CBG MEB

Public Assessment Report

Scientific discussion

Fenylefrine Added Pharma 50 microgram/ml and 100 microgram/ml, solution for injection

(phenylephrine hydrochloride)

NL License RVG: 117236, 117234

Date: 22 May 2018

This module reflects the scientific discussion for the approval of Fenylefrine Added Pharma 50 microgram/ml and 100 microgram/ml, solution for injection. The marketing authorisation was granted on 31 August 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
LD50	Median Lethal Dose
MAH	Marketing Authorisation Holder
NTP	National Toxicology Program
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Fenylefrine Added Pharma 50 microgram/ml and 100 microgram/ml, solution for injection, from Added Pharma B.V.

The product is indicated for treatment of hypotension during spinal, epidural and general anaesthesia.

A comprehensive description of the indications and posology is given in the SmPC.

In the Netherlands, there are two registered medicinal products of similar composition with similar indications for the intended use of treatment of hypotension: Fenylefrine Aguettant 50 microgram/ml, solution for injection (registered 19 November 2015 by Laboratoire Aguettant through procedure SE/H/1415/01) and Fenylefrine Unimedic 50 microgram/ml and 100 microgram/ml, solution for injection (registered 6 January 2016 by Unimedic AB through procedure SE/H/1551/001).
The product applied for is identical in its quantitative and qualitative composition to Phenylephrine Renaudin 50 µg/ml and 100 µg/ml, solution for injection which has been registered in France by Laboratoire Renaudin since 25 August 2011.
Similar medicinal products are registered in the EU for more than ten years: e.g. Phenylephrine Injection BP 10 mg/ml which has been registered in the UK by Amdipharm UK Limited since 17 November 1999.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC, a so called bibliographic application based on the well-established medicinal use of phenylephrine hydrochloride.

Indication
The originally proposed indication was:
- Treatment of hypotension during general anaesthesia and loco-regional anaesthesia whether spinal or epidural anaesthesia, given for a surgical or obstetric procedure.
- Prevention of hypotension during spinal anaesthesia given for a surgical or obstetric procedure.

The MAH provided published clinical literature for the proposed indications. Following comments of the involved member states, a revised indication was accepted. The assessment of proposed indications is discussed in section IV.

II. QUALITY ASPECTS

II.1 Introduction

Phenylephrine Added Pharma is a solution for injection and contains as active substance 50 microgram/ml or 100 microgram/ml of phenylephrine, corresponding to 60.9 microgram or 121.8 microgram of phenylephrine hydrochloride.

- The 100 µg/ml solution is packed in 5 ml, 10 ml and 20 ml Type I glass ampoules or 50 ml Type II glass vials. The vials are closed by a bromobutyl compound infusion stopper. Stoppers are maintained by an aluminium cap protected by a plastic flip-off.
- The 50 µg/ml solution for injection is packed in 10 ml Type I pharmaceutical-grade glass ampoules.

The excipients are sodium chloride, sodium citrate dihydrate, citric acid monohydrate, water for injections and nitrogen or argon as headspace gas.

II.2 Drug Substance

The active substance is phenylephrine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Phenylephrine hydrochloride is a white or almost white

crystalline powder, easily soluble in water and in ethanol 96%. Since the drug product is a solution and the substance is freely soluble in water particle size polymorphism and isomerisation are not considered to be relevant.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. It includes additional tests for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for three pilot scale batches.

Stability of drug substance
The active substance is stable for three years when stored under the stated conditions. Assessment thereof was part of granting the CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. From chemical pharmaceutical point of view the well-established use has been substantiated. Since the drug product concerns a solution for injection no bioequivalence studies are required. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is adequately described. Process validation data on the product have been presented for 15 pilot scaled batches, three batches per packaging. The manufacturing process is adequately validated for the production of the drug product.

Control of excipients
The excipients comply with the Ph.Eur. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for clarity, coloration, identification, extractable volume, pH, osmolality, related substances, assay, sterility, particulate matter and bacterial endotoxins. The release and shelf life specifications are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 15 pilot scale batches from the production site have been provided along with batch analytical data from 15 production scale batches, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on 12 pilot scaled batches stored at 40°C/75% RH (6 months), 30°C/65% RH (up to 36 months), 25°C/60% RH (up to 36 months) and 5°C (6 months) packed in ampoules and three pilot scaled batches stored at 40°C/75% RH (6 months), 30°C/65% RH (24 months), 25°C/60% RH (24 months) and 5°C (6 months). The conditions used in the stability studies are according to the ICH stability guideline.

