COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Noradrenaline Sun 0.5 mg/ml solution for infusion in pre-filled syringe

(noradrenaline tartrate)

NL/H/5073/001/DC

Date: 13 June 2022

This module reflects the scientific discussion for the approval of Noradrenaline Sun 0.5 mg/ml solution for infusion in pre-filled syringe. The procedure was finalised at 7 April 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
BHA	Butylated hydroxy anisole
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
DHPCs	Direct healthcare professional communications
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ERP	European Reference Product
HPLC	High-performance liquid chromatography
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
TSE	Transmissible Spongiform Encephalopathy
TAMC	Total aerobic microbial count
TYMC	Total combined yeasts and molds count

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Noradrenaline Sun 0.5 mg/ml solution for infusion in pre-filled syringe, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for treatment of hypotensive emergencies in patients with shock. Noradrenaline is indicated in adults.

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, 1ml ampoule which has been registered in Germany by Sanofi-Aventis Germany GmbH since 2003.

The concerned member states (CMS) involved in this procedure were Germany, Spain, France, Italy, Poland, Romania and the United Kingdom.

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 reference product:

- Change in therapeutic indications.
- Change in pharmaceutical form.
- Change in strength.

Scientific advice

Noradrenalin Sun has been compared with the ERP Arterenol. The MAH initially proposed Noradrenaline concentrate for solution for infusion 1 mg/ml, Hospira, UK as ERP, however, in view of Brexit, the MAH was advised by the BfArM (the German Federal Institute for Drugs and Medical Devices) scientific advice letter on 11 June 2018 to take Arterenol as ERP.

II. QUALITY ASPECTS

II.1 Introduction

Noradrenaline Sun is a ready-to-use solution for intravenous infusion in a in pre-filled syringe of 50 ml. It is a clear and colourless or yellowish solution free from visible particles. The unit dose composition is presented in sufficient details.

Each ml of solution contains 1.0 mg noradrenaline tartrate, equivalent to 0.5 mg noradrenaline. Each 50 ml pre-filled syringe contains 50 mg noradrenaline tartrate equivalent to 25 mg noradrenaline.

One 50 ml pre-filled syringe made of cyclic olefin copolymer is fitted with a chlorobutyl elastomer screw cap along with a bromobutyl plunger stopper.

The excipients are disodium edetate (E386), butylated hydroxy anisole (BHA; E320), 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. Noradrenaline solutions have a long standing and well-known use as vasoconstrictor for immediate restoration of blood pressure in acute hypotensive states such as shock.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of three steps. In step I and II, substages of the active substance are formed. Briefly, the manufacturing process consists of a reaction with a solvent, reduction of substage I, resolution of substage II and purification and drying of the final stage. Adequate specifications have been adopted for starting materials, solvents and reagents. In addition to the detailed descriptions for all substages, detailed flow-charts are provided. The active substance has been adequately characterised.

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 additional requirements. These additional requirements are based on the following test methods: tests on organic impurities, residual solvents, bacterial endotoxins, total aerobic microbial count (TAMC), total combined yeasts and molds count (TYMC) and high-performance liquid chromatography (HPLC) analysis. Genotoxic impurities have been adequately discussed. All solvents used in the active substance manufacturing process have been adequately discussed. The ASMF-holder adequately evaluated all potential elemental impurities in line

with ICH Q3D. The ASMF-holder made clear that there is no risk on formation of nitrosamines.

Batch analytical data demonstrating compliance with the active substance specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines. The batches have been stored for 18 months (two batches) and 12 months (one batch) at 25°C/60% RH. All three batches have been stored at 40°C/75% RH for 6 months. Based on the data submitted, a retest period could be granted of 12 months when stored under the conditions as given on the active substance product label, which are: 'Store in well closed container at 2-8°C and protected from light.'

Several precaution measures are taken to limit the content of oxygen, the influence of light and the entrance of humidity. Adequate specifications have been set for the primary packaging material, in accordance with concerning Ph. Eur and Commission Regulation (EU) requirements.

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 drug product differs in composition from the ERP as follows:

- The medicinal product is a prefilled syringe of 0.5 mg/ml in a 50 ml syringe and is ready-to-use, whereas the reference product is a solution of 1 mg/ml in an 1 ml ampoule, to be further diluted for use.
- The medicinal product contains BHA and disodium edetate, the reference product not.
- The reference product contains metabisulfite, the medicinal product not.

Based on measurement of S-Noradrenaline levels a final formulation was developed. The formulation does not generate protons in aqueous solution which catalyses S-isomer formation, and both disodium edetate and BHA do not have any impact on this. The levels of both these excipients have been optimised based on the levels of "Any unspecified Impurity" wherein the selected levels ensure that the levels remain below the ICH Q3 (B) threshold. During initial development studies the levels of disodium edetate was followed in long-term (24 months) and accelerated (6 months) studies. All results were close to 100% and no significant differences were seen, therefore, it was decided to no longer monitor disodium edetate levels.

Adequate formulation optimisation studies have been performed including functionality, photostability, sterility and several compatibility studies. The results of these studies were acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The process consists of: preparation of bulk solution, sterile filtration, filling and stoppering of pre-fillable syringes, terminal sterilisation, leak testing, visual inspection and labelling, coding and packing operation. Various reports from the filter manufacturer are provided regarding the filter cartridges used for the sterile filtration of the bulk solution. All reports together demonstrate that the chosen filters are suitable and adequate for sterilising filtration of the bulk solution. The empty syringes and plunger stoppers are sterilised by gamma-irradiation.

Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines. For all manufacturing steps critical process parameters (CPP) are identified. With the proven acceptable ranges for each CPP, all CPP ranges are considered acceptable. For all stages in the manufacturing process in-process controls with acceptance criteria have been established.

Control of excipients

All used excipients comply with the concerning Ph. Eur. Monograph. For specifications, analytical methods, validation of the methods and justification of the specifications reference is made to the Ph. Eur. monographs. In this pharmaceutical form no functionality-related characteristics are relevant for the substances at issue. Therefore, it is adequate to test them in line with the Ph. Eur. monograph with no additional test.

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 description, identification of noradrenaline and BHA, pH and degree of colouration of the solution, extractable volume, uniformity of dosage units, break-loose and glide force, particulate contamination, sterility, bacterial endotoxins, weight loss of the prefilled syringe, assays of BHA, disodium EDTA and related substances by HPLC and assays of R-noradrenaline and S-noradrenaline by chiral HPLC.

The specification for the physiological active R-Noradrenaline is set at not lower than 90% during shelf-life. The shelf-life specification for S-Noradrenaline of not more than 10% will be applied. The chiral HPLC method for R-Noradrenaline has been validated for identification, specificity, forced degradation studies, linearity, range, precision, accuracy, solution stability and robustness. All other HPLC test methods (nitrosamine related substances, S-noradrenaline, BHA) have been adequately validated.

A full evaluation on the risk of elemental impurities and of nitrosamine impurity was provided. Based on the review, it is concluded that levels of elemental impurities are within the safety recommendations of the concerning ICH guideline. Furthermore, nitrosamine impurities are not present in the manufacturing process and there is also no possibility of contamination from other sources. Therefore, no further evaluation and control is required.

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 specifications.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C/40% RH (18 months), 30°C/65% RH (12 months) and 40°C/25% RH (6 months). On basis of the data submitted, a shelf-life was granted of 12 months. A photostability study is included in the submitted data which showed that the product is sensitive to light. The labelled storage conditions of the drug product are: 'do not store above 25°C' and 'store the pre-filled syringe in the original package 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 member states consider that Noradrenaline Sun 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 Ecotoxicity/environmental risk assessment (ERA)

Since Noradrenaline Sun is intended as a substitute for similar noradrenaline containing 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 medicine and has essential similarity with the reference product Arterenol, which is available on the European market. Reference is made to the preclinical data obtained with the reference product. 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 tartrate is a well-known active substance with established efficacy and tolerability. However, since the drug product differs in three clinically relevant aspects from the reference product, this procedure concerns a hybrid application. Therefore, the MAH specifically addressed the clinical efficacy and clinical safety of the drug product. A clinical overview has been provided, which is based on scientific literature. The overview sufficiently justifies why there is no need to generate additional clinical data. The member states agreed that no further clinical studies are required.

