COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Noradrenaline hameln 0.2 mg/ml, solution for infusion (noradrenaline tartrate)

NL/H/4957/001/DC

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This module reflects the scientific discussion for the approval of Noradrenaline hameln 0.2 mg/ml, solution for infusion. The procedure was finalised at 1 December 2021. 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
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics
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 hameln 0.2 mg/ml, solution for infusion, from hameln pharma gmbh.

The product is indicated for use as an emergency measure in the restoration of blood pressure in cases of acute hypotension. The medicine should be used in adults only.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the European reference product (ERP) Arterenol 1 ml, 1 mg/ml solution for injection, 1 ml ampoule which has been registered in Germany by Sanofi-Aventis Germany GmbH since 2003.

The concerned member states (CMS) involved in this procedure were Czech Republic, Denmark, Finland, Germany, Hungary, Italy, Norway, Poland and Slovakia.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, due to the following differences with the ERP:

- Change in therapeutic indication
- Change in pharmaceutical form
- Change in strength

II. QUALITY ASPECTS

II.1 Introduction

Noradrenaline hameln is a ready-to-use solution for intravenous infusion. It is a clear and colourless or almost colourless solution free from visible particles. The unit dose composition is presented in sufficient details. Each ml of solution contains 0.4 mg noradrenaline tartrate, equivalent to 0.2 mg noradrenaline. Each 50 ml vial contains 20 mg noradrenaline tartrate, equivalent to 10 mg noradrenaline. The vials are made of clear, colourless neutral type I glass, and closed with a grey, type I bromobutyl rubber stopper and a tear-off aluminium cap.

The excipients are disodium edetate, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water.

II.2 Drug Substance

The active substance is noradrenaline tartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a crystalline white or almost white powder, freely soluble in water and slightly soluble in ethanol.

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 an additional CEP requirement for one specific residual. Controls for microbiological quality and bacterial endotoxins are also included. The specification is acceptable in view of the route of synthesis and the various European guidelines. A limit for the inactive S-isomer has been introduced. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for five years 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 are explained. The initial focus of the development was to develop a product that meets the requirements of the USP and BP drug product monographs. However, due to the lack of a control for the S-isomer, the current monographs are considered outdated. Therefore, the MAH has done additional studies and introduced controls of the S-isomer in the active substance and at release and during shelf-life of the drug product. Further, the MAH has committed to continue development of the drug product to achieve further tightening of the release and shelf life specification for the S-

isomer limits. The current level of control is adequate, also in view of the current compendial requirements and the clinical use of the product.

Manufacturing process

The manufacture is a straight-forward process of preparing and filtration of the solution, filling the vials and autoclaving the filled vials. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Microbiological attributes

The drug product is intended for parenteral use and requirements for injections in the Ph.Eur. monograph on Parenteral preparations. Sterility must be ensured by applying a suitable sterilisation procedure: terminal sterilisation is chosen. The packaging prevents microbial contamination. Bacterial endotoxins test and sterility test are part of batch release testing.

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/opalescence, colour of solution, (sub-)visible particles, extractable volume, osmolality, pH, identity of noradrenaline, related substances, assay of noradrenaline, S-isomer, content of sodium edetate dihydrate, bacterial endotoxins and sterility. The current release- and shelf-life specifications for assay and S-isomer impurity are acceptable. 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. Adequate risk assessments on nitrosamines have been provided. No risk for presence of nitrosamines in the drug product was identified.

Stability of drug product

Stability data on the product have been provided for three batches stored at 5°C ±3°C (36 months), at 25°C/60% RH (6 months) and one additional batch stored at 'below 25°C' for three months. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in colourless neutral glass, type I, closed with a bromobutyl rubber stopper, type I closure, and a tear-off top cap. Photostability studies showed that the product is not very sensitive for light and does not need to be stored protected from light. Based on the data submitted, a shelf-life for the unopened vial was granted for three years. The labelled storage conditions are 'Store in a refrigerator (2°C - 8°C). Do not freeze.' Results have also been provided of accelerated stability studies, with and without protection from light. In view of those results the product may also be stored outside of the refrigerator at a temperature of up to 25°C for a maximum of 6 months, after

which it should be discarded. After first opening, this medicinal product should be used immediately.

