COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mykronor 5 microgram/ml, solution for injection/infusion (noradrenaline tartrate)

NL/H/5186/001/DC

Date: 9 May 2022

This module reflects the scientific discussion for the approval of Mykronor 5 microgram/ml, solution for injection/infusion. The procedure was finalised at 2 July 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
ERP	European Reference Product
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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mykronor 5 microgram/ml, solution for injection/infusion, from Laboratoire Aguettant.

The product is indicated for restoration and maintenance of peri-operative blood pressure following hypotension induced by spinal or general anaesthesia 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) Noradrenaline (Norepinephrine) 1:1000, concentrate for solution for infusion, which has been registered in Ireland by Pfizer Healthcare Ireland since 10 April 1995. The justification to use this product is based on information received from Ireland.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Luxembourg, Norway, Portugal, Romania, Sweden and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as therapeutic indication, pharmaceutical form and strength differ from the ERP.

Scientific Advice was given by MEB on 23 August 2018, which was followed by the MAH.

II. QUALITY ASPECTS

II.1 Introduction

Mykronor is a ready-to-use, clear and colourless solution, practically free from visible particles with a pH of 3.5 – 4.0 and an osmolality of 260 – 320 mOsm/kg. One ml contains 10 microgram of noradrenaline (norepinephrine) tartrate monohydrate, equivalent to 5 microgram noradrenaline base anhydrous.

The solution is packed in a 20 ml clear type II glass vial closed with a chlorobutyl stopper and an aluminium cap.

The excipients are sodium chloride, disodium edetate, hydrochloric acid (pH adjustment) 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.

The CEP procedure is used for two active substance sources. 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 for each drug product manufacturer 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. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each source.

Stability of drug substance
The active substance is stable up to five years depending on the manufacturer 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. 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 products. No incompatibility with the active substance is reported.

The MAH has taken the received scientific advice from the NL MEB into consideration, e.g. with respect to the applied EDTA concentration.

It is known from literature that noradrenaline in solutions for injection / infusion could racemise from the desired L-isomer to the undesired D-isomer. The current level of control

of racemisation in the drug substance and the drug product is considered sufficient, also in view of the current compendial requirements and the clinical use of the product.

Manufacturing process

The manufacturing process consists of preparation of bulk solution of all components in water, volume make up, filtration, filling, 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 Ph. Eur. monograph. 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 and colour of solution, identity of noradrenaline, identity of EDTA, pH, osmolality, noradrenaline assay, EDTA content, related substances, extractable volume, subvisible particles, visible particles, bacterial endotoxins and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The tests and specification at release and at end of shelf-life are indicated. All physical-chemical tests and their specifications are considered acceptable. The current release- and shelf-life specifications are acceptable.

The risk of nitrosamine impurity has been evaluated in the drug product manufacturing process, excipients and packaging materials used, manufacturing equipment used and cleaning procedure. Based on the review, it is concluded that nitrosamine impurities are not present in manufacturing process and there is no possibility from other sources. Hence, no additional control or evaluation is required. The provided nitrosamine risk evaluation is considered acceptable. No specific risks for nitrosamine formation or agents who could induce this formation, are identified.

The analytical methods have been adequately described and validated. Forced degradation studies have been performed and confirm the stability indicating nature of the method for assay and related substances.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches of the minimal proposed size from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches stored at 25°C (24 months), 30°C, and 40°C (six months) in accordance with applicable European guidelines. In view of the stability results, the storage condition will be restricted to *Not above 25°C*. A photostability study was performed, which demonstrates that the noradrenaline product is sensitive to light. On basis of the data submitted, a shelf life of 24 months was granted. The

labelled storage conditions are: ”Store below 25°C. Store the vial in the outer carton to protect from light. Do not freeze.”

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 Mykronor has an acceptable chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- Performing additional development of the drug product to further optimise the release and shelf life specification limits.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

An environmental risk assessment has been provided and was deemed acceptable. However, since Mykronor is intended for hybrid substitution, this will not lead to an increased exposure to the environment. Therefore, the ERA was not necessary and was not discussed further.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Noradrenaline (Norepinephrine) 1:1000 which is available on the European market. Reference is made to the preclinical data obtained with the innovator 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. 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

Mykronor 5 microgram/ml, solution for injection/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). Mykronor contains EDTA, NaCl, HCl and water as excipients. The other noradrenaline solution for injection/infusion does not contain EDTA. However, it is not expected that EDTA will affect the pharmacokinetics following IV administration. Commercially available solutions for infusion contain 100 to 500 µg/ml. The Mykronor solution contains 5 µg/ml. This lower concentration is allowed via a hybrid application.

IV.3 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 Mykronor.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- None
Important potential risks	- Risk of medication error
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.

The risk management plan was considered acceptable.

IV.4 Discussion on the clinical aspects

For this hybrid authorisation, reference is made to the clinical studies and experience with the innovator product Noradrenaline (Norepinephrine) 1:1000. 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. Furthermore, the difference in strength is considered not to affect the bioavailability and in line with a hybrid application, and is considered acceptable. A clinical overview with relevant references was provided and no new clinical studies were required. Risk management is adequately addressed. Changes in pharmaceutical form and strength have been adequately discussed and are acceptable.

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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with four 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

Mykronor 5 microgram/ml, solution for injection/infusion has a proven chemical-pharmaceutical quality and is a hybrid form of Noradrenaline (Norepinephrine) 1:1000, Concentrate For Solution For Infusion. Noradrenaline (Norepinephrine) 1:1000 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.

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 Mykronor with the reference

product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 July 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