COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Noradrenaline Added Pharma 0.5 mg/ml, solution for infusion

(noradrenaline tartrate)

NL/H/4759/001/DC

Date: 8 May 2020

This module reflects the scientific discussion for the approval of Noradrenaline Added Pharma 0.5 mg/ml, solution for infusion. The procedure was finalised at 18 December 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SSC	Surviving Sepsis Campaign
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Noradrenaline Added Pharma 0.5 mg/ml, solution for infusion, from Added Pharma B.V.

The product is indicated for blood pressure control in acute hypotensive states.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of noradrenaline. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. "Medicinal use" does not exclusively mean "use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

Noradrenaline solution for intravenous use has a European Union Reference Date (EURD) of 1962. The MAH has not provided data about the extent of use of noradrenaline in the EU, but widespread use can be accepted based on its place in critical care guidelines. Noradrenaline solutions have a long standing and well known use as a vasoconstrictor for the emergency restoration of blood pressure in acute hypotensive states such as shock.

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

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC as noradrenaline solutions have a long standing and well known use as a vasoconstrictor for the emergency restoration of blood pressure in acute hypotensive states such as shock.

II. QUALITY ASPECTS

II.1 Introduction

Noradrenaline Added Pharma is a ready-to-use, colourless to very light brown-yellow coloured, clear solution, almost free from visible particles. One ml contains 0.5 mg noradrenaline (as tartrate). One vial of 50 ml contains 25 mg noradrenaline. The solution has a pH between 3.0 and 4.5 and osmolality between 280 and 320 mOsmol/kg.

The solution is packed in type II glass vials of 50 ml with butyl rubber stopper capped with an aluminium cap wearing a polypropylene flip off.

The excipients are: sodium chloride, sorbitol (E420), sodium citrate (E331), tartaric acid (E334) and water for injections.

II.2 Drug Substance

The active substance is noradrenaline tartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline white or almost white powder, is freely soluble in water and slightly soluble in ethanol. No polymorphisms are described for this substance.

The CEP procedure is used for 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

A CEP has 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. and CEP. Additional tests for microbiological purity and bacterial endotoxins are included. No description of the applied analytical method is included; reference is made to the Ph. Eur. monograph, Ph. Eur. general texts and the CEP. This is acceptable. Confirmations of suitability of the Ph. Eur. methods for bacterial endotoxins and microbiological purity are provided. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP 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. The product is based on similar products which are already authorised in France. No information is provided on development test batches and the analytical results. Based on the history of the product, this is acceptable. Noradrenaline tartrate is soluble in water and is present in the drug product in dissolved form. Therefore, potential polymorphic forms and particle size distribution are not critical drug substance properties. The excipients are commonly used in parenteral product. No incompatibility with the active substance is reported.

Manufacturing process
The manufacturing process consists of sterilisation of containers and closures, preparation of bulk solution of all components in water, volume make up, pre-filtration, filling and stoppering, and sterilisation. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with their applicable Ph. Eur. monograph. The specifications are acceptable.

Microbiological attributes
The calculation of the limit for bacterial endotoxins is presented. The chosen limit is in line with the requirement in Ph. Eur.

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 and colour of solution, identity, pH, osmolality, assay, related substances, extractable volume, particulate matter, bacterial endotoxins, and sterility. 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 three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches of the minimal proposed commercial size stored at 25°C (24 months) and 30°C (18 months). In addition, a stability

study at 5°C has been performed. A photostability study in line with ICH Q1B requirements has been performed, confirming that the finished product is not sensible to light. On basis of the data submitted, a shelf life was granted of 18 months. The chemical and physical in-use stability has been demonstrated in polypropylene syringes for 24 hours at 20°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

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 member states consider that Noradrenaline Added Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Introduction

No non-clinical studies have been performed by the MAH. Extensive preclinical tests concerning pharmacology and toxicology have been described in the literature. The MAH selected the most relevant studies/reviews which are used in the non-clinical overview to support this application. Since noradrenaline can be regarded as a well known substance it is agreed that a non-clinical overview based on literature review is appropriate and no additional studies are required from the MAH.

III.2 Pharmacology

Noradrenaline is a sympathomimetic monoamine with potent alpha-1 and beta-1 adrenergic receptor agonist activity, negligible beta-2 receptor activity. It is the major neurotransmitter in post-ganglionic adrenergic neurones, stored in chromaffin granules of the nerve axons. The systemic source of noradrenaline is the adrenal medulla, from which it is released, as a hormone, with adrenaline in times of psychological and physical stress. Systemically, it also acts as a precursor to adrenaline. Pharmacological effects of noradrenaline include a pressor response (peripheral vasoconstriction, increase in systolic and diastolic blood pressure), reflex slowing of the heart rate and reduction in kidney, liver, skin and skeletal muscle perfusion.

