Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Dobutamine hydrochloride
Dasomin®

PL/W/0003/pdWS/001

Rapporteur:	Poland (PL)
Finalisation procedure (day 120):	2.01.2013
Date of finalisation of PAR	**21.01.2013**

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	DASOMIN
INN (or common name) of the active substance(s):	Dobutamine hydrochloride
MAH (s):	Pharmis Biofarmacêutica, Lda, Portugal
Pharmaco-therapeutic group (ATC Code):	C01CA07
Pharmaceutical form(s) and strength(s):	concentrate for solution for infusion, 250 mg/ 20 ml

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections: SmPC : 4.1, 4.2, 4.4, 4.8, 5.1, 5.2;
PIL : 1,2,3.

Summary of outcome

☐ No change

☒ Change

☐ New study data

☐ New safety information: section(s):

☐ Paediatric information clarified: section(s):

☒ New indication: 4.1, 4.2

4.1 Therapeutic indications

Paediatric population

Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock."

4.2 Posology and method of administration

Paediatric population

For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2 – 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1,0 micrograms/kg/minute will produce a response.

There is reason to believe that the minimum effective dosage for children is higher than for adults. Caution should be taken in applying high doses, because there is also reason to believe that the maximum tolerated dosage for children is lower than the one for adults. Most adverse reactions (tachycardia in particular) are observed when dosage was higher than/equal to 7.5 micrograms/kg/minute, but reducing or termination of the rate of dobutamine infusion is all that is required for rapid reversal of undesirable effects.

A great variability has been noted between paediatric patients in regard to both the plasma concentration necessary to initiate a hemodynamic response (threshold) and the rate of hemodynamic response to increasing plasma concentrations, which demonstrates that the

required dose for children cannot be determined a priori and should be titrated in order to allow for the supposedly smaller “therapeutic width” in children.

Method of administration

For continuous intravenous infusion using an infusion pump, dilute to a concentration of 0.5 to 1 mg/mL (max 5mg/mL if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%. Infuse higher concentration solutions through central venous catheter only. Dobutamine intravenous infusion is incompatible with bicarbonate and other strong alkaline solutions.

Neonatal intensive care: Dilute 30 mg/kg body weight to a final volume of 50 mL of infusion fluid. An intravenous infusion rate of 0.5 mL/hour provides a dose of 5 micrograms/kg/minute.

4.4 Special warnings and precautions for use

Paediatric population

Dobutamine has been administered to children with low-output hypoperfusion states resulting from decompensated heart failure, cardiac surgery, and cardiogenic and septic shock. Some of the haemodynamic effects of dobutamine hydrochloride may be quantitatively or qualitatively different in children as compared to adults. Increments in heart rate and blood pressure appear to be more frequent and intense in children. Pulmonary wedge pressure may not decrease in children, as it does in adults, or it may actually increase, especially in infants less than one year old. The neonate cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect seems to be more often observed in adult patients than in small children. Accordingly, the use of dobutamine in children should be monitored closely, bearing in mind these pharmacodynamic characteristics.

4.8 Undesirable effects

Paediatric population

The undesirable effects include elevation of systolic blood pressure, systemic hypertension or hypotension, tachycardia, headache, and elevation of pulmonary wedge pressure leading to pulmonary congestion and edema, and symptomatic complaints.

5.1 Pharmacodynamic properties

Paediatric population

Dobutamine also exhibits inotropic effects in children, but the haemodynamic response is somewhat different than that in adults. Although cardiac output increases in children, there is a tendency for systemic vascular resistance and ventricular filling pressure to decrease less and

for the heart rate and arterial blood pressure to increase more in children than in adults. Pulmonary wedge pressure may increase during infusion of dobutamin in children 12 months of age or younger.

Increases in cardiac output seems to begin at iv infusion rates as low as 1.0 micrograms/kg/minute, increases in systolic blood pressure at 2.5 micrograms/kg/minute, and heart rate changes at 5.5 micrograms/kg/minute.

The increase of dobutamine infusion rates from 10 to 20 micrograms/kg/minute usually results in further increases in cardiac output.

5.2 Pharmacokinetic properties

Paediatric population

In most paediatric patients, there is a log-linear relationship between plasma dobutamine concentration and hemodynamic response that isconsistent with a threshold model.

Dobutamine clearance is consistent with first-order kinetics over the dosage range of 0.5 to 20 micrograms/kg/minute. Plasma dobutamine concentration can vary as much as two-fold between paediatric patients at the same infusion rate and there is a wide variability in both the plasma dobutamine concentration necessary to initiate a hemodynamic response and the rate of hemodynamic response to increasing plasma concentrations. Therefore, in clinical situations dobutamine infusion rates must be individually titrated.

New proposed PIL wording:

- Section 1: What Dasomin is and what it is used for;
- Section 2: What you need to know before you use Dasomin;
- Section 3: How to use Dasomin;

1. What Dasomin is and what it is used for

(.....)

Paediatric population

Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.

2. What you need to know before you use Dasomin

(.....)

Children

Increments in heart rate and blood pressure appear to be more frequent and intense in children than in adults. The new-born baby cardiovascular system has been reported to be less sensitive to dobutamine and hypotensive effect (low blood pressure) seems to be more often observed in adult patients than in small children.