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 Sun 0.5 mg/ml solution for infusion in pre-filled syringe is a parenteral formulation without excipients that may interact with the active substance. Therefore, Noradrenaline Sun fulfils the exemption mentioned in the Guideline on the investigation of Bioequivalence, which states that a bioequivalence study is generally not required if the product is administered as an aqueous intravenous solution containing the same active substance as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98 Rev. 1/Corr).

IV.3 Clinical efficacy and clinical safety

Noradrenaline Sun differs from the reference product in three clinically relevant aspects, namely:

- Therapeutic indications.
- Pharmaceutical form. The drug product is a prefilled syringe and is ready-to-use, whereas the European reference product is a solution in an ampoule, 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.

The change in therapeutic indications is acceptable since the reference product indication has been limited to patients with shock which persists after adequate fluid volume replacement. However, noradrenaline can be used as an emergency measure to maintain supply to the coronary and cerebral arteries until blood volume replacement therapy can be

instituted. Therefore, the indication 'treatment of hypotensive emergencies in patients with shock. Noradrenaline is indicated in adults' is acceptable for Noradrenaline Sun.

The changes in pharmaceutical form and strength (being a ready-to-use pre-filled syringe), compared to the reference medicinal product Arterenol (1 mg/ml solution for injection, to be diluted before use), have been justified as well. On advice by the Agency (CBG/MEB, The Netherlands) the MAH has referred to Noradrenaline Aguettant, solution for infusion, which was registered via an European procedure (UK/H/5538/001). The pharmaceutical form of Noradrenaline Aguettant is similar to Noradrenaline Sun since it is administered to patients without dilution. To minimise the risk of medication errors due to changes in the pharmaceutical form and strength, the MAH has adequately described additional risk minimisation measures. These measures are considered sufficient to minimise the risk of medication errors.

Overall, the clinical efficacy and safety of Noradrenalin Sun have been appropriately addressed. Changes in therapeutic indications, pharmaceutical form and strength are acceptable and sufficient measures are taken to minimise the risk of medication errors. Therefore, no new clinical studies were required for this hybrid application.

IV.4 Risk Management Plan (RMP)

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 Sun. Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are required.

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

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

The MAH adequately described the risk of medication errors in the RMP. The routine risk minimisation measures as shown in Table 2 were included in the RMP and are considered sufficient to minimise the risk of medication errors.

Table 2. Summary table of Risk minimisation measures

Safety concern	Risk minimisation measures
Medication error	Routine risk minimisation measures: - SmPC section 1, 4.1, 4.2, 4.9, 5.1 and 6.5 - Package leaflet section 3, 4, 5 and 6 Additional risk minimisation measures: - Noradrenaline Sun differs from Arterenol regarding the: • product name • concentration

	• administration device • inbuilt distinguishing features in terms of appearance • usage (Noradrenaline Sun is ready-to-use) • prescription - Direct healthcare professional communications (DHPCs), if decided at national level, to inform healthcare professionals on the risk of medication errors.

IV.5 Discussion on the clinical aspects

For this hybrid authorisation, reference is made to clinical studies and experience with the European reference product Arterenol. The MAH demonstrated through bibliographical data that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. A clinical overview with relevant references was provided and no new clinical studies were required. Changes in therapeutic indications, pharmaceutical form and strength have been adequately discussed and are acceptable. Adequate risk minimization measurements are described to minimise the risk of medication errors.

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 3 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 Sun 0.5 mg/ml solution for infusion in pre-filled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Arterenol 1 ml, 1 mg/ml solution for injection. This European reference product 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 was 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 Sun with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 April 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
NL/H/5073/001/001	Type IB – B.II.f.1.b.1: To extend the shelf life of Noradrenaline Sun from one year to 18 months.	NA; variation is implemented in final SmPC	17 November 2021	Approval	