An increase in particulate matter was observed in all batches at all storage conditions except the 5°C. At 5°C this parameter was not tested. However, the parameter stayed well within the limit for all batches. No other trends were observed in any of the batches.
Based on the provided stability data the proposed shelf life of 36 months is acceptable. Based on the photostability study it is adequately demonstrated that the drug products should be stored in the outer packaging in order to protect from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Fenylefrine Added Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Primary pharmacology
Phenylephrine belongs to the class of sympathomimetic active substances of the chemical family of the phenylethanolamines. Phenylephrine has mainly direct effects on adrenergic receptors. It has predominantly α adrenergic activity and is without significant stimulating effects on the central nervous system at usual doses.
Phenylephrine is a selective agonist of the α1-adrenergic receptors of smooth muscles of the blood vessels; in general their activation leads to a stimulating post-synaptic effect of vasoconstriction. This results in a marked vasoconstriction and consequently an increase in the systolic and diastolic blood pressures resulting in reflexes of bradycardia of increased vagal activity. Phenylephrine also induces a vasoconstriction at the level of skin and mucous membranes, and is used as a mydriatic by contracting the dilating muscle of the pupil.
The activation of the α2-receptors located in the pre-synaptic nervous endings by phenylephrine inhibits the production of endogenous neurotransmitters. The stimulation of the α2-receptors of the cholinergic nervous endings in the gastro-intestinal tract can arise from the inhibitory effects of the α-agonists at this site.
Phenylephrine can activate the α-adrenergic receptors but at concentrations somewhat more elevated than for the α1-adrenergic receptors. It does not stimulate neither the α-adrenergic receptors of the bronchi or peripheral blood vessels (α2-adrenergic receptors) nor of the heart (α1-adrenergic receptors).
The α-adrenergic effects of phenylephrine would result from an inhibition of the production of adenosine 3', 5'-monophosphate by inhibition of the enzyme adenylcyclase while the α-adrenergic effects would be the consequence of the stimulation of the adenylcyclase activity.
Phenylephrine also has an indirect effect by release of norepinephrine from its sites of storage.
The intravenous administration of phenylephrine induces immediate effects on the general blood circulation and they have a duration of about 15 to 20 minutes.
The pharmacological effects of phenylephrine diminish at least partially by storage of the molecule in the peripheral tissues.

Safety pharmacology
The acute administration of phenylephrine can induce various side-effects, primarily attributable to excessive pharmacologic activity (vasoconstriction), the most serious being rise in blood pressure, ventricular arrhythmia and cardiac infarction among very sensitive patients.
For other possible secondary reactions following the administration of phenylephrine, refer to reports in current medical practice and the SmPC.

The potential to induce arrhythmias and reflex bradycardia are well known side effects of phenylephrine. Adequate information is included in the SmPC, under sections 4.4 and 4.8.

Pharmacodynamic drug interactions
The possible interactions of drugs with phenylephrine include:

- non selective inhibitors of monoamine oxidases (IMAO): potentiated effect of the depressive amines by the IMAO
- tricyclic antidepressants: increase of the vasopressive response of phenylephrine
- ergoline alkaloids : excessive increase of blood pressure
- sympathomimetic bronchodilating agents: tachycardia or possibly arrhythmias
- propanolol and other β-adrenergic blocking agents: blocking of the cardio-stimulant effects
- phentolamine and other α-adrenergic blocking agents: decrease of the pressive response
- selegiline, moclobemide, methyldopa, anesthetics (e.g. halothane): possibly serious arrhythmias.

III.2 Pharmacokinetics

Distribution
Phenylephrine appears to be distributed quickly in all peripheral tissues with possibility of storage in some organic compartments. Its penetration in the central nervous system remains minimal and its passage in milk seems limited.
In a metabolism study conducted in 15 volunteers with tritiated phenylephrine the volume of distribution calculated was 340 litres.

