Public Assessment Report

Decentralised Procedure

Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion

(noradrenaline tartrate)

Procedure No: UK/H/5669/001/DC

UK Licence No: PL 40201/0001

NOVOCAT FARMA, S.A
LAY SUMMARY
Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion.
(noradrenaline tartrate)

This is a summary of the Public Assessment Report (PAR) for Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion (PL 40201/0001; UK/H/5669/001/DC). This product will be referred to as Noradrenaline solution for Infusion in the remainder of this summary, for ease of reading.

This summary explains how Noradrenaline solution for Infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Noradrenaline solution for Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Noradrenaline solution for Infusion and what is it used for?
Noradrenaline solution for Infusion is a medicine with ‘well-established use’. This means that the medicinal use of the active substance of Noradrenaline solution for Infusion is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Noradrenaline solution for Infusion is used in an emergency to increase blood pressure to normal levels.

How does Noradrenaline solution for Infusion work?
Noradrenaline solution for Infusion contains the active ingredient noradrenaline tartrate, which maintains the blood pressure to normal levels.

How is Noradrenaline solution for Infusion used?
Noradrenaline solution for Infusion is given by a health professional as an infusion into the vein. It is first diluted before being administered into a vein.

The usual dose is between 0.4 and 0.8 mg per hour. The initial dose depends on patient’s medical condition. The dosage of Noradrenaline solution for Infusion will be adjusted accordingly following assessment of response.

This medicinal product can only be obtained with a prescription from a doctor.

For further information on how Noradrenaline solution for Infusion is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Noradrenaline solution for Infusion have been shown in studies?
As noradrenaline tartrate is a well-known substance, and its use in emergency to increase blood pressure to normal levels is well-established, the applicant presented data from the scientific literature. The literature provided confirmed the efficacy and safety of noradrenaline tartrate for the proposed indication.

What are the possible side effects of Noradrenaline solution for Infusion?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

For the full list of restrictions, see the package leaflet.
For the full list of all side effects reported with Noradrenaline solution for Infusion, see section 4 of the package leaflet available on the MHRA website.

**Why was Noradrenaline solution for Infusion approved?**
The use of Noradrenaline solution for Infusion in an emergency to increase blood pressure to normal levels is well-established in medical practice and documented in the scientific literature. No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Noradrenaline solution for Infusion outweigh the risks and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Noradrenaline solution for Infusion?**
A risk management plan (RMP) has been developed to ensure that Noradrenaline solution for Infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Noradrenaline solution for Infusion including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Noradrenaline solution for Infusion**
The Republic of Ireland and the UK agreed to grant a Marketing Authorisation for Noradrenaline solution for Infusion on 10th March 2015. A Marketing Authorisation was granted in the UK on 31st March 2015.

The full PAR for Noradrenaline solution for Infusion follows this summary.

For more information about treatment with Noradrenaline solution for Infusion, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the Member States considered that the application for Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion (PL 40201/0001; UK/H/5669/001/DC) is approvable. The product is a prescription-only medicine (POM) and is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and the Republic of Ireland as Concerned Member State (CMS). The application was made under Article 10a, well-established use, of Directive 2001/83/EC, as amended, claiming to be an application for a product containing an active substance of well-established use.

The medicinal product contains the active substance noradrenaline tartrate. Noradrenaline is a sympathomimetic agent with a preferential effect on alpha and beta1-adrenergic receptors, but with little effect on beta2 receptors. It is stored in granules in sympathetic nerve axons and the adrenal medulla, and acts the major neurotransmitter in postganglionic adrenergic neurones and a neurohormone released with adrenaline into the circulation from the adrenal gland. The pharmacological effects are peripheral vasoconstriction, increased systolic and diastolic blood pressure, reflex slowing of the heart rate and reduction in blood flow in the kidneys, liver, skin and skeletal muscle.

No new non-clinical or clinical studies were necessary for this application, which is acceptable given that this is a bibliographic application for a product containing an active substance of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Both Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 210 – 10th March 2015). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 40201/0001) for this product on 31st March 2015.
II QUALITY ASPECTS

II.1 Introduction
The product is a concentrate for solution for infusion. Each ml contains 2 mg noradrenaline tartrate equivalent to 1 mg noradrenaline base.
One ampoule of 2 ml contains 4 mg noradrenaline tartrate equivalent to 2 mg noradrenaline base.
One ampoule of 4 ml contains 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base.
One vial of 20 ml contains 40 mg noradrenaline tartrate equivalent to 20 mg noradrenaline base.

Other ingredients consist of the pharmaceutical excipients sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injection. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin.

The finished product is packed into 2 ml and 4 ml colourless glass ampoules (5 ampoules in a pack) and 20 ml vials (5 vials in a pack) containing sterile concentrate for solution for infusion.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substance
INN: Noradrenaline tartrate
Chemical name: \((1\text{R})-2\text{-amino-1-(3,4-dihydroxyphenyl)}\text{) ethanol hydrogen (2R,3R)-2,3-dihydroxybutanedioate monohydrate}\)

Structural formula:

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\[\text{Molecular formula: } C_{8}H_{11}NO_{3} \cdot C_{4}H_{6}O_{6} \cdot H_{2}O \]
Molecular mass: 337.3 g/mol
Appearance: White or almost white, crystalline powder.
Solubility: Noradrenaline tartrate is freely soluble in water and slightly soluble in alcohol.
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Noradrenaline tartrate is the subject of an active substance master file (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.
An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been provided, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, concentrate for solution for infusion for parenteral dosing.

A satisfactory account of the pharmaceutical development has been provided.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated on a pilot scale and has shown satisfactory results. The Marketing Authorisation Holder has committed to perform process validation on future full scale production batches.

Finished Product Specification
The finished product specification proposed is acceptable. The test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 15 months for unopened vials and ampoules with storage conditions ‘Do not store above 25°C’ and ‘Store in the original package to protect from light’.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when diluted to 4 mg/litre and 40 mg/litre noradrenaline base in sodