestinal Wall	Yes	Placebo
0120008	Multi organ failure	Multi organ failure	Yes	Dopamine

2.7.8.4. Laboratory findings

No clinical laboratory results were submitted by the applicant. Section 12.4 of the Clinical Trial Report states “No data to present”. For effects on dopamine on thyroid hormone levels and pituitary function, please see literature discussion above.

2.7.8.5. In vitro biomarker test for patient selection for safety

N/A

2.7.8.6. Safety in special populations

N/A

2.7.8.7. Immunological events

N/A

2.7.8.8. Safety related to drug-drug interactions and other interactions

No interaction studies were performed by the applicant or reported in the literature review. The following interactions are already listed in the applicant’s SmPC:

- Sensitization of the myocardium by anaesthetics, specifically cyclopropane or halogenated hydrocarbon anaesthetics
- Pharmacodynamic interactions with α- and β-Blockers, antagonising the peripheral vasoconstrictive and cardiac effects of dopamine, respectively.
- Interaction with monoamine oxidase (MAO) inhibitors resulting in a potentiation of effect and duration of action of dopamine.
- Interaction with phenytoin, which may result in hypotension and bradycardia.
- Dopamine may increase the effect of diuretic agents.
- Ergot alkaloids may lead to excessive vasoconstriction.
- Tricyclic antidepressants and guanethidine may potentiate the pressor response to dopamine.

The list may be amended in analogy to already authorised dopamine products by including the following information:

- Increased risk of gangrene in case of combination with ergot alkaloids.
- Alkalising substances should not be added, because this may lead to inactivation of dopamine.
- Metoclopramide can impair the dopamine effect.
- Dopamine may increase blood glucose level and may therefore interfere with antidiabetic medications.
- Dopamine may lead to false positive results, when urinary catecholamine excretion is determined.

2.7.8.9. Discontinuation due to adverse events

N/A(According to module 16.2.1, there were no discontinued patients in the HiP trial).

2.7.8.10. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.7.9. Discussion on clinical safety

Due to the small treatment arms, the HiP trial provides only limited safety data.

The applicant proposed to extend the safety population with a PAES in a retrospective observational controlled study (see above under efficacy section).

The applicant has reported 121 SAEs (in 40 patients; D: n=20; P: n=20) and 26 non-serious AEs (in 17 patients; D: n=8; P: n=9). Due to the aforementioned size limitation of the HiP trial, the discussion of the reported SAEs was combined with an analysis of literature, the latter mainly being based on an extensive literature review submitted by the applicant. Among the serious adverse events reported in HIP trial there were conditions characteristic for preterm neonates in both dopamine and placebo groups.

This analysis has revealed that most of the adverse events of dopamine are due to its pharmacodynamic actions on dopamine- as well as α- and β-adrenergic receptors. The total number of reported AEs was numerically higher with dopamine (D) as compared to placebo (P) (65 vs. 56), which was mainly driven by the SOCs “Surgical and medical procedures” (D: n=7; P: n=4) and “Vascular Disorders” (D: n=8; P: n=5). Within the SOC “Vascular Disorders”, the imbalance disfavouring dopamine is mainly driven by intracerebroventricular and pulmonary haemorrhages. An association of early use of inotropes with an increased risk of intracerebroventricular haemorrhage was also reported in the literature. The risk may be controlled by limiting the time periods between infusion changeovers. A maximum time to changeover of 24 h is currently mentioned in section 4.2 of the SmPC. Another imbalance was observed, when all instances associated with infections were summed up across SOCs, revealing more infections with dopamine as compared to placebo (D: n=18; P: n=12). Various AEs related to bronchiolitis occurred more frequently in the dopamine group as compared to the placebo arm (D: n=9: P: n=6). An association between dopamine use and an increased risk of infections is supported by literature and reflected in the SmPC. In addition, dopamine shows endocrine effects. Literature shows that a suppression of pituitary function leads to a reduced release of prolactin, growth hormone and thyrotropin. The latter results in a reduction of thyroid hormones. Moreover, a rebound effect is observed after dopamine discontinuation. The acute and long-term consequences of the pituitary suppression and of the rebound effect are not completely clear.

Moreover, the literature suggests various pulmonary effects of dopamine. First, there may be adverse effects on respiratory function and oxygenation. Second, an increase in pulmonary artery pressure has been observed in a part of the paediatric patients treated with dopamine. A warning statement is included in section 4.4.

Literature further suggests that reduced perfusion and oxygen supply in the gastrointestinal tract may occur due to the peripheral vasoconstriction induced by dopamine. This may lead to further

complications, e.g. an increased susceptibility to necrotising enterocolitis. In the HiP trial, a minor numerical imbalance was observed with regard to (suspected) necrotising enterocolitis/necrosis of intestinal wall (D: n=3; P: n=2). Vasoconstriction is mentioned as AE in section 4.8 of the SmPC.