Metabolism
The metabolism of phenylephrine is quite similar in animals and humans. Phenylephrine is metabolised in the liver by monoamine oxidase.
The respective fractions of recovered products in humans urine within 24 hours after administration of the molecule by inhalation or by oral route is as follows: about 60% of a dose is in the form of the parent compound or in the form of combined phenylephrine, 30% to 35% of the amount appears in the form of metahydroxymandelic acid or its degradation products (sulphate or glucuronide) and 8% to 9% in the form of metahydroxyphenylglycol or its degradation products (sulphate or glucuronide).

Excretion
Phenylephrine is excreted mainly by the kidney as m-hydroxymandelic acid and phenol conjugates. Its elimination half-life is approximately three hours.
The elimination of phenylephrine is primarily urinary: 90% of the administered amount is eliminated by the kidneys within 24 hours, mainly in the glucuronide-conjugated (60% to 80%) and sulpha-conjugated (20% to 30%) forms.
After administration by intraperitoneal route in Wistar rats, 72% of an amount of tritiated phenylephrine was collected in the urine of 24 hours: 16% is represented by free phenylephrine and its sulphate and glucuronide conjugates and roughly 56% consist of metahydroxymandelic acid (6%) and metahydroxyphenylglycol (50%), or their sulphate or glucuronide conjugates.
A metabolism study was conducted in 15 volunteers with tritiated phenylephrine showed that the elimination by renal route was similar between the intravenous (i.v.) and per os (p.o.) modes of administration: 86% and 80% of the administered dose, respectively.
The bioavailability showed a great difference with a factor of 0.38 between the i.v. and p.o. modes of administration, 16% and 2.6% of the administered dose being found as the parent compound, i.e. free phenylephrine, respectively.

No information regarding pharmacokinetics in animal species is presented. The nonclinical overview refers to the clinical part of the dossier for data on pharmacokinetics of phenylephrine in humans. This is agreed.

III.3 Toxicology

Single-dose toxicity
The LD50 values of phenylephrine in various laboratory animal species according to the mode of administration are the following:

Oral route	:	mice	= 120 mg/kg b.w.
		rat	= 350 mg/kg b.w.
Intravenous	:	mice	= 1 120 µg/kg b.w.
		rat	= 440 µg/kg b.w.
		rabbit	= 500 µg/kg b.w.
Subcutaneous	:	mice	= 22 mg/kg b.w.
		rat	= 27 mg/kg b.w.
		rabbit	= 22 mg/kg b.w.
Intraperitoneal	:	mice	= 89 mg/kg b.w.
		rat	= 17 mg/kg b.w.
Intramuscular	:	rabbit	= 7 200 µg/kg b.w.

According to the posology in the SmPC, the maximum recommended intravenous bolus dose is 100 microgram. This corresponds to 1.7 microgram/kg in a 60 kg person. This dose is far below the LD50 values in animals.

Repeat-dose toxicity

Studies of 2 and 12-week duration followed by a carcinogenesis study for 103 weeks were carried out with phenylephrine within the framework of the National Toxicology Program (NTP).
The 2-week duration studies in mice (63, 125, 250, 500 and 1,000 ppm (mg/kg in diet)) and in rats (125, 250, 500, 1,000 and 2,000 ppm (mg/kg in diet)) did not highlight any anomaly in relation to the treatment.

The 12-week duration study in mice (1,250, 2,500, 5,000, 10,000 and 20,000 ppm (mg/kg in diet)) revealed anomalies only at the highest concentrations tested:

- mortality during the course of the study in males (2 out of 10 and 3 out of 10 from the 10,000 and 20,000 ppm groups, respectively) but not in females.
- mean final bodyweight of the treated males lower than that of the controls (18% at 10,000 ppm; 35% at 20,000 ppm). The mean final bodyweight of the females of all treated groups was 10% to 32% lower when compared to the controls.
- food consumption at 20,000 ppm (males and females) higher than that of the controls.
- inflammatory lesions (acute keratitis, panophthalmia or phthisis of the ocular bulb) in three out of then males and two out of ten females of the 20,000 ppm group.
- relative and absolute weights of the adrenals (males and females) and relative weight of the heart (females) higher than that of the controls at the concentration of 20,000 ppm.
- Beside these few minors anomalies only found at high concentrations of phenylephrine the results of the histopathological examinations were normal for the totality of other organs examined (including the adrenals and heart).

The 12-week duration study in rats (1,250, 2,500, 5,000, 10,000 and 20,000 ppm) revealed anomalies similar to those observed in mice. Additional findings included:

- a chronic keratitis at 10,000 ppm and 20,000 ppm (males and females).
- a minimal to moderate testicular atrophy and an atrophy of the seminal vesicle at 20,000 ppm.
- a slight to moderate atrophy of the ovaries at 20,000 ppm group.

No other macroscopic anomaly was evidenced and the results of the microscopic examination were normal (including for the testes, the seminal vesicles and the ovaries).

Concerning the organ weights and the macro- and microscopic examinations some variations from normality were observed but without clear relation to the treatment. No further treatment related abnormalities were evidenced during the histopathological examination of the other organs at the end of the study.

The observed effects are considered not to be clinically relevant since they occurred only at high doses (≥10,000 ppm).
No exposure data are available. However, this deficiency is acceptable on the condition that there is sufficient clinical experience with the active substance.

Genotoxicity

The *in vitro* genotoxic potential of phenylephrine was evaluated within the framework of the NTP. In these studies phenylephrine hydrochloride was:

- not mutagenic in four strains of Salmonella typhimurium (TA100, TA1535, TA1537 and TA98) in presence and in absence of metabolic activation system.
- of equivocal result in the mice lymphoma test at the L6178Y/TK+/- locus: the high concentration tested was toxic for the growing cells.
- positive in the sister chromatids exchange test (SCEs).
- negative in the test for chromosomal aberrations in Chinese hamster ovarian cells (CHO).

The information concerning the genotoxicity of phenylephrine obtained from NTP is acceptable. Phenylephrine is not considered to be a genotoxic compound.

Carcinogenicity

A carcinogenicity study (103 weeks) was conducted in mice and rats according to the protocols established by international organisations and subjected to Good Laboratory Practice (GLP).

In mice, mean dose levels of phenylephrine were: 130 mg/kg body weight (b.w.) and 260 mg/kg b.w. in males and about 140 mg/kg b.w. and 280 mg/kg b.w. in females.
In rats, mean dose levels of phenylephrine were: 22 mg/kg b.w. and 47 mg/kg b.w. in males and about 26 mg/kg b.w. and 54 mg/kg b.w. in females.

Based on the results from the two year rodent carcinogenicity studies, there is no evidence for a carcinogenic potential of phenylephrine.

Reproductive and developmental toxicity

Pregnancy

There is scant information on the reproductive toxicology of phenylephrine in animals. Sympathomimetic amines as a group have shown reproduction toxicity. There might be an increased risk of vascular disruption effects because of its vasoconstrictive activity. Reprotox reports foetal growth restriction and premature delivery in the offspring of pregnant rabbits treated with phenylephrine at dose levels equivalent to those used in humans. Similar dose levels of phenylephrine administered to sheep late in pregnancy produced acidosis and hypoxemia in the foetuses.
Human pregnancy data with phenylephrine are limited, but clinical practice does not point to an adverse effect on reproduction. For the sympathomimetic amines as a group, an association was found between first trimester use and minor malformations (not life-threatening or major cosmetic defects), gastroschisis, hemifacial microsomia, inguinal hernia, and clubfoot. Epinephrine has also been associated with cardiovascular and limb malformations. As also discussed for pseudoephedrine, exposure to phenylephrine in the first trimester may lead to a small increased risk of clubfoot, eye and ear defects, congenital heart disease and endocardial cushion defect. Phenylephrine has been associated with hematoma, ectrodactyly and heterotaxy. However, causation has not been established in these studies.
Chronic use of phenylephrine during pregnancy is unlikely in view of the proposed indication, i.e. treatment and prevention of hypotension during spinal anaesthesia obstetrical surgery.

Lactation

Although no data are available on the secretion of phenylephrine into human milk, probably very low amounts will be transferred into milk. In addition, phenylephrine may supress milk production. Because no information is available on the use of intravenous phenylephrine during breastfeeding, the effect on milk production and the exposure of the child are unknown. Because of the lack of data, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with phenylephrine taking into account the benefit of breast feeding for the child and the benefit of therapy for the mother.

