IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Sinora 0.08mg & 0.16mg solution for infusion, from on 24th April 2020 for the on-going treatment of hypotensive emergencies with escalating noradrenaline dose requirements,.

This is an application based on Article 10a of Directive 2001/83/EC (bibliographic application). IE was the RMS for this decentralised procedure, with UK as the only CMS.

The products are prescription-only medicinal products.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Sinora 0.08mg & 0.16mg solution for infusion
Name(s) of the active substance(s) (INN)	Norepinephrine Bitartrate
Pharmacotherapeutic classification (ATC code)	C01CA03 Norepinephrine
Pharmaceutical form and strength(s)	0.08mg & 0.16mg solution for infusion
Marketing Authorisation Number(s) in Ireland (PA)	PA22835/001/001-002
Marketing Authorisation Holder	Sintetica GmbH
MRP/DCP No.	IE/H/564/001-002/DC
Reference Member State	IE
Concerned Member State	UK (Northern Ireland)

II. QUALITY ASPECTS

II.1. Introduction

This application is for Sinora 0.08 mg/ml & 0.16 mg/ml solution for solution.

II.2 Drug substance

The active substance is norepinephrine tartrate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The product contains either 0.08 mg/ml & 0.16 mg/ml of norepinephrine in the form of the norepinephrine tartrate.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the relevant pharmacopoeial monographs and EU guidelines, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging Material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with the relevant Ph. Eur./EU legislation.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Sinora 0.08 mg/ml & 0.16 mg/ml solution for solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Noradrenaline tartrate is a widely used and well-known active substance and the pharmacodynamic, pharmacokinetic and toxicological properties of noradrenaline tartrate are well known. The applicant has not provided additional non-clinical safety studies and further studies are not required. An overview based on literature review is appropriate.

The non-clinical overview has been written by Stefano Camnasio, PhD who is a suitably trained qualified scientist employed by Sintetica SA, Mendrisio. A signed statement and CV is provided and dated 29th of March 2018. The report refers to 56 publications up to the year 2014 and is not dated.

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is adequate. No new data were found that would alter the risk-benefit balance for noradrenaline tartrate.

The GLP status of the studies described in the published scientific literature cannot be verified.

III.2 Pharmacology

Noradrenaline causes peripheral vasoconstriction via alpha-adrenoreceptor agonism, leading to increased peripheral resistance and increased systolic and diastolic blood pressure, with reflex slowing of heart rate to maintain cardiac output. Noradrenaline also directly stimulates β-adrenergic receptors of the heart (β1-adrenergic receptors) but has little effect on those of the

bronchi or peripheral blood vessels (β2-adrenergic receptors). It is believed that α-adrenergic effects result from inhibition of the production of cyclic adenosine-3′, 5′-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity. The overview of pre-clinical pharmacology based on literature review is adequate.

III.3 Pharmacokinetics

Noradrenaline is a widely used and well-known active substance. Noradrenaline is ineffective after oral administration as it is destroyed in the GI tract and noradrenaline is poorly absorbed after s.c. administration due to locally reduced blood flow. Hence, noradrenaline is indicated for administration by i.v. infusion. Noradrenaline is rapidly metabolized by COMT and MAO and the major metabolites are Normetanephrine and VMA, which are both pharmacologically inactive. Metabolism takes place predominantly in the liver and sympathetic nerves. After i.v. administration, Noradrenaline has a short duration of action of 1 - 2 min. Noradrenaline metabolites are excreted in urine primarily as the sulfate conjugates and, to a lesser extent, as the glucuronide conjugates. Only small quantities of noradrenaline are excreted unchanged. Noradrenaline crosses the placenta but not the blood-brain-barrier. The overview of pre-clinical pharmacokinetics based on literature review is adequate.

III.4 Toxicology

The major toxic effects of Noradrenaline in dogs, cats and rabbits were a deterioration of cardiac function (focal degeneration and necrosis of myofibres and subendocardial haemorrhage). Noradrenaline can also cause tissue necrosis and sloughing at the site of injection. Noradrenaline may impair placental perfusion and induce fetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to fetal asphyxia in late pregnancy. In sheep, Noradrenaline can decrease serum prolactin and reduce milk production. The overview of pre-clinical toxicology based on literature review is adequate.