Dopamine-induced vasoconstriction can also lead to skin necrosis and gangrene. Literature suggests that in rare cases, dopamine may cause gangrene also at doses <10 µg/kg/min and in patients without pre-existing vascular disease.

In section 4.4, the current version of the applicant's SmPC informs about the necessity of fluid replacement in hypovolaemic patients prior to dopamine initiation. Other dopamine products for infusion on the market contain hypovolaemia as a contraindication in the SmPC.

However, vasopressor therapy has little role in the management of patients with purely haemorrhagic or hypovolaemic shock and may be harmful in this setting. In this context, it is noted that only infants born before 28 weeks GA and without signs of shock were eligible for inclusion in the HiP trial. Consequently, the dopamine efficacy and safety in shock conditions (and in case of different aetiologies of shock) in newborns was not clinically tested by the applicant and this information was derived purely from the literature.

Hypovolaemia should be corrected prior to dopamine administration, which is reflected in the SmPC. Hypokalaemia may be mainly caused by dilution effects, when large amounts of potassium-free solutions are infused.

Finally, the role of dopamine in the development of "Retinopathy of Prematurity" (ROP) is discussed controversially in the literature, and only a minor numerical imbalance has been found in the HiP data (D: n=5; P: n=4). Currently, there is no clear indication that there is a causal relationship between ROP and dopamine use.

Additional expert consultation

Please, see Minutes from the SAG CV in Section 2.7.6 Discussion on Clinical Efficacy.

2.7.10. Conclusions on the clinical safety

The safety results from the HiP trial are limited. The applicant's literature review was the most important source for safety information. Although dopamine can be considered a well-established and relatively safe drug, specifically as, due to the short half-life, its action can be easily controlled, some concerns were raised and were addressed in the SmPC. Most importantly, the HiP safety data as well as the literature suggest an increased risk of haemorrhages, specifically of intracerebroventricular haemorrhages in dopamine-treated patients. Literature data suggests that the risk of intracerebroventricular haemorrhages could be somewhat reduced by limiting the time periods between infusion changeovers. Moreover, it appears that dopamine may have detrimental effects on immune function, resulting in an increased incidence of infections. Furthermore, the inhibitory effect of dopamine on pituitary function (reduction of thyroid hormone levels, reduced prolactin and growth hormone) and the rebound effect upon discontinuation should be assessed with regard to their safety relevance for a paediatric population.

2.8. Risk Management Plan

2.8.1. Safety concerns

The applicant proposed the following summary of safety concerns in the updated RMP version 0.4:

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

2.8.2. Pharmacovigilance plan

No additional pharmacovigilance activities are proposed. Routine pharmacovigilance is considered sufficient to identify and further characterise all safety concerns included in the RMP.

2.8.3. Risk minimisation measures

Summary table of risk minimisation activities by safety concern:

Safety concern	Risk minimisation measures
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
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
Increase in pulmonary artery pressure	Routine risk minimisation measures:

Safety concern	Risk minimisation measures
	SmPC section 4.4 PL section 2 – Prescription only medicine Additional risk minimisation measures: None
Pregnancy, lactation and fertility	Routine risk minimisation measures: SmPC section 4.6 PL section 2 – Prescription only medicine Additional risk minimisation measures: None

2.8.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

The applicant is reminded that the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

2.9. Pharmacovigilance

2.9.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Based on limited data on target population (neonates, infants and children), the PRAC Rapporteur is of the opinion that a separate entry in the EURD list for dopamine (indicated for hypotension in neonates, infants and children) is needed, as it cannot follow the already existing entry for dopamine (with PSUR cycle 13 years). The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD for dopamine

(PSUSA/00001161) is 09.10.1975. The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed therapeutic indication is:

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

The main goal in treating paediatric patients with clinically relevant hypotension leading to shock and/or severe damage to brain or other organs is to improve organ perfusion and oxygenation and long-term mortality and morbidity. Parameters used for clinical decision making in the acute situation, such as blood pressure, haemodynamic parameters, laboratory measurements, cerebral blood flow and oxygenation, are easier to obtain and relevant in the acute situation, but not necessarily predictive for long-term outcome in the context of drug development.

3.1.2. Available therapies and unmet medical need

Administration of fluids is a mainstay of the therapeutic approach in many paediatric patients presenting with hypotension and haemodynamic instability.

The inotropic and peripheral vasoconstrictor effects of dopamine predominate in the newborn period, although there is controversy surrounding the existence of any vasodilator effects in renal, coronary and cerebral circulations.

Dobutamine is a synthetic catecholamine with beta-adrenergic actions with inotropic effects but without the tendency for peripheral vasoconstriction.

Epinephrine is an endogenous catecholamine that acts directly and dose-dependently on α-1 and α-2, β-1 and β-2 adrenoreceptors, with vasopressive and inotropic actions, respectively.

Norepinephrine is often used as a second- or a third-line antihypotensive agent. It is an endogenous sympathomimetic amine that acts on the vascular and myocardial α-1 receptors with a mild to moderate β-1 adrenoreceptor agonism.