Local tolerance

A study of local tolerance of 14 days was carried out in rabbits with a proprietary medical product, (MYDRIASERT, ophthalmic insert containing phenylephrine and tropicamide). Although the mode of application does not correspond to that of an injection by intravenous route it is of interest for the

evaluation of local phenomena of irritation being induced by the active substance. MYDRIASERT was inserted for a duration of six hours per day.
This study showed a weak irritating effect on the conjunctivae at the site of administration. Similar findings are reported for Visadron eye drops containing phenylephrine hydrochloride (http://db.cbg-meb.nl/IB-teksten/h04518.pdf).
The pH of a solution of phenylephrine at 1% ranges between 4.5 and 5.5, which is a value rather close to neutrality. Thus, an irritating effect of the medical product is not expected in the case of an injection correctly carried out in the patient.
Necrosis of the surrounding tissues close to the injection site can occur in the event of extravasation. In this case it is advisable to infiltrate 5 mg to 10 mg of phentolamine (diluted in 10 to 15 ml of isotonic sodium chloride solution) in the site of the extravasation. Phenylephrine hydrochloride injection is a registered medicinal product in the US. The product information of that product indicates that the extravasation of phenylephrine can cause skin and subcutaneous necrosis (FDA Product Information of Phenylephrine Hydrochloride Injection. This warning has been included in section 4.8 of the SmPC of Fenylefrine Added Pharma.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Fenylefrine Added Pharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

The application for Fenylefrine Added Pharma is based on well-established use. This is endorsed, since phenylephrine hydrochloride has been registered for this indication for a long time and the dose is not increased. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Phenylephrine hydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

When administered intravenously, phenylephrine follows a bi-exponential decline with rapid distribution (α-phase half-life <5 min) from the central compartment to peripheral tissues and end organs. Phenylephrine has a rapid onset of blood pressure response (<5 min). The time to offset the drug effect is approximately 10-15 min which is consistent with the initial rapid elimination from the systemic circulation. The steady-state volume of distribution of approximately 340 litre suggests a high distribution into organs and peripheral tissues. Phenylephrine is extensively metabolised by the liver with only 16% of the dose excreted unchanged in the urine. Deamination by mono-amino oxidase is the primary metabolic pathway resulting in the formation of the major metabolite (m-hydroxymandelic acid) which accounts for 57% of the total administered dose. The average total serum clearance is approximately 2100 ml/min. The observed phenylephrine plasma terminal elimination half-life was 2.5 hours. No information on pharmacokinetics in special patient groups (elderly, patients with hepatic or renal impaired) has been found in literature.

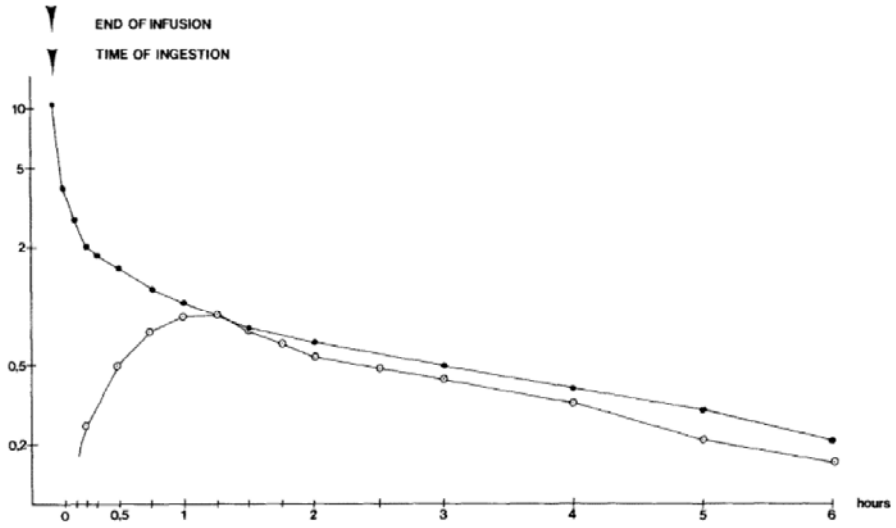

Figure 1: From Hengstmann and Goronzy, 1982: Average serum levels of ^{3}H *-PE after iv (•-• n=4, dose 0.84 mg) and oral (o-o, n=3, dose 0.99 mg) administration.*

Concentration time curve phenylephrine.

IV.3 Pharmacodynamics

Phenylephrine belongs to the class of the sympathomimetic active substances of the chemical family of the phenylethanolamines. The pharmacodynamic effects of phenylephrine can be understood from its peripheral vasoconstrictive action (both arterial and venous); there seems to be little or no direct effect on the heart. In normotensive patients this will increase systemic vascular resistance, blood pressure and afterload and decrease stroke volume and cardiac output; through the baro-reflex, bradycardia can occur. In patients with hypotension based on peripheral vasodilatation, as caused by spinal or epidural anaesthesia, enhanced preload may restore most haemodynamic parameters to baseline values.