Accordingly, the use of dobutamine in children should be monitored closely.

3. How to use Dasomin

(.....)

Use in Children

For all paediatric age groups (neonates to 18 years) an initial dose of 5 micrograms/kg/minute, adjusted according to clinical response to 2 – 20 micrograms/kg/minute is recommended. Occasionally, a dose as low as 0.5-1,0 micrograms/kg/minute will produce a response. The required dose for children should be titrated in order to allow for the supposedly smaller “therapeutic width” in children.

II. RECOMMENDATION[1]

According to the MAH no further action is required. The Rapporteur disagrees with such conclusion.

Results of one of first European study assessing efficacy and safety of dobutamine use in children with cardiovascular failure were published by D. Schranz of University in Mainz, Germany (Eur J Pediatr,1982). He concluded that dobutamine is a potent inotropic drug in newborns, infants and children, no side effects were observed. Since this publication, for almost 30 years dobutamine is widely used in all age subsets of paediatric population, mainly for treatment of cardiogenic or septic shock. Only in the PubMed using key words “dobutamine in children” 265 records could be found. Strong recommendations for dobutamine use in children are published. One of the most recently published international guideline on treatment of septic shock (“Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock” Intensive Care Medicine, 2008) recommends use of dobutamine in children with refractory to fluids administration septic shock. Results of the European EuLoCOS –Paed survey published in 2011 showing that dobutamine is a part of standard care of children with low cardiac output syndrome after open heart surgery (W. Vogt, Arch Dis Child, 2011). Controlled, randomized clinical trials to confirm efficacy and safety of dobutamine use in all age subsets of paediatric population can’t be performed nowadays for obvious ethical reasons. Such treatment is already a standard of care in critically ill newborns, infants and children worldwide.

The MAH should take such facts into consideration. The SPC needs to be updated. On 6th December, 2011 response of the MAH has been received. The MAH agreed with comments of the Rapporteur and proposed modification of the SPC.

III. INTRODUCTION

There have been no paediatric studies sponsored for Dasomin® by the MAH, however the report submitted by the MAH on 26 August, 2011 includes review of the several published reports on dopamine hydrochloride in the paediatric population.

An expert overview has been provided.

The MAH stated that the Company does not foresee any regulatory procedures as a result of the submitted report.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing

[1] *The recommendation from section V can be copied in this section*.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

In absence of clinical studies sponsored by MAH, no information is available for this section.

IV.2 Non-clinical aspects

Reproduction studies in rats and rabbit have revealed no evidence of impaired fertility, harm to the foetus or teratogenic effects due to dobutamine. No additional preclinical data are available from published scientific literature.

IV.3 Clinical aspects

1. Introduction

Literature search on dobutamine use in children have been performed using the SciFinder Database. Almost 270 records were found. Twenty of them were used in the PSUR submission covering the period of 2005-2009. Another 30 publications are included into the MAH report.

2. Clinical studies

Summaries of 30 published articles on dobutamine (but not Dasomin® as it is mentioned in the report) use in children are included to the report. Explanation, based on which criteria these articles were chosen is not provided by the MAH. Articles were published between 1982 and 2011.

The articles selected for the MAH report discuss the use of dobutamine in paediatric patients of different age (from neonates to adolescents) in various indications: treatment of cardiogenic or septic shock, dobutamine stress echocardiograpy, management of scorpion sting cases. Interestingly more than 1/3 of articles are related to the dobutamine stress echocardiography. All of them confirmed usefulness of such tests, additionally provide information that dobutamine infusion were safe and well tolerate.

Some of papers chosen by the MAH are related to typical clinical application of dobutamine in paediatric population.

Habib et all published in 1992 results of a study on pharmacokinetics and pharmacodynamics of dobutamine in critically ill children. It was a prospective study of pediatric patients receiving continuous infusions of dobutamine in a stepwise format from 2.5 to 10.0 micrograms/kg/min.

Twelve children ranging in age from 1 month to 17 yrs treated in the paediatric intensive care unit was included in the study. Results of the study confirmed that dobutamine in critically ill paediatric patients is an effective inotropic drug.

Berg in 1993 performed a pharmacokinetics and pharmacodynamics study in intensive care. Results of the study confirms that dobutamine effectively improves systolic function in critically ill children. Hemodynamic responses to dobutamine generally follow a predicted log-linear dose-response model. Dobutamine clearance in this study was consistent with first-order kinetics. The wide variability in hemodynamic responses and clearance kinetics indicate that dobutamine infusions must be titrated individually.

In 2007 Berg concluded that inotropic therapy (including dobutamine) is a well-established practice for children with advanced congestive heart failure . He reported that such therapy could be used also out of paediatric intensive care unit. He reported prolonged used of inotropic therapy (milrinon or dobutamine) at home in 14 paediatric patients with heart failure. Results of the study confirmed that prolonged, continues infusion of dobutamine in children with heart failure is safe and effective.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

According to the MAH no further action is required. The Rapporteur disagrees with such conclusion. Rapporteurs recommendation were supported by HU, NL, FR and UK.

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- **Recommendation**

Type IB variation to be requested from the MAH by <date>

According to worksharing procedure outcome, the following changes of SmPC (PIL) are recommended to be submitted via variations procedure:

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VI. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Dasomin, Pharmis Biofarmacêutica, Lda,