Milrinone, a PDE inhibitor, can improve left ventricular function and reduce pulmonary (venous and arterial) hypertension.

In neonates, vasopressin has been predominantly used for catecholamine-resistant shock.

In preterm infants, corticosteroids are also used to improve haemodynamic state and increase blood pressure.

3.1.3. Main clinical studies

The applicant has submitted published studies to support the proposed indication.

Controlled prospective clinical studies in paediatric patients

Septic shock

Ventura AM. Et al., Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock Critical Care Medicine 2015; 43: 2292-2302.

It was a Double-Blind Prospective Randomised Controlled single centre trial conducted in Brazil. Primary endpoint: 28-day mortality.

120 patients were evaluable, 63 on dopamine, 57 on epinephrine. Baseline characteristics and therapeutic interventions were largely similar. Small numerical imbalances were seen for age (Dopamine vs. Epinephrine): 39.6 (46.3) vs. 56.9 (58.2) months, and Pediatric Risk of Mortality (15.7 (10.4) vs. 13.3 (9.9)).

There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and 4 (7%) in the epinephrine group (p = 0.033). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1-37.8; p = 0.037) and healthcare-associated infection (HAI) (odds ratio, 67.7; 95% CI, 5.0-910.8; p = 0.001). Patients in the dopamine group also died significantly earlier during the course of the disease than those in the epinephrine group (p = 0.047). HAI occurred in 18 of 63 patients in the dopamine group (28.5%) and four of 57 patients in the epinephrine group (2.3%). Ventilator-associated pneumonia was the main site of infection and was diagnosed in 11 of 18 patients in the dopamine group and two of four patients in the epinephrine group.

Ramaswamy KN et al., Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock, (Pediatr Crit Care Med 2016; 17:e502–e512)

Primary endpoint: Resolution of shock within first hour of resuscitation

29 children were randomised to the epinephrine group and 31 to the dopamine group (all completers). Baseline characteristics were largely balanced including SOFA and PRISM III scores, with the exception of a numerical imbalance in age (Epinephrine vs. Dopamine) mean age 7 (1 – 11) vs. 4 (0.8 – 8) years.

Resolution of shock was achieved in 16 children (26.6%) within the first hour of resuscitation; 12 (41.4%) had received epinephrine and four (12.9%) dopamine as the first-line vasoactive therapy (p = 0.019). Resolution of shock in the first hour was more likely with epinephrine as compared to dopamine (OR, 4.8; 95% CI, 1.3–17.2). Achievement of normal systolic blood pressure, heart rate normal for age, and urine output was similar between both the groups.

The proportion of children who achieved resolution of shock within 6 hours of resuscitation was numerically higher in children who received epinephrine (48.3%) than dopamine (29%), (OR, 2.01; 0.7–5.7; p = 0.18). The day-28 all-cause mortality in the study cohort was 53.3% (32/60): 48.3% (14/29) in the epinephrine group and 58.1% (18/31) in dopamine group (RR, 0.83; 95% CI, 0.51–1.34; p = 0.605). No significant difference was observed between the two groups on survival analysis (log-rank p = 0.27).

Baske K et al., Epinephrine versus dopamine in neonatal septic shock: a double-blind randomized controlled trial. European Journal of Pediatrics 2018; 177: 1335–1342

Primary endpoint: 'reversal of shock' during first 45 min of vasoactive drug infusion.

20 neonates were randomised to the epinephrine group and 20 to the dopamine group. Patient characteristics were largely balanced: mean gestational age (epinephrine vs. Dopamine) 30.3 ± 3.4 vs. 30.7 ± 2.9 wks., Birth weight (g) 1100 (926, 1400) vs. 1181 (892, 1540). There were some imbalances in different outcome measures numerically favouring one or the other treatment. Mortality was numerically slightly in favour of epinephrine (n = 14 (70%) vs. n = 16 (80%).

Cardiac disease

Laitinen P. et al., Amrinone Versus Dopamine-Nitroglycerin After Reconstructive Surgery for Complete Atrioventricular Septal Defect. Journal of Cardiothoracic and Vascular Anesthesia, 1997; 11: 1997: 870-874

Thirty-two infants with complete atrioventricular septal defect were included. Amrinone loading dose, 2 mg/kg, followed by a maintenance infusion, 7.5 µg/kg/min, was given to 17 infants before separation from cardiopulmonary bypass. The remaining 15 patients received a combination of dopamine, 5 µg/kg/min, and nitroglycerin, 1 microgram/kg/min. The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass.

Amrinone provided a higher cardiac output, more favourable oxygen dynamics, and lower pulmonary vascular resistance than a combination of dopamine and nitroglycerin.

