

Public Assessment Report

Scientific discussion

Fenylefrin Unimedic (phenylephrine hydrochloride)

SE/H/1551/01-02/MR

This module reflects the scientific discussion for the approval of Fenylefrin Unimedic. The procedure was finalised on 2015-10-21. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Unimedic AB has applied for a marketing authorisation for Fenylefrin Unimedic, 0.05 mg/ml and 0.1 mg/ml, solution for injection. The active substance is phenylephrine hydrochloride; a potent vasoconstrictor that acts almost exclusively by stimulation of alpha-1-adrenergic receptors. Arterial vasoconstriction is accompanied by venous vasoconstriction which gives an increase in blood pressure and reflex bradycardia. The potent arterial vasoconstriction results in an increase in the resistance which results in reduction of the cardiac output.

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 α_1 -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 chromatide 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 is considered unlikely to represent a risk to the environment.

III.6 Discussion on the non-clinical aspects

No new non-clinical data have been supplied with this application and none are required for an application of this type. Phenylephrine is a sympathomimetic agent with mainly direct effects on alpha-adreno receptors. The drug causes marked arterial vasoconstriction during intravenous infusion. The short duration of action of phenylephrine suggests a rapid distribution, metabolism and elimination from the body. Toxicology data on phenylephrine are limited. There is no evidence for a carcinogenic potential of phenylephrine. Reproductive toxicity has not been sufficiently investigated in animals.

Based on the long clinical experience and the intended short term use during anaesthesia the identified deficiencies in the non-clinical data are considered to be acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical part of the application was submitted as a bibliography. No new clinical data have been supplied with this application and none are required for an application of this type. A clinical expert report has been written by a suitably qualified person and is satisfactory.

IV.2 Pharmacokinetics

The pharmacokinetic data of phenylephrine are limited. However, since the indication is hypotension during anaesthesia and phenylephrine is dosed i.v., based on clinical effect, by anaesthesiologists and patients are carefully monitored PK becomes secondary and the lack of data is considered acceptable.

IV.3 Pharmacodynamics

Phenylephrine is a potent vasoconstrictor that acts almost exclusively by stimulating alpha-1 adrenergic receptors. Such arterial vasoconstriction is also accompanied by venous vasoconstriction which gives an increase in blood pressure and reflex bradycardia. Phenylephrine appears to have little effect on the beta receptors of the heart. When given intravenously it slows the heart rate but increases the stroke output thereby causing a rise in systolic and diastolic pressures.

IV.4 Clinical efficacy

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, although reflex bradycardia may occur. Phenylephrine is frequently used for hemodynamic support in patients in septic shock, during spinal anesthesia for cesarean delivery and in cardiac and vascular surgery.

This application is literature based only. The submitted literature data gives an overview of the current knowledge of the beneficial effects of phenylephrine. It is considered that the Applicant has sufficiently shown that the use of phenylephrine is well established.

IV.5 Clinical safety

The most common adverse events were bradycardia, hypertensive episodes, nausea and vomiting. Hypertension was more frequent with high doses. The hemodynamic adverse effects can be explained by the pharmacodynamics properties of phenylephrine

In general, sympathomimetics should be used with caution in patients with cardiovascular disorders, who may have an increased susceptibility to their effects. Particular care is needed in patients with cardiac arrhythmias, ischaemic heart disease, or hypertension. All sympathomimetics should generally be avoided in severe hypertension, although alpha agonists are particularly hazardous; they should also be used with caution in patients with occlusive vascular disease, who are at increased risk of peripheral ischaemia.

IV.6 Risk Management Plans

Safety specification

Summary table of safety concerns as approved in RMP

Important identified risks	Arterial hypertension
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	Arrhythmia
<i>Important potential risks</i>	Extravasation
<i>Missing information</i>	Use during pregnancy

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 MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. **Issue is resolved.**

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 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, although reflex bradycardia may occur. 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 sufficiently shown that the use of phenylephrine is well established.

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. As phenylephrine has been frequently used in the critical care setting in patients with hypotension and shock, some of the reported serious adverse events and deaths are probably related to the underlying disease and not related to the use of phenylephrine.

Symptoms of phenylephrine overdosage include headache, vomiting, hypertension and reflex bradycardia and other cardiac arrhythmias. Treatment should consist of symptomatic and supportive measures. The hypertensive effects may be treated with an alpha-adrenoceptor blocking drug, such as phentolamine.

For the obstetric setting, phenylephrine is often used to treat hypotension or maintain blood pressure in women undergoing caesarean delivery under spinal anesthesia. The most common maternal adverse events reported in the literature were bradycardia, reactive hypertension, nausea and vomiting. In multiple obstetric studies, fetal effects of phenylephrine have been studied. There appears to be no fetal/neonatal safety signal in terms of fetal acidosis, Apgar score, neurobehavioral development. However, no longer-term follow-up data on infants are available.

In summary, phenylephrine has been used for decades in a wide range of patient populations, disease states and clinical settings. Its clinical use is well-established. In general, phenylephrine is administered in a clinical setting with high controlled surveillance activities. Overall, literature data suggests that phenylephrine is well-tolerate. The safety profile is well-known and no new safety concern has been found.

The benefit/risk ratio is considered positive and Fenylefrin Unimedic, 0.05 mg/ml and 0.1 mg/ml, solution for injection is 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 Mutual recognition for Fenylefrin Unimedic, 0.05 mg/ml and 0.1 mg/ml, solution for injection was positively finalised on 2015-10-21.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)