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 hameln has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH will continue development of the drug product to achieve further tightening of the release and shelf life specification for the S-isomer limits.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Noradrenaline hameln is intended for substitution of similar noradrenaline products, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of the European reference product Arterenol. Reference is made to the preclinical data obtained with the ERP. 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. However, since this procedure concerns a hybrid application in which the drug product differs in three clinically relevant aspects from the ERP, the MAH specifically addressed the clinical efficacy and clinical safety of the drug product (see section IV.3).

IV.2 Pharmacokinetics

No new pharmacokinetic studies were considered needed for this hybrid application. The MAH presented bibliographical data to describe the absorption, bioavailability, distribution, elimination, excretion and metabolism of noradrenaline. Sufficient references were provided to support the presented data on pharmacokinetics.

Noradrenaline hameln 0.2 mg/ml, solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98).

IV.3 Pharmacodynamics

No new pharmacodynamic studies have been conducted by the MAH. The MAH presented bibliographical data to describe an overview of general pharmacodynamic properties of noradrenaline. Primary pharmacology of noradrenaline is well known. Noradrenaline induces a rapid pharmacological response following the initiation of IV infusion. This results in an increased systolic and diastolic blood pressure and a less pronounced decrease in the pulse rate. The duration of action is short. This response is seen in different patients populations with hypotension of a different origin.

Aside hemodynamic effects of noradrenaline on systemic blood pressure, noradrenaline has also a cardiac effect, cardiopulmonary and beneficial effects on flap skin blood flow, metabolic and calorigenic effects. All these effects are rather predictable and can be sufficiently explained by the mechanism of action and driven by the wide spread adrenoceptors in the human body.

IV.4 Clinical efficacy

Noradrenaline hameln 0.2 mg/ml, solution for infusion differs from the reference product in three clinically relevant aspects, namely:

- Pharmaceutical form. The drug product is a solution ready-to-use, whereas the European reference product is a solution to be further diluted.
- Strength. The drug product has a higher concentration of the active substance than the European reference product has after the necessary dilution.
- Indication. The drug product is indicated for use in case of acute hypotension, where the European reference product is indicated for septic shock.

The changes in pharmaceutical form and strength have been justified. The ERP product is a concentrate solution of 1 mg/ml and needs to be diluted to a concentration of 0.5-5 mg/ml. Thus, at the time of administration, patients are exposed to similar dilution concentrations. Furthermore, the difference in strength is considered not to affect the bioavailability since both products are aqueous solutions.

The evaluation of the clinical efficacy of noradrenaline has also been performed on a bibliographic basis. The MAH described several studies to support the efficacy of noradrenaline.

The MAH reported three literature studies on dose-response (Onwochei et al., 2017, Ngan Kee, 2017, Chen et al., 2018). Patients included women undergoing elective caesarean delivery. Doses of norepinephrine ranged from 6 to 8 microgram, as well as infusion of 5-10 µg/kg/h of norepinephrine in patients who undergo caesarean delivery under spinal anaesthesia was effective to reduce hypotension incidence without significant adverse effects on maternal and neonatal outcomes.

Further, the MAH presented various randomised controlled studies (Ngan Kee et al., 2015, El Shafei et a.l, 2015, Agrawal et al., 2011, Nathan et al., 2011, Myburgh et al., 2008, Russell et al., 2008, Jeon et al., 2006, Albanèse et al., 2005, De Backer et al., 2003, Duranteau et al., 1999, Tran et al., 1997, Martin et al., 1993, Hajjar et al., 2017, Patel et al., 2002, Wang et al., 2019) and non-controlled studies (Benchekroune et al., 2008, Oldenburg et al., 2001, Martin et al., 1994, Desjars et al., 1987), showing that noradrenaline is as effective compared to dopamine, ephedrine and phenylephrine for the maintenance of systolic blood pressure (SBP) in cases of:

- spinal anaesthesia,
- refractory orthostatic hypotension due to primary autonomic failure, and
- in patients presenting with a septic or other forms of shock.

This effect is currently well known, in line with the pharmacology data and widely used for its efficacy in clinical practice.