Laitinen P. et al., Amrinone Versus Dopamine and Nitroglycerin in Neonates After Arterial Switch Operation for Transposition of the Great Arteries. Journal of Cardiothoracic and Vascular Anesthesia, Vo113, No 2 (April), 1999: pp 186-190. (63)

Thirty-five neonates with transposition of the great arteries participated. A loading dose of amrinone, 2 mg/kg, followed by a maintenance infusion of 7.5 µg/kg/min, was administered to 16 neonates before separation from cardiopulmonary bypass. The remaining 19 patients were administered a combination of dopamine, 5 µg/kg/min, and nitroglycerin, 1 µg/kg/min. The circulatory state of the patients was evaluated from 4 to 18 hours after cardiopulmonary bypass. Open-label epinephrine infusion was administered in both groups as required.

With the dosage regimen used, supplemented with epinephrine, amrinone provided a higher cardiac output and more favourable oxygen dynamics than a combination of dopamine and nitroglycerin.

Booke PD et al., Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. British Journal of Anaesthesia 1995; 74: 419-42

Blinded, three-period, two-treatment, crossover design study in 19 children, aged 2-54 months, requiring high-dose inotropic support after cardiac surgery, given either dopamine or dobutamine at a dose of 7.5-20 ug/kg/min, respectively.

Dobutamine and dopamine were equipotent inotropes. In five children given neither enoximone nor phenoxybenzamine, dopamine, in a dose of 7.5 ug/kg/min or more, produced significant mean increases in PAP and PVRI (P = 0.04), compared with the same dose of dobutamine. The investigators decided not to continue with this dose regimen due to this observation.

Hypoxic Ischaemic Brain Injury

Diessa TG et al., The Journal of Paediatrics 1981; 99: 772-776 (51)

Fourteen severely asphyxiated infants were entered into a double-blind study designed to compare the effects of dopamine (2.5 /µg/kg/ minute) or placebo (dextrose in water). Systolic BP of at least 50mmHg was an inclusion criterion. Mean weight (kg) 2.96 ± 0.49 vs. 3.46 ± 0.34, Gestational age (wk) 41.1 ± 1.5 vs. 39.8 ± 0.89, 1-minute Apgar 1.7 ± 2 vs. 2.4 ± 3; 5-minute Apgar 3.1 ± 2.1 vs. 4.0 ± 2,2.

Echocardiographically determined shortening fraction and mean velocity of circumferential fibre shortening increased when compared to pre-infusion values ($p < 0.05$). There was no significant change in these echo indices of cardiac function in the placebo-treated group. Systolic blood pressure rose in the dopamine group when compared to pre-dopamine infusion values and to the post infusion values of the placebo group (P less than 0.001 and 0.025, respectively). Diastolic blood pressure increased to a small degree in the dopamine group. There was no significant change in heart rate or echocardiographically measured systolic time intervals.

In addition to the literature, the applicant submitted the clinical study report of the HIP Study in ELGANS.

HIP study

The main evidence of efficacy and safety in ELGANs submitted was a single phase III multicentre, randomised, pragmatic, double blind study in extremely preterm infants with hypotension comparing dopamine (n=29) with a more permissive approach by using placebo fluids and allowing for lower BP levels (n=29). Two Co-primary endpoints were predefined:

- Survival free of neurodisability at 2 years corrected gestational age (GA).

- Survival up to 36 weeks corrected GA free from severe brain injury based on 36 week cranial ultrasound.

3.2. Favourable effects

The key demonstrated favourable effect of dopamine, both in extremely preterm hypotensive infants and in other hypotensive conditions, is an increase in arterial blood pressure. An increase in arterial blood pressure has been described in almost all of the hypotensive instances in the paediatric population.

In the HIP study changes in mean BP from 0 to 2 hours differed between the placebo and dopamine groups (p=0.028 for group × time interaction). The largest difference between the two groups was at 30 min (difference in means 4.4 mmHg, 95% CI 1.8 to 7.1, p=0.001).

3.3. Uncertainties and limitations about favourable effects

There are several uncertainties.

Hypotension in the paediatric patient population < 18 years of age.

Septic shock

A clinically relevant benefit beyond a blood pressure increase has not been demonstrated.

In one randomised trial (Ventura et al., 2015) there were 13 (20.6%) deaths in the dopamine group and 4 (7%) in the epinephrine group (p = 0.033). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1-37.8; p = 0.037) and healthcare-associated infection (HAI) (odds ratio, 67.7; 95% CI, 5.0-910.8; p = 0.001).

In another randomised trial (Ramaswamy; Pediatr Crit Care Med 2016; 17:e502–e512) comparing dopamine with epinephrine, effects on BP and HR were comparable. Resolution of shock was achieved in 16 children (26.6%) within the first hour of resuscitation; 12 (41.4%) had received epinephrine and four (12.9%) dopamine as the first-line vasoactive therapy (p = 0.019). Resolution of shock in the first hour was more likely with epinephrine as compared to dopamine (OR, 4.8; 95% CI, 1.3–17.2). The day-28 all-cause mortality in the study cohort was 53.3% (32/60): 48.3% (14/29) in the epinephrine group and 58.1% (18/31) in dopamine group (RR, 0.83; 95% CI, 0.51–1.34; p = 0.605). No significant difference was observed between the two groups on survival analysis (log-rank p = 0.27).