III.5 Ecotoxicity/environmental risk assessment

Since Sinora 0.08 & 0.16 mg/ml Solution for Infusion 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.6 Discussion on the non-clinical aspects

Noradrenaline titrate is a widely used and well-known active substance. This application was made under the legal basis of well-established use. Information on the nonclinical pharmacology, pharmacokinetics and toxicology were supported by a review of the published literature on noradrenaline. No additional studies were conducted by the applicant and no further studies are required.

IV. CLINICAL ASPECTS

The HPRA is satisfied that relevant GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption and Distribution
Orally ingested noradrenaline is destroyed in the gastrointestinal tract, and the drug is poorly absorbed after subcutaneous injection. Noradrenaline must therefore be administered intravenous by infusion into a large vein, as there is risk of necrosis of the overlying skin from prolonged vasoconstriction. After intravenous administration, a pressor response occurs rapidly. The drug has a short duration of action, and the pressor action stops within 1 - 2 minutes after the infusion is discontinued. (AHFS DI, 2009) For septic shock and trauma patients, the terminal elimination half-life ranged from 2.0 to 6.8 min, and was significantly longer in more severely ill patients. (Beloeil H, 2005) Noradrenaline localizes mainly in sympathetic nervous tissue. Noradrenaline is rapidly cleared from plasma by a combination of cellular reuptake and metabolism. The drug crosses the placenta but not the blood brain barrier. (AHFS DI, 2009)

Metabolism and Elimination
The pharmacologic actions of noradrenaline are terminated primarily by uptake and metabolism in sympathetic nerve endings. The drug is metabolized in the liver and other tissues by a combination of reactions involving the enzymes catechol-O-methyltransferase and monoamine oxidase (MAO). The major metabolites are normetanephrine and 3-methoxy-4-hydroxy mandelic acid (vanillylmandelic acid), both of which are inactive. Other inactive metabolite include 3-methoxy-4-hydroxyphenylglycol, 3,4- dihydroxymandelic acid, and 3,4-dihydroxyphenylglycol. Noradrenaline metabolites

are excreted in urine primarily (84% to 96%) as inactive metabolites as the sulfate conjugates and, to a lesser extent, as the glucuronide conjugates. Only small quantities noradrenaline are excreted unchanged (AHFS DI, 2009).

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. It is believed that α-adrenergic effects result from inhibition of the production of cyclic adenosine-3′, 5′-monophosphate (cAMP) by inhibition of the enzyme adenyl cyclase, whereas β-adrenergic effects result from stimulation of adenyl cyclase activity (AHFS DI, 2009).
Noradrenaline is the major neurotransmitter in postganglionic adrenergic neurones, and is stored in granules in the nerve axons. Small amount of noradrenaline is also present in the adrenal medulla and is released with adrenaline. Evidence indicates a differentiated secretion of noradrenaline and adrenaline from the catecholamine producing structures (adrenergic nerve terminals, the suprarenal medulla and chromaffin cells in the tissues) depending on the functional requirements of the organism (Von Euler US, 1954). Thus noradrenaline is released during conditions which involve primarily circulatory needs (blood pressure homeostasis) and the nervous regulation of smooth muscle activity.
The major effects of noradrenaline relate to its α-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. β-stimulant effects of noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the central nervous system (CNS) (Richards DW Jr 1954, Martindale, 2014).

IV.4 Clinical Efficacy

This application presents publications from clinical trials, guidelines and meta-analyses data. The submitted literature data gives an overview of the current knowledge of the efficacy of noradrenaline.
The available data sufficiently show that the use of noradrenaline in different clinical settings is well-established for the proposed indication "emergency restoration of blood pressure in cases of acute hypotension". The indication, dose range and cautions requiring a reduction in dosage are supported by the relevant literature.

IV.5 Clinical Safety

Noradrenaline has been used for decades in a wide range of patient population. The literature and post-marketing data suggests that noradrenaline is well-tolerated. The overall safety profile is established and generally known. Noradrenaline has an acceptable adverse event profile when contraindications and precautions are considered properly. In general, noradrenaline is administered in a clinical setting with high controlled surveillance activities.