III.3 Pharmacokinetics

Noradrenaline is rapidly inactivated in the gastro-intestinal tract following oral administration and is poorly absorbed subcutaneously. After intravenous administration Noradrenaline has a half-life of about 1 to 2 minutes in plasma. Noradrenaline is rapidly cleared from plasma by both cellular reuptake and metabolism. It does not readily cross the blood-brain barrier. Noradrenaline undergoes hepatic methylation by catechol-o-methyltransferase and deamination by monoamine oxidase to terminal metabolite 4-hydroxy-3-methoxymandelic acid. Intermediate metabolites include normetanephrine and 3,4- dihydroxymandelic acid. Noradrenaline is mainly eliminated as glucuronide or sulphate conjugates of the metabolites in the urine.

III.4 Toxicology

Acute toxicology data in animals are described in the pharmaco-toxicological documentation. Due to the absence of repeat-dose toxicity, genotoxicity and carcinogenicity data specific to noradrenaline, data from such studies of adrenaline given as aerosol were presented. No carcinogenic effects were observed in these studies. Although both compounds are related, the adrenaline data obtained in animals exposed by a different route of exposure than the intended clinical route of exposure are only of limited value for the assessment of noradrenaline in this application.
Limited embryo-foetal developmental and no reproductive toxicity data were included in this application. Based on its pharmacology, it is expected that noradrenaline may affect placental and uterine blood flow. Noradrenaline may also lead to contractions of the gravid uterus. Consequently, noradrenaline should not be used during pregnancy unless the benefit for the mother outweighs the potential risk for the foetus. In view of the well-established clinical safety profile of adrenaline, the omissions in the non-clinical data package are sufficiently justified.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Noradrenaline is a naturally occurring endogenous substance of the human body. It is an organic chemical in the catecholamine family that functions in the brain and body as a hormone and neurotransmitter. Its general function is to call the brain and body for action. Noradrenaline release is lowest during sleep and rises during wakefulness. It reaches higher levels during situations of stress or danger, in the so-called fight-or-flight response.
As a drug product, noradrenaline is widely used as an injectable medicine for the lifesaving treatment of critically low blood pressure in Europe since 1962. It is not anticipated that the prevalence of critically low blood pressure will rise in the general population. Therefore, marketing authorisation of the product will not pose an increase of environmental exposure to the active substance or the drug product.

III.6 Discussion on the non-clinical aspects

The registration for this product is based on well-established use. This is endorsed, since noradrenaline has been registered for this indication for a long time. 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

Noradrenaline 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

After intravenous injection, noradrenaline induces a rapid pharmacological response but the product has a limited duration of action and the pressor response stops within 1 to 2 minutes after the end of the injection. A steady-state plasma concentration is achieved within 5–10 minutes from the start of a constant infusion. The plasma concentrations of noradrenaline are between 167 and 220pg/mL (mean value: 203 +/- 10pg/mL). Noradrenaline is rapidly eliminated from the plasma; its elimination half-life of the order of 2 to 2.5 minutes. Noradrenaline metabolites are excreted in the urine primarily as sulphate conjugates and to a lesser extent as glucuronide conjugates. Only very small amounts of noradrenaline are eliminated in unchanged form. There is no experience on treatment in patients with renal- and hepatic impairment. No literature data could be retrieved concerning treatment in patients with renal- and hepatic impairment.

IV.3 Pharmacodynamics

Noradrenaline is a direct-acting catecholamine sympathomimetic with pronounced effects on α-adrenergic receptors; it also stimulates β1-receptors but has little effect on β2-receptors. The vasopressor effect of noradrenaline on the vessels that results in a rapid increase in systolic and diastolic blood pressure is well known. Secondary pharmacology of noradrenaline is driven by the wide spread of the adrenoceptors all over the body. Noradrenaline acts not only on alpha receptors that are found on muscle inside the walls of peripheral blood vessels, but also on pregnant uterus or ureter, stimulating the contraction of these muscles as well. Moreover, noradrenaline stimulates glycogenolysis and gluconeogenesis from adipose tissue and liver. Stimulation of beta 1 receptors influences

myocardium (e.g. positive inotropic and chronotropic effects). All these effects are rather predictable and can be sufficiently explained by the mechanism of action.

There is considerable inter-individual variation in response to noradrenaline. Conflicting data is presented, with some studies showing good correlation between dosing and plasma concentrations and other studies showing no correlation between the dose and the PK. The only covariate that influenced noradrenaline clearance was the severity of illness. Further, pharmacodynamics response to noradrenaline was found not to correlate with noradrenaline plasma concentration in adults. Therefore, in adults, unpredicted PK & PD inter-individual variability remains unexplained.