In a retrospective cohort study in preterm infants (< 35 wks GA) with septic shock (Nissimov S et al., European Journal of Pediatrics 2023; 182:1029–1038), were investigated over 10 years who received Dopamine or Norepinephrine as primary therapy for hypotension during sepsis. A total of 156 infants were included, 113 received DA and 43 NE. After propensity score adjustment, Norepinephrine was associated with lower episode-related mortality [adjusted odds ratio (95% CI) 0.55 (0.33, 0.92)], pre-discharge mortality [0.60 (0.37, 0.97)], post-illness new diagnosis of significant neurologic injury [0.32 (0.13, 0.82)], and subsequent occurrence of NEC/sepsis among the survivors [0.34, (0.18, 0.65)].

This is paralleled by a study in adults, that showed an increased mortality in patients with septic shock, when treated with dopamine vs. norepinephrine (De Backer et al., Crit Care Med 2012; 40: 725-730).

Another retrospective cohort study in 118 children with fluid-refractory septic shock (Kohn-Loncarica et al., 2020, Revista Brasileira de Terapia Intensiva 32(4):551-556.) also revealed a numerically higher mortality with dopamine than with epinephrine. Mortality was 5% for the Epinephrine Group versus 9% for the Dopamine Group (p = 0.64). However, the result was inconclusive due to major baseline differences between the groups. After exclusion of patients with oncological diseases, the negative imbalance favouring epinephrine with respect to mortality disappeared.

On the contrary, a very recent multicentre cohort study (Foote HP et al., Journal of Perinatology (2023) 43:1274–1280) of infants in the neonatal intensive care unit with an episode of septic shock indicated a worse outcome with epinephrine. Inborn infants less than 120 days old with an episode of septic shock with a median (IQV) gestational age of 25 weeks (24, 28) and a median birth weight of 760 g (605 g, 1174 g) were investigated. Five hundred infants (31%) had early onset sepsis. Overall mortality was 50%. Compared to infants who were treated with dopamine alone, adjusted odds of mortality were higher for those who received epinephrine alone (aOR 4.7 [95% CI: 2.3–9.2]). The study was also inconclusive due to the observational design. Even more, in the publication baseline characteristics of infants were only provided for the overall group of patients without differentiation between the different treatment groups, thereby largely hampering an assessment of the drug effects.

In all of the 3 of the randomised controlled trials investigating the administration of dopamine vs. epinephrine in paediatric patients with septic shock mortality was either significantly or numerically

higher in the dopamine group. A higher mortality was also observed in an additional retrospective cohort study in preterm infants. This goes in line with results from a study in adults also indicating that administration of dopamine, as compared with norepinephrine, may be associated with higher rates of death among patients with septic shock (De Backer et al., Crit Care Med 2012; 40: 725-730). In the study by Ventura a higher rate of in hospital acquired infections was observed in patients treated with dopamine. Taken all of the information together, the totality of evidence currently may not be robust enough to finally conclude on a detrimental effect of dopamine and to justify a contraindication for a first line treatment in paediatric patients with septic shock. A warning statement reflecting the concerns and the uncertainty regarding clinical outcome and stating that treatment with dopamine is not recommended in this instance was added to the SmPC.

Cardiac shock, traumatic brain injury, hypoxic brain ischaemia, drug overdose and toxic agents.

No reliable data on clinically relevant outcome data beyond an effect on BP and haemodynamics are available. In adults, dopamine was associated with an increased 28-day rate of death among patients with cardiogenic shock as compared to norepinephrine (De Backer D N Engl J Med 2010;362:779-789; Rui et al., Medicine (Baltimore). 2017 Oct;96(43):e8402). Despite of differences between adult and paediatric patients with cardiogenic shock, the data should have some relevance at least for the older adolescent patients but raises concerns irrespectively of age. Little information is available about a second line administration in children with this condition.

Extreme preterm infants with hypotension (indication no longer pursued)

There are no data showing a clinical benefit with respect to short-term and long-term clinical outcome. The Co-primary endpoints did neither show a statistically significant superiority of one treatment strategy over the other nor is it possible to conclude on equivalence or non-inferiority.

There was no statistically significant difference between the active and control arms in the co-primary end-point of survival free of neurodevelopmental disability at 2 years adjusted GA (48.1% in the dopamine group compared to 25.0% in the placebo arm, OR 2.79 (0.89-1.71, p value 8.72), an endpoint of particular clinical relevance for the long term outcome but influenced by many factors unrelated to dopamine use..

The co-primary outcome of survival free of ultrasound abnormality at 36 weeks GA was reached by 18/29 (62%) in the dopamine group and by 20/29 (69%) in the placebo group (OR 0.74, 95% CI 0.25 to 2.18).