As noradrenaline is a potent vasoconstrictor, administration must be through a cannula placed in a central vein. Administration through peripheral veins is not appropriate. Concerns related to text in the product information suggesting that peripheral administration might be appropriate were raised by CMS-UK. The applicant has taken this into account and has amended the product information accordingly.

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 Sinora 0.08 mg/ml Solution for Infusion and Sinora 0.16 mg/ml Solution for Infusion. Risk management plan, version 0.3, signed 19 December 2019, is considered acceptable.

Safety specification

Summary of safety concerns	
Important identified risk	• Acute Glaucoma in patients anatomically pre-disposed • Bradycardia and cardiac arrhythmias • Drug interactions with significant clinical consequences • Necrosis and Peripheral ischaemia (including gangrene of the extremities)

Important potential risk	• Use during pregnancy • Medication error resulting in under or over exposure to norepinephrine
Missing Information	• Use in patients with renal or hepatic insufficiency • Use in paediatric population • Use during breast-feeding

Pharmacovigilance plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Acute glaucoma in patients anatomically pre-disposed	**Routine risk minimisation measures:** SmPC Section 4.8 PIL Section 4 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None
Bradycardia and cardiac arrhythmias	**Routine risk minimisation measures:** SmPC Section 4.4, 4.5, 4.8, 4.9 PIL Section 2, 4 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None
Necrosis and Peripheral ischaemia (including gangrene of the extremities)	**Routine risk minimisation measures:** SmPC Section 4.4, 4.8 PIL Section 4 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None
Drug interaction with significant clinical consequences	**Routine risk minimisation measures:** SmPC Section 4.5 PIL Section 2 *Prescription only medicine and use restricted under the supervision of experienced clinicians-*	None
Use during pregnancy	**Routine risk minimisation measures:** SmPC Section 4.6 PIL Section 2 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None
Medication error resulting in under or over exposure to norepinephrine	**Routine risk minimisation measures:** SmPC Section 4.2, 6.6 PIL Section 6 *Include the sentence "**DO NOT DILUTE**"*	None

	on the packaging of the ready-to-use formulations. *Prescription only medicine and use restricted under the supervision of experienced clinicians.* **Additional risk minimisation measures:** DHPC	
Use in patients with renal or hepatic insufficiency	**Routine risk minimisation measures:** SmPC Section 4.2 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None
Use in paediatric population	**Routine risk minimisation measures:** SmPC Section 4.2 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None
Use during breast-feeding	**Routine risk minimisation measures:** SmPC Section 4.6' PIL Section 2 *Prescription only medicine and use restricted under the supervision of experienced clinicians.*	None

Periodic Safety Update Report (PSUR):

The PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

Based on the information provided by the applicant, the clinical aspects of the application are considered to be acceptable.

V. OVERALL CONCLUSIONS

The pharmacodynamic and pharmacokinetic characteristics of noradrenaline are considered to be well established.

The published literature sufficiently shows that the efficacy of noradrenaline in the proposed indication is well-established in clinical use. The proposed indication and dosage recommendations are in line with other approved noradrenaline-containing agents.

The overall safety profile is established and generally known. Noradrenaline has an acceptable adverse event profile when contraindications and precautions are considered properly. The adverse reactions can be promptly and adequately to handled, taking into account that noradrenaline is used in situations where the patient is under strict monitoring.

Following the comments from the CMS, the applicant has amended the indication and posology to reflect the concerns of the CMS. In addition the applicant has altered the text to ensure that the product is only recommended for administration through a cannula placed in a central vein.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

In conclusion, the benefit/risk profile of the product is considered to be positive and therefore a marketing authorisation has been granted.

VI. REVISION DATE

September 2022

VII. UPDATES

SCOPE	**PROCEDURE NUMBER**	**PRODUCT INFORMATION AFFECTED**	**DATE OF START OF PROCEDURE**	**DATE OF END OF PROCEDURE**
Transfer	N/A	MAH and PA number Package Leaflet New MA Holder: Sintetica GmbH New PA number: PA22835/001/001-002	N/A	09/09/2022