The MAH provided also four systematic reviews to further support the efficacy of noradrenaline (Ayni et al., 2015, Vasu et al., 2012, De Backer et al., 2012, Xu et al.,2019). The first three reviews concerned patients with septic shock, the last review concerned patients

who received norepinephrine for the prevention and treatment of maternal hypotension. In the systematic review of Ayni et al (2015) compared to dopamine (866 patients, 450 events), norepinephrine (832 patients, 376 events) was associated with decreased all-cause mortality, RR 0.89 (95% CI 0.81 - 0.98), corresponding to an absolute risk reduction of 11%. The study of Vasu et al (2012) there was statistically significant superiority of norepinephrine over dopamine for the outcome of in-hospital or 28-day mortality: pooled RR: 0.91 (95% CI 0.83 to 0.99; P = 0.028). In the third meta-analysis study in patients with septic shock, dopamine administration was associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration (De Backer et al, 2012). In the fourth study (Xu et al (2019)), there was no difference in effectiveness between norepinephrine and phenylephrine for the treatment of maternal hypotension (odds ratio [OR] 0.64; 95% CI 0.37 - 1.10, P = 0.11), and there was no difference in the occurrence of hypertension (OR 0.74; 95% CI 0.33 - 1.62, P = 0.45). This systematic review and meta-analysis show norepinephrine provides similar efficacy to manage maternal hypotension compared to phenylephrine. Overall, these data support the data of the earlier mentioned clinical studies supporting the efficacy of noradrenaline.

Based on the efficacy information, the following indication has been proposed: “Indicated for use as an emergency measure in the restoration of blood pressure in cases of acute hypotension.”, which deviates from the indication as presented in the SmPC of the ERP (Arterenol; “Septic shock, when circulatory stabilization cannot be achieved through volume therapy alone”). Although most literature makes reference to patients with septic shock, the MAH sufficiently justified with the available data that noradrenaline is also evaluated and effective for the maintenance of SBP in cases of spinal anaesthesia, refractory orthostatic hypotension due to primary autonomic failure, and in patients presenting with septic or other forms of shock. The newly proposed indication is therefore deemed acceptable.

In conclusion, the MAH has reasonably addressed that the data as described in the literature could to an important extent be bridged to the current product. This is considered acceptable.

IV.5 Clinical safety

The safety evaluation of noradrenaline is also based on scientific literature to evaluate the overall safety experience with noradrenaline. Norepinephrine is generally safe, effective and well tolerated. However, since it is a peripheral vasoconstrictor its adverse effects include cardiac disorder particularly arrhythmia and bradycardia hypertension (possibly associated with reflex bradycardia) headache were associated with norepinephrine. The MAH has provided an overview of general safety data of noradrenaline and provided references to specific SmPC wording. The SmPC 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 Noradrenaline hameln.

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

Important identified risks	None
Important potential risks	Risk of medication errors
Missing information	None

Next to routine pharmacovigilance activities and routine risk minimisation measures, the MAH proposed a direct healthcare professional communication (DHPC) as an additional risk minimisation activity for the important potential risk of 'Risk of medication error'. Implementation of the additional risk minimisation measures and details of the controlled distribution system will be agreed with the competent authority of each individual member state in the EU.

IV.7 Discussion on the clinical aspects

For this hybrid authorisation, reference is made to the clinical studies and experience with the reference product Arterenol. A clinical overview with relevant references was provided and no new clinical studies were required. Considering that both the test and reference formulations are to be administered as an aqueous intravenous solution containing the same active substance, a bioequivalence study is not necessary. Risk management is adequately addressed. The clinical efficacy and safety of Noradrenaline hameln have been appropriately addressed. Changes in pharmaceutical form, strength and indication compared to the ERP have been adequately discussed and are acceptable.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the ERP Arterenol. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

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 hameln 0.2 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Arterenol 1 ml, 1 mg/ml solution for injection,

1ml ampoule. Arterenol is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. Clinically relevant changes that were made compared to the reference product have been adequately addressed and the clinical efficacy and clinical safety profiles were considered acceptable.

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 essential similarity has been demonstrated for Noradrenaline hameln with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 December 2021.

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

LITERATURE REFERENCES

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