LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fenylefrin Aguettant
(phenylephrine hydrochloride)

SE/H/1849/01/DC
2019-0064

This module reflects the scientific discussion for the approval of Fenylefrin Aguettant. The procedure was finalised on 2019-12-20. 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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Laboratoire Aguettant has applied for a marketing authorisation for Fenylefrin Aguettant, 100 µg/ml, solution for injection/infusion. The active substance is phenylephrine, a potent vasoconstrictor which acts almost totally by stimulation of α1-adrenergic receptors. Such arterial vasoconstriction is also accompanied by venous vasoconstriction. It produces an increase in blood pressure and reflex bradycardia. Phenylephrine appears to have little effect on the β-receptors of the heart. When given intravenously, it slows the heart rate with a resulting increase in stroke output causing a rise in systolic and diastolic blood pressure.

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/EC 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 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

Very limited 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

Phenylephrine is a potent vasoconstrictor which has been used for many years to treat hypotension in different clinical settings, notably in critical care, anaesthesia and cardiology. Hypotension may in these situations threaten vital organ perfusion and oxygenation. Immediate and effective treatment is required.

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 acting by stimulating α-adrenergic receptors. The vasoconstriction is mediated by primarily α1-receptors in arteries and by α1- and α2-receptors in veins. The resulting arterial vasoconstriction increases the systemic vascular resistance, leading to increased blood pressure, increased left ventricular stroke work index, and reduced cardiac output. The increased blood pressure activates baroreceptors with subsequent reduction of the heart rate and increase of stroke volume, which also increases the systemic blood pressure.

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 has been used for decades to treat hypertension during neuroaxial and general anaesthesia. The publications submitted support that phenylephrine has been used in the EU for more than 10 years in the proposed indication. The submitted literature data gives an overview of the current knowledge of the beneficial effects of phenylephrine. The available data sufficiently supports the posology proposed in the application. It has been shown that the use of phenylephrine in different clinical settings is well established.

IV.5 Clinical safety

Sufficient scientific support from the literature has been provided for the information in the SmPC. The use of phenylephrine in different patient populations for the treatment of hypotension during spinal, epidural and 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. Some of the reported serious adverse events and deaths are probably related to the underlying disease and not to the use of phenylephrine.

In summary, phenylephrine has been used for decades in a wide range of patient populations, disease states and clinical settings. Its clinical use, efficacy and safety profile are considered well-established. The dose is titrated to effect. Intravenous phenylephrine is administered in a clinical setting with health care professionals familiar with hemodynamic monitoring and the use of vasopressors.

Overall, the submitted literature supports that phenylephrine is well-established in the intended indication. The safety profile is sufficiently characterised.

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 Aguettant.

Safety specification

Summary of safety concerns	
Important identified risks	Hypersensitivity Arrhythmia
Important potential risks	Extravasation
Missing information	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 submitted Risk Management Plan, version 1.3 signed 22-Oct-2019 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

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.

IV.7 Discussion on the clinical aspects
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.

The submitted literature data gives an overview of the current knowledge of the beneficial effects of phenylephrine. The available data also supports the posology proposed in the application. It has been shown that the use of phenylephrine in different clinical settings is well established.

Sufficient scientific data from the literature has been provided to support the information in the product information. The use of phenylephrine in different patient populations for the treatment of hypotension during spinal, epidural and general anaesthesia is well established. No new safety concern has been identified.

The benefit-risk balance is positive.

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 Phenylephrine Jenson 50 micrograms/ml, solution for injection in pre-filled syringe with regards to content and Suxamethonium Aguettant 50 mg/ml, solution injectable with regards to 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.

The submitted literature data gives an overview of the current knowledge of the beneficial effects of phenylephrine. The available data also supports the posology proposed in the application. The

Applicant has sufficiently shown that the use of phenylephrine in different clinical settings is well established.

The Applicant´s overview of clinical safety is brief but provides sufficient support for the information in the SmPC. The use of phenylephrine in different patient populations for the treatment of hypotension during spinal, epidural and general anaesthesia is well established. No new safety concern has been identified.

The benefit/risk ratio is considered positive and Fenylefrin Aguettant, 100 µg/ml, solution for injection/infusion is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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 Aguettant, 100 µg/ml, solution for injection/infusion was positively finalised on 2019-12-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se