LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fenylefrin Stragen
(phenylephrine hydrochloride)

SE/H/1415/01/DC

This module reflects the scientific discussion for the approval of Fenylefrin Stragen. The procedure was finalised on 2015-09-28. 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

Stragen Nordic A/S has applied for a marketing authorisation for Fenylefrin Stragen, 50 micrograms/ml, solution for injection in pre-filled syringe. The active substance is phenylephrine hydrochloride (potent vasoconstrictor that acts almost exclusively by stimulating alpha-1-adrenergic receptors).

For approved indications, see the Summary of Product Characteristics.

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

The applicant, Stragen Nordic A/S applied through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, DE, DK, ES, FI, IE, IT, LU, NL, NO, PT and UK as concerned member states (CMS).

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

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 non-clinical expert report has been written by a suitably qualified person and is satisfactory.

III.2 Pharmacology

Phenylephrine is a sympathomimetic agent that produces its local and systemic actions by acting on α1-adrenergic receptors in peripheral vascular smooth muscle. It can also activate β-adrenergic receptors but at concentrations more elevated than for the α1-adrenergic receptors. Parenteral administration of phenylephrine causes a rise in systolic and diastolic pressures, a decrease in cardiac output, and a considerable increase in peripheral resistance.

III.3 Pharmacokinetics

No information regarding pharmacokinetics in animal species was presented. This is considered acceptable for an application of this type.

III.4 Toxicology

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 in rats and mice, using dietary administration, it is concluded that there is no evidence for a carcinogenic potential of phenylephrine.

Information regarding reproductive and developmental toxicity seems to be very limited. The available non-clinical data are insufficient to evaluate the reproductive toxicity potential of phenylephrine.

Phenylephrine is a local irritant and may cause tissue necrosis in case of extravasation.

III.5 Ecotoxicity/environmental risk assessment

The $PEC_{surfacewater}$ value for phenylephrine is well below the guideline limit value of 0.01 µg/L. The Log Kow of phenylephrine is -3.2, which is below the PBT threshold as specified in the guideline. In conclusion, phenylephrine is not considered to pose a risk to 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 sympathomimetic agent with effects mainly on α1-adrenergic receptors. The drug causes marked arterial vasoconstriction during intravenous

infusion. 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

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

This application is literature based and presents publications from trials conducted in different countries. No new clinical trials have been performed by the Applicant.
The Applicant has performed a systematic literature search from the database Medline via PubMed using the following key words: phenylephrine, intravenous, hypotension, anaesthesia, anaesthesia general, anaesthesia spinal, anaesthesia epidural, clinical studies. The MHRA, ANSM and Theriaque web sites were consulted. A manual search was also performed. Most of the efficacy data were retrieved from published studies in the obstetric population.

IV.5 Clinical safety

The most common adverse events were bradycardia, hypertensive episodes, nausea and vomiting. Hypertension is 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

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 Stragen.

Summary of safety concern

Summary of safety concerns	
Important identified risks	Arterial hypertension Arrhythmias
Important potential risks	Extravasation
Missing information	Use in paediatric population

Having considered the data in the safety specification the RMS considers that the RMP is acceptable. If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

The RMS, having considered the data submitted, is of the opinion that the proposed risk minimisation measures (i.e. routine pharmacovigilance) is sufficient to minimise the risks of the product in the proposed indication.

Summary of the RMP

The RMP is approved.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results 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.

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 anaesthesia, particularly in relation to caesarean 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

for the treatment of hypotension during spinal, epidural or general anaesthesia 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 over dosage 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 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 in the treatment of hypotension during spinal, epidural or general anaesthesia 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 tolerated. The safety profile is well known and no new safety concern has been found.

VII. APPROVAL

The Decentralised procedure for Fenylefrin Stragen, 50 micrograms/ml, solution for injection in pre-filled syringe was positively finalised on 2015-09-28.

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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
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