IV.4 Clinical efficacy

Literature data based on the Surviving Sepsis Campaign (SSC) Guideline[1] and Cochrane Database of Systematic Reviews[2] has been presented, which included only comparative data between different vasopressors and recommendations with respect to the first line choice of vasopressor in shock. According to the Recommendations given in the SSC guideline, the first-choice vasopressor in patients with sepsis is noradrenaline. This recommendation is based on the better efficacy/safety profile of noradrenaline compared to other vasopressors. For example, it was shown that noradrenaline use resulted in lower mortality (risk ratio (RR), 0.89; 95% confidence interval (CI), 0.81–0.98, high-quality evidence) and lower risk of arrhythmias (RR, 0.48; 95% CI, 0.40–0.58; high-quality evidence) compared with dopamine[3].
Human and animal studies suggest that the infusion of epinephrine may have deleterious effects on the splanchnic circulation and produces hyperlactatemia. However, clinical trials do not demonstrate worsening of clinical outcomes. Further, large studies comparing vasopressin to other vasopressors in septic shock are lacking; most of the data regarding vasopressin support a sparing effect on noradrenaline dose, and there is uncertainty about the effect of vasopressin on mortality. Noradrenaline, therefore, remains the first-choice vasopressor to treat patients with septic shock. Yet, recommendations of the noradrenaline use in the SSC guideline may only be considered supportive for this well-established use application.

The second literature source presented was the Cochrane Database of Systematic Reviews. It compares the effect of one vasopressor regimen (vasopressor alone, or in combination) versus another vasopressor regimen on mortality in critically ill participants with shock. It included randomised controlled trials undertaken to investigate the effects of vasopressors in the treatment of patients with any kind of circulatory failure (term used for 'shock'). Only

[1] Rhodes, A., Evans, L.E., Alhazzani, W. et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Critical Care Medicine. 45(3), 486–552 (2017). https://doi.org/10.1097/CCM.0000000000002255
[2] Gamper G, Havel C, Arrich J, Losert H, Pace NL, Müllner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD003709. DOI: 10.1002/14651858.CD003709.pub4.
[3] Avni, T., Lador A., Lev S., Leibovici L., Paul M., Grossman A. Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis PLoS ONE 10(8): e0129305. doi:10.1371/ journal.pone.0129305

data on noradrenaline was presented . The investigators reported no differences in mortality outcomes in any of the studies comparing different vasopressors or combinations. In particular, for the comparison between dopamine and noradrenaline, which included most participants, no differences in mortality was observed. There were also no differences found in any of the secondary outcomes (morbidity, health-related quality of life, measures of anxiety and depression) with the exception of number of arrhythmias observed in patients with dopamine compared to those treated with noradrenaline.

In addition to the meta-analyses, the MAH provided a comprehensive overview of studies in which noradrenaline was investigated mostly in comparison to other vasopressor medicinal products. The available data sufficiently show that the use of noradrenaline is well-established for the proposed indication by the relevant literature.

The proposed indication is acceptable and in line with registered SmPC of comparable products. The proposed initial dose of 0.05-0.15 µg/kg/min is in line with the dose recommendations of other Noradrenaline products available on the market and as used in several of the presented studies.

IV.5 Clinical safety

The safety evaluation of noradrenaline is based on the reference textbooks, international literature and several public safety databases (Lareb, EudraVigilance and WHO). These documents/sources evaluate the overall safety experience with noradrenaline.

In general, most of the side effects of noradrenaline are caused by the excessive stimulation of the sympathetic nervous system that originates from the stimulation of α-receptors on the blood vessels (causing vasoconstriction leading to hypertension and peripheral ischaemia) and cardiac β-receptors (causing tachycardia and arrhythmias). These are well-known effects of noradrenaline and are listed in the SmPC of other Noradrenaline products available on the market.

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 Noradrenaline Added Pharma.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	- Medication errors
Missing information	None

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

addition, a Direct Healthcare Professional Communication (DHPC) has been included as an additional risk minimisation measure. This DHPC should be distributed to hospital pharmacists and intensive care anaesthetists upon marketing of the product.

IV.7 Discussion on the clinical aspects

Altogether it is considered that efficacy of noradrenaline in blood pressure control in acute hypotensive states has been established. Noradrenaline is a well known and effective vasopressor. Most of the side effects of noradrenaline are well described and are caused by the excessive stimulation of the sympathetic nervous system that originates from the stimulation of α-receptors on the blood vessels (causing vasoconstriction leading to hypertension and peripheral ischaemia) and cardiac β-receptors (causing tachycardia and arrhythmias). Overall, the clinical benefit/risk balance is considered to be positive.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Noradrenaline Added Pharma 0.5 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality in view of the present European regulatory requirements. The efficacy has been demonstrated for the indication blood pressure control in acute hypotensive states and that the safety issues that were identified are adequately addressed by SmPC warnings and the Risk Management Plan. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 December 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse