LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Fenylefrin Unimedic
# (phenylephrine hydrochloride)

# SE/H/1551/03/DC

**This module reflects the scientific discussion for the approval of Fenylefrin Unimedic. The procedure was finalised on 2017-07-05. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

Unimedic AB has applied for a marketing authorisation for Fenylefrin Unimedic, 10 mg/ml, concentrate for solution for injection/infusion. The active substance phenylephrine hydrochloride is the same as in Fenylefrin Unimedic, 0.05 mg/ml and 0.1 mg/ml, solution for injection, marketed by Unimedic AB since 2015.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

## III.1 Introduction

No new nonclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written which is considered to be acceptable. Some deficiencies which would normally preclude an approval have been identified but are considered to be overruled by the long clinical experience.

## III.2 Pharmacology

Phenylephrine is a potent vasoconstrictor. It is a postsynaptic α1-receptor agonist with little effect on β-receptors of the heart. Parenteral administration of phenylephrine causes a rise in systolic and diastolic pressures, a slight decrease in cardiac output and a considerable increase in peripheral resistance, while coronary blood flow is increased. Phenylephrine also causes pulmonary vessel constriction and subsequent increase in pulmonary arterial pressure.

## III.3 Pharmacokinetics

No formal non-clinical pharmacokinetic studies have been presented by the applicant and due to the stated lack of non-clinical data the applicant only presents data on metabolism.

## III.4 Toxicology

Non-clinical single and repeat dose toxicity data on phenylephrine appear to be limited. The potential Genotoxicity and Carcinogenicity of phenylephrine have been studied within the National Toxicology Programme. In vitro, phenylephrine was found to be negative in the Ames assay and in a chromosome aberration assay but positive in the mouse lymphoma assay and also positive in a sister chromatid exchange assay. However, in an in vivo rat micronucleus assay phenylephrine was concluded to be negative. Based on two carcinogenicity studies, one two year study in rat and one two year study in mice, it is concluded that there is no evidence for a carcinogenic potential of phenylephrine in rats or mice.

There is scant information on the reproductive toxicology of phenylephrine and non-clinical data are concluded to be insufficient. However, it is recognized that the product is intended for short term use during anaesthesia. The uncertainties due to the insufficiency of data are reflected in the SmPC.

## III.5 Ecotoxicity/environmental risk assessment

Phenylephrine is concluded not to be a PBT-substance and it is agreed that no additional data or further evaluation of the environmental impact is needed. In accordance with Guideline, an ERA is not considered to be needed for this extension since it is not expected to result in any significant increase in the extent of the use of phenylephrine.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

No new data have been provided for this extension application.

## IV.2 Pharmacodynamics

No new data have been provided for this extension application.

## IV.3 Clinical efficacy

The new strength, Fenylefrin Unimedic 10 mg/ml, is a concentrated solution and should be diluted before administration. As Fenylefrin Unimedic 0.05 and 0.1 mg/ml, Fenylefrin Unimedic 10 mg/ml is intended for the treatment of hypotension during spinal, epidural and general anaesthesia.

The applicant submitted a clinical overview based solely on bibliographical data. The main literatures reviewed are concerning phenylephrine treatment in the clinical setting of neuroaxial surgery, cardiac and vascular surgery, critical care for hypotension related to shock and prevention and treatment of hypotension related to caesarean delivery. Six key studies investigating the clinical efficacy of phenylephrine for treatment or prevention of hypertension during spinal anaesthesia in women under caesarean delivery were presented. Phenylephrine effects on BP, Heart Rate, Neonatal Outcome and effects on Nausea and Vomiting were discussed based on the study outcome. Other publications include studies with phenylephrine treatment during surgical procedures (e.g cardiac and vascular surgery), anesthesia procedures ( e.g epidural and general anesthesia) and medical conditions (e.g shock). Few publications related to use of phenylephrine in the target paediatric population and meta-analysis with the comparison of the clinical efficacy between Ephedrine and phenylephrine were also discussed.

The applicant presented a comprehensive overview of Phenylephrine drug-drug interactions. The drug-drug interaction included in the proposed SmPC was considered adequately justified by the applicant.

In conclusion, the Applicant has provided reasonable amount of data supporting a clinical efficacy of phenylephrine treatment for the proposed indication.

## IV.4 Clinical safety

The Applicant has provided an adequate overview of the safety profile of Fenylefrin Unimedic. The adverse reactions are generally adequately reflected in the proposed SmPC.

The most commonly reported cardiovascular adverse event appears to be bradycardia, likely due to baroreceptor-mediated vagal stimulation and consistent with the pharmacological effect of phenylephrine. Some of the reported serious adverse events and deaths are probably related to the underlying disease and not to the use of phenylephrine.

Symptoms of phenylephrine overdose include headache, vomiting, hypertension and reflex bradycardia and other cardiac arrhythmias. Treatment should consist of symptomatic and supportive measures.

The most common maternal adverse events reported in women undergoing caesarean delivery under spinal anaesthesia were bradycardia, reactive hypertension, nausea and vomiting.

Overall, the safety profile is well-known and no new safety signal is evoked. The safety profile for Phenylephrine 10mg/ml administered after appropriate dilution is not considered to be differed from Phenylephrine 0.05 and 0.1 mg/ml.

## IV.5 Risk Management Plans

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Fenylefrin Unimedic.

Safety specification

Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | Arterial hypertension<br>Arrhythmia |
| Important potential risks | Extravasation<br>Medication error |
| Missing information | Use during pregnancy<br>Use in paediatric population |

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

An updated RMP should be submitted:

- At the request of the RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

# V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Fenylefrin Abcur, SE/H/1255/01-02/IB/03 regarding content and Hydroklortiazid Evolan (Asp no. 2009-0092–0094, MT no.42126-42128) regarding layout.
The bridging report submitted by the applicant has been found acceptable.

# VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Phenylephrine is a potent α-adrenergic-specific vasoconstrictor that increases systolic blood pressure, diastolic blood pressure, and mean arterial pressure, without affecting inotropy or chronotropy. It also causes reflex bradycardia. Phenylephrine is frequently used for hemodynamic support in patients in septic shock, during spinal, epidural and general anesthesia, particularly in relation to cesarean delivery and in cardiac and vascular surgery.

The submitted literature data gives an overview of the current knowledge of the beneficial effects of phenylephrine. The Applicant has provided reasonable amount of data supporting a clinical efficacy and safety of phenylephrine treatment for the proposed indication. No new pre-clinical or clinical studies were performed, which is acceptable given that phenylephrine has been used for decades in a wide range of patient populations, disease states and clinical settings and the safety profile of the active substance is considered well established. The safety profile for Phenylephrine 10mg/ml administered after appropriate dilution is not considered to differ from Phenylephrine 0.05 and 0.1 mg/ml.

The quality of Fenylefrin Unimedic is found adequate. There are no objections to approval of Fenylefrin Unimedic, from a non-clinical and clinical point of view. The product information is acceptable.

The application is therefore recommended for approval.

**List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The Decentralised procedure for Fenylefrin Unimedic, 10 mg/ml, concentrate for solution for injection/infusion was positively finalised on 2017-07-05.

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# Public Assessment Report – Update

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
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*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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