No significant difference was observed for the following secondary outcome measures (Dopamine vs. Placebo, n (%), Odds ratio (95%CI, p value):

- Mortality up to week 36: 6 (21) vs. 7 (24) OR 0.82 (0.24 to 2.83) p= 0.75;
- Severe ultrasound abnormality: 5 (17) vs. 5 (17) OR 1.00 (0.26 to 3.91) p = 1;
- Grade 3/4 IVH: 5 (17) vs. 2 (7) OR 3.06 (0.51 to 18.41) p = 0.22;
- PVL: 2 (7) vs.2 (7) OR 1.04 (0.13 to 8.37) p = 0.97;
- Any ultrasound abnormality: 16 (55) vs. 13 (45) OR 1.51 (0.54 to 4.26) p = 0.43;
- NEC: 1 (3) vs. 4 (14) OR 0.22 (0.02 to 2.13) p = 0.19;
- SIP 3: (10) vs. 3 (10) OR 1.00 (0.18 to 5.42) p = 1;
- BPD*: 17 (74) vs.14 (64) OR 1.87 (0.45 to 7.68) p = 0.39;
- Duration of inotrope (hours) (n = 21 and 22): 17.8 (7.5–30.6) vs. 13.7 (6.1–24.5) OR 1.46 (0.84 to 2.56) p = 0.18.

*(Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leucomalacia; SIP, spontaneous intestinal perforation; *in the patients that survived up to 36 weeks)*

It is therefore uncertain, whether the effect of dopamine on arterial BP translates into clinical benefit.

Dopamine had no significant effect on rScO2 compared to placebo in hypotensive infants.

Currently, the criteria to initiate dopamine are unclear in the absence of clear data showing whether treatment e.g. at MABP below GA or a more permissive approach by allowing lower BP values in the absence of signs of impaired tissue perfusion is of advantage.

Furthermore, a GCP inspection revealed several critical issues at the sponsor site, questioning the reliability of the data.

3.4. Unfavourable effects

Well-known unfavourable effects of dopamine are the cardiovascular adverse effects, specifically hyper- and hypotension, tachy- and bradycardia as well as ectopic heart beats, palpitations, conduction and ECG abnormalities and (potentially fatal) ventricular arrhythmias. Limited evidence from the literature suggests an association of early inotrope use with an increased risk of intra-cerebroventricular haemorrhage (small numerical imbalance also seen in the HiP study, below). Moreover, according to some clinical evidence from the literature, dopamine administration appears to increase the risk of infections (also suggested by HiP study results, see below), possibly due to negative effects on T lymphocyte functionality. Another potentially unfavourable effect of dopamine is the transient suppression of pituitary function (and concomitantly of thyroid hormone levels), which is followed by a pronounced rebound effect after dopamine discontinuation. Furthermore, dopamine may reduce chemoreceptor sensitivity, affecting the ventilatory response, and an increase in pulmonary artery pressure has been observed in a part of the paediatric patients treated with dopamine. Moreover, dopamine has been shown to cause ventilation-perfusion mismatch and an imbalance between oxygen delivery and consumption, the latter most likely due to dopamine-induced increased oxygen consumption in the tissues. In addition, dopamine-induced vasoconstriction, with increased risk at higher dopamine doses, may result in reduced tissue perfusion and in tissue damage, e.g., resulting in gangrene or an increased susceptibility to necrotising enterocolitis.

Dopamine may show reduced efficacy in hypovolaemic patients, which requires correction of hypovolaemia before considering dopamine use. An association between dopamine administration and retinopathy of prematurity has been reported in the literature.

Due to the limited number of participants in the HiP study, the differences in AEs between dopamine- and placebo-treated patients were mostly small. In the following, only unfavourable effects with larger differences between the treatment arms are mentioned or those, for which an association with dopamine is also discussed in the literature. A comparably large numerical difference was observed with regard to AEs possibly related to infections (Dopamine: n=18; Placebo: n=12). A smaller imbalance was observed with regard to haemorrhages (intraventricular haemorrhages of various grade, including right subependymal bleed [Dopamine: n=6, Placebo: n=4]; pulmonary haemorrhage [Dopamine: n=2, Placebo: n=0]). Other (minor) imbalances pertain to “Retinopathy of prematurity” (DA: n=5; PLc: n=4) and (suspected) necrotising enterocolitis, necrosis of intestinal wall (DA: n=3; Plc: n=2).

3.5. Uncertainties and limitations about unfavourable effects

An increased risk of infections in dopamine-treated patients is suggested by the HiP trial data. In addition, a limited number of literature reports suggests an association between dopamine administration and increased risk of infection. Although the evidence is rather limited, it seems mechanistically plausible.

Reduced perfusion of tissues due to dopamine-induced vasoconstriction is a well-known effect of dopamine, specifically at higher doses, when α-adrenoceptors are stimulated. Gangrene is a well-known adverse event resulting from peripheral vasoconstriction. Literature data also suggest that dopamine may reduce perfusion of other tissues, e.g. in the gastrointestinal tract.

