LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Fenylefrin Abcur
(phenylephrine hydrochloride)

SE/H/1255/01-02/DC

This module reflects the scientific discussion for the approval of Fenylefrin Abcur . The procedure was finalised at 2013-01-24. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Abcur AB has applied for a marketing authorisation for Fenylefrin Abcur, solution for injection, 0.05 mg/ml and 0.1 mg/ml. The active substance is phenylephrine hydrochloride. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Fenylefrin Abcur is presented in the form of a solution for injection containing phenylephrine hydrochloride which corresponds to 0.05 mg/ml or 0.1 mg/ml of phenylephrine. The excipients are citric acid, sodium chloride, sodium citrate and water. The solution for injection is filled in ampoules.

II.2 Drug Substance

Phenylephrine hydrochloride has a monograph in the Ph Eur.

Phenylephrine hydrochloride is a white or almost white crystalline powder which is freely soluble in water and in ethanol (96 per cent). The structure of phenylephrine hydrochloride has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Fenylefrin Abcur, solution for injection is formulated using excipients described in the current Ph Eur. None of the excipients are of human or animal origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as sensitivity to oxidation.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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

III.2 Pharmacology

Phenylephrine is a sympathomimentic agent with mainly direct effects on alpha-adreno receptors. It can also activate β-adrenergic receptors but at concentrations more elevated than for the α1-adrenergic receptors. The drug causes marked arterial vasoconstriction during intravenous infusion. The intravenous administration of phenylephrine induces immediate effects on the general blood circulation that last about 15 to 20 minutes.

III.3 Pharmacokinetics

Phenylephrine appears to be distributed quickly in all peripheral tissues with a possible storage in some compartments. Its penetration in the central nervous system seems to be low and its passage in milk seems limited. The elimination of phenylephrine is primarily urinary and elimination via the renal route seems to be similar between the i.v. and p.o. routes; 86% and 80% of the administered dose, respectively. The short duration of action of phenylephrine (about 20 minutes after intravenous injection) suggests a rapid distribution, metabolism and elimination from the body.

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.

Regarding reproductive and developmental toxicity, no reports or detailed data have been submitted. It is therefore not possible to perform any assessment regarding the possible reproductive and developmental toxic effects of phenylephrine.

III.5 Ecotoxicity/environmental risk assessment

The $PEC_{surfacewater}$ value for phenylephrine is 0.0586 ng/L, which is well below the guideline limit value of 0.01 µg/L (=10 ng/L). It is concluded that phenylephrine is unlikely to represent a risk for the environment following its prescribed usage in patients.

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 sympathomimentic 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Phenyleprine is a sympathomimetic substance with dominating α_1-adrenergic properties and minimal β-adrenergic effects. The resulting peripheral vasoconstriction is the main primary pharmacological effect. The substance is used in anaesthesia practice mainly to counteract excessive vasodilation caused by anaesthesia.

IV.2 Pharmacokinetics

Phenylephrine is administered as an intravenous injection or infusion and has a volume of distribution after single dose of 340 litres. The elimination half-life is approximately three hours and phenylephrine is mainly excreted by the kidney as m-hydroxymandelic acid and phenol conjugates. Except for the information presented above the information on the pharmacokinetics of phenylephrine for IV infusion for treatment of hypotension is limited. This is acceptable for this type of product, that is to be administered intravenously and with a dosing interval adjusted according to its clinical effect.

IV.3 Pharmacodynamics

Phenylephrine is a selective agonist of the α_1-adrenergic receptors of smooth muscles of the blood vessels. In general, the activation of the α_1-adrenergic receptors leads to a marked vasoconstriction and consequently an increase in systolic and diastolic blood pressure. Phenylephrine also induces vasoconstriction of the vessels in skin and mucous membranes, as well as mydriasis by contracting the dilating muscle of the pupil. Phenylephrine causes reflectory bradycardia.

Phenylephrine can also activate the β-adrenergic receptors, but at somewhat higher concentrations than for the α1-adrenergic receptors. It does neither stimulate the β-adrenergic receptors of the bronchi nor the β_2-adrenergic receptors in the peripheral blood vessels or the β_1-adrenergic receptors of the heart.

The intravenous administration of phenylephrine induces immediate effects on the circulation and its duration is about 15 to 20 minutes.

IV.4 Clinical efficacy

Hypotension is a common complication of anaesthesia. In general, the use of phenylephrine to treat hypotension caused by excessive vasodilation from effects of general anaesthetics can be considered a well established part of anaesthesia practice. The Applicant has provided a literature review and sufficient references to substantiate the clinical efficacy of phenylephrine for the indication in the application.

IV.5 Clinical safety

The Applicant has provided a review of the safety profile of phenylephrine. Adverse reactions are mainly a consequence of the pharmacodynamic profile of phenylephrine and they are well known. Potential adverse reactions are adequately described in the SmPC and use of phenylephrine should be restricted to health care personnel with adequate knowledge of the substance.

IV.6 Discussion on the clinical aspects

Phenylephrine has a well established role in European anaesthesia practice. It is used to counteract excessive vasodilatation during anaesthesia. The safety profile is well known and usage should be restricted to health care personnel with adequate knowledge of the substance.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The bridging suggested in this procedure could not be accepted due to lack of evidence that the parent PL referred to, had been assessed and accepted. The applicant has committed to do a User test or to submit another bridging to a similar product as soon as possible after finalization of this DCP procedure. (SE/H/1255/01-02/DC)

The risk/benefit ratio is considered positive and Fenylefrin Abcur, solution for injection, 0.05 mg/ml and 0.1 mg/ml is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Fenylefrin Abcur, solution for injection, 0.05 mg/ml and 0.1 mg/ml was successfully finalised on 2013-01-24.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se