IV.4 Clinical efficacy

Indication
The MAH provided data to support that phenylephrine has been in well-established use in the sought indications.

Regarding the proposed indication “Treatment of hypotension during general anaesthesia and loco-regional anaesthesia whether spinal or epidural anaesthesia, given for a surgical or obstetric procedure.” the MAH has provided data from three published studies that support efficacy of phenylephrine in the treatment of hypotension during anaesthesia and supported well-established use, since they were published before 2006 in an EU member state. Additionally, in the UK, Phenylephrine Injection BP 10 mg/ml solution for injection has been registered for “*the treatment of hypotensive states, e.g. circulatory failure, during spinal anaesthesia or drug-induced hypotension*.” since 1999, which supports well-established use for this “treatment” indication for phenylephrine.

Concerning “*Prevention of hypotension during spinal anaesthesia given for a surgical or obstetric procedure*”, the MAH has provided literature either published in 2006 or later and/or from states outside the EU. Furthermore, support for the extensive use over ten years of phenylephrine in the prevention of hypotension during anaesthesia has not been provided. Accordingly, the use of phenylephrine for the prevention of spinal anaesthesia induced hypotension is not considered well-established in the EU for at least ten years.

Therefore the MEB concluded that the “prevention” indication is not acceptable and, in order to harmonise with other phenylephrine products, the indication has been reworded as follows: *“Treatment of hypotension during spinal, epidural and general anaesthesia*.”

Posology
In the clinical overview, the posology of phenylephrine was sufficiently substantiated with five reviews and articles (1996-2009) by the MAH. In general surgery the treatment of arterial hypotension is based on vascular filling and the use of vasopressor agents, which contain phenylephrine, ephedrine, noradrenaline and adrenaline; it has a fast and short duration of action (5 to 10 minutes) by intravenous route. Hypotension can be managed in bolus between 50 and 100 µg or in perfusion with an initial flow between 25 and 50 µg/min which can be increased progressively to reach the desired effect. A perfusion can prove to be necessary to maintain the effect.

IV.5 Clinical safety

The MAH has sufficiently substantiated the safety of the use of phenylephrine in the proposed indication with clinical documentation which was based on medical references textbooks, international literature, several public safety databases (Lareb, MHRA, Eudra Vigilance and WHO) and post-marketing experience of phenylephrine of Laboratoire Renaudi. Additionally, section 4.8 of the recently approved phenylephrine IV in the Netherlands was submitted. The most common adverse events were bradycardia, hypertensive episodes, nausea and vomiting. The most adverse effects can be understood as exaggerated pharmacology. Furthermore, the safety profile of phenylephrine is well-known in other member states and in the submitted literature no new safety concerns has been identified. Therefore, the safety profile is considered acceptable.

IV.6 Risk Management Plan

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 Fenylefrine Added Pharma.

Summary table of safety concerns as approved in RMP

Important identified risks	• Arterial hypertension • Arrhythmia
Important potential risks	• Extravasation
Missing information	• Use in paediatric population • Use during pregnancy

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Fenylefrine Added Pharma is considered widely established. For this authorisation, reference is made to clinical studies and experience with phenylephrine hydrochloride. Phenylephrine hydrochloride has been shown to be effective in the treatment of hypotension during spinal, epidural and general anaesthesia. The provided clinical overview is sufficient. No new clinical studies were conducted. This is accepted.

V. USER CONSULTATION

A user consultation with target patient groups on the patient leaflet (PL) has been performed on the basis of a bridging report making reference to Phenylephrine 10 mg/ml, solution for Injection or Infusion. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fenylefrine Added Pharma 50 microgram/ml and 100 microgram/ml, solution for injection has a proven chemical-pharmaceutical quality. Fenylefrine Added Pharma is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Fenylefrine Added Pharma was authorised in the Netherlands on 31 August 2016.

VII. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Product name change	IB	15-12-2016	27-01-2017	Approval	N
--	IA	20-02-2017	21-04-2017	Approval	N
MAH address change	IA	10-07-2017	09-08-2017	Approval	N