Although the temporary suppression of pituitary function and the following rebound effect have been clearly described in the literature, it is currently unclear, whether a short-term administration of dopamine in neonates may cause negative acute and long-term consequences, specifically with regard to reduced thyroid function. Moreover, it is still unclear, whether the strong rebound effect after dopamine discontinuation may have adverse consequences for the patients.

The unfavourable effect on respiratory function and the potential to increase pulmonary artery pressure are supported by the literature, but may only be clinically relevant for subgroups of patients. Although an association between dopamine use and retinopathy of prematurity has been repeatedly reported, a causal relationship is considered unlikely.

3.6. Effects Table

Table 18. Effects Table for Neoatricon

Effect	Short Description	Unit	Treat-ment[a]	Control[a]	Uncertainties/ Strength of evidence	References
Favourable Effects						
Blood pressure stabilisation in hypotensive extremely preterm Infants	Increase in mean arterial BP	mmHg	dopamine	Placebo fluid	Largest mean difference: 4.4 mmHg, 95% CI 1.8 to 7.1, p=0.001 Reliability of the data is in question considering several critical findings at the sponsor cite at a GCP inspection.	HIP study
Blood pressure stabilisation in hypotensive paediatric patients (sepsis, cardiac, brain injury, brain ischaemia, toxins, drug overdose)	Increase in mean arterial BP					Ample evidence from published literature

Effect	Short Description	Unit	Treat-ment[a]	Cont rol[a]	Uncertainties/ Strength of evidence	References
Unfavourable Effects[b]						
Cardiovascular effects	hyper- and hypotension, tachy- and bradycardia, ectopic heart beats, palpitations, conduction and ECG abnormalities, (potentially fatal) ventricular arrhythmias.				Commonly known from numerous literature reports and referred to in the SmPCs of dopamine products for infusion	
Intra-cerebroventricular haemorrhage	Increase of blood pressure caused by early inotrope use may increase the risk of intra-cerebroventricular haemorrhage in preterm neonates.				Suggested by some literature reports, by the HiP data and by theoretical considerations.	Abdul Aziz AN et al (2020)
Increased risk of infection	Mechanism could be suppression of prolactin release (see also next effect below), which may impair T cell functionality and increases risk of infection.				Supported by some literature reports, by the HiP data and by theoretical considerations.	Bernton EW et al. (1988) Devins SS et al. (1992) Ventura AM et al. (2015) Hatachi T et al. (2018) Hotta M et al. (2020)
Transient suppression of pituitary function with rebound effect after dopamine discontinuation	Suppression of pituitary function leads to reduction of thyroid hormone (T4 and T3) levels as well as to reduced prolactin and growth hormone levels.				Well-established effect of dopamine. However, the acute and long-term consequences for the patients are not entirely clear.	Van den Berghe G et al (1994) Filippi L et al (2004 a,b)

Effect	Short Description	Unit	Treat-ment[a]	Cont rol[a]	Uncertainties/ Strength of evidence	References
Increased risk of hypoxia	Dopamine can depress local vasoconstriction in response to alveolar hypoxia, which normally keeps perfusion appropriately matched to ventilation in the lung Dopamine can depress the chemoreceptor drive to ventilation normally induced by arterial hypoxemia. Dopamine can cause an imbalance between oxygen delivery (DO_2) and consumption (VO_2).				Suggested by some literature reports	Shoemaker WC et a. (1989) Van de Borne P et al. (1998) Li J et al (2006)
Increased pulmonary artery pressure	Dopamine can increase pulmonary artery pressure, probably by α-adrenoceptor-mediated vasoconstriction				Clear evidence from literature	For example: Driscoll DJ et al (1979) Booker PD et al (1995) Outwater KM et al (1990) Liet JM et al. (2002)

Effect	Short Description	Unit	Treat-ment[a]	Cont rol[a]	Uncertainties/ Strength of evidence	References
Reduced tissue perfusion	Dopamine-induced vasoconstriction may result in reduced tissue perfusion and in tissue damage, e.g., resulting in gangrene or an increased susceptibility to necrotising enterocolitis. The risk is increased at higher dopamine doses.				Reduced organ perfusion at high dopamine doses is to be expected due to excessive vasoconstriction. Case reports for gangrene available in the literature; association with necrotising enterocolitis suggested by literature.	Reduced bowel perfusion, necrotising entero-colitis: Zhang J et al (1999) Garg PM et al (2022) Gangrene: e.g., Maggi JC et al (1982) Koerber RK et al. (1984)
Reduced efficacy in hypovolaemic patients	Correction of hypovolaemia is required before considering dopamine use.				Strong evidence, common clinical practice.	
Retinopathy of prematurity	Common condition in preterm neonates; abnormal growth of blood vessels in the retina				Association reported, most likely no causal relationship	e.g., Mizoguchi MB et al. (1999) Allegaert K et al. (2004)

[a]The columns “treatment” and “control” were not filled, due to the diversity of conditions in the literature reports that were the main source of information in this procedure. In the HiP study, treatment was volume administration (10 mL/kg of 0.9% saline administered over 20 min), followed by dopamine in 5% dextrose (5 µg/kg/min of dopamine, increased by 5 µg/kg/min increments every 30 min up to a maximum of 20 µg/kg/min). In the control group of the HiP study, volume was administered, followed by placebo (5% dextrose).

[b]Only the most important unfavourable effects are mentioned. Other effects like nausea, vomiting, headache etc. are well-known and listed in the SmPCs of dopamine products for infusion already authorized for adult patients.

Abbreviations:
Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Importance of favourable effects

Treatment of hypotension in haemodynamically instable paediatric patient from birth to < 18 years of age.

There is ample evidence in the published literature that dopamine increases blood pressure, and clinical experience has accumulated over decades when administering dopamine in haemodynamically instable paediatric patients with hypotension. Although not directly demonstrated in the target population, the aim of stabilising blood pressure is to improve organ perfusion and oxygen delivery. In this regard, efficacy can be considered established. There are safety concerns in specific patient groups. Two controlled studies in the paediatric population, and one study in adults indicate a numerical/significant increase in mortality in sepsis associated hypotension, putting a question mark on the importance of the BP stabilising effect of dopamine. Controlled long-term data in other shock- or hypotensive conditions are not available for the paediatric population. In addition, in adults, first line administration of dopamine was associated with an increased 28-day rate of death among patients with cardiogenic shock (De Backer D N Engl J Med 2010;362:779-789).

Clinical data available reflect information available for dopamine as a first line drug. No reliable information is available when dopamine is administered in cases where other vasoactive drugs fail to achieve a sufficient response on blood pressure.

ELGANS

Stabilising cardiovascular function and haemodynamics is of key importance in patients with shock. Dopamine has a demonstrated effect on arterial blood pressure. However, it is less certain whether the haemodynamic profile of dopamine leading to an increase in blood pressure to some degree by a positive inotropic effect, but dose dependently more by vasoconstriction is favourable. Evaluation of the clinical state of preterm hypotensive infants is not restricted to single measurements of BP but involves among others assessment of cardiac haemodynamics, tissue perfusion, avoidance of BP variability and of peak BP values and well adjusted BGA values in order to avoid metabolic acidosis. Drugs like dobutamine with a less pronounced effect on arterial blood pressure increase left ventricular output which may be an advantage for tissue perfusion. In preterm infants the dopamine induced increase in MABP was not accompanied by an effect on rScO2 compared to placebo. Long-term benefit with respect to clinical endpoints covering survival free of cerebral abnormalities as detected by ultrasound at wk 36 GA and survival free of neurodevelopmental disability at 2 years did not show a benefit over a permissive treatment strategy with fluid administration and allowing for lower BP values.

An indication for the treatment of ELGANs is no longer pursued by the applicant.

Importance of unfavourable effects

Among the unfavourable effects of dopamine listed in section 4.8 of the currently proposed SmPC, the cardiac effects (e.g., ectopic heart beats, tachycardia, bradycardia, widened QRS complex, ventricular arrhythmias) are considered most important, specifically, as dopamine may be used to treat hypotension in patients during or after cardiac surgery. Some cardiac effects, especially ventricular arrhythmias, may even be fatal.

From the unfavourable effects suggested by the literature (and supported by the HIP trial), the potentially increased risk of infection is considered to be of high importance. Reduced perfusion of tissues due to dopamine-induced vasoconstriction is also considered highly important, as it may result

in irreversible and/or potentially life-threatening complications like gangrene or necrotising enterocolitis.

The suppression of pituitary function by dopamine is only temporary, and is followed by a rebound effect upon dopamine discontinuation. However, it is considered an important unfavourable effect, unless it can be clearly excluded that it has no acute adverse consequences and also does not impair long-term development in preterm neonates. Moreover, it has to be excluded that the pronounced rebound effect after dopamine discontinuation does not lead to serious acute consequences.

The unfavourable effect on respiratory function may be important, as it may result in hypoxia.

The potential of dopamine to increase pulmonary artery pressure in particular at higher doses above 10 µg/kg/min is considered important, specifically for patients with established pulmonary hypertension and in the context of cardiac diseases and cardiac surgery, but has also to be considered in patients at risk for an increased pulmonary pressure and in situations where the haemodynamics have not been sufficiently characterized yet.

Retinopathy of prematurity might be considered important, but so far, a causal relationship with dopamine use has not been confirmed in the literature.

Well-known unfavourable effects like headache, nausea or vomiting are considered less important since they do not result in negative long-term consequences and are reversible when dopamine is discontinued.

3.7.2. Balance of benefits and risks

In conclusion, the benefit/risk balance is considered positive for the treatment of hypotension in haemodynamically unstable neonates, infants and children < 18 years.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall benefit/risk balance of Neoatricon is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Neoatricon is favourable in the following indication(s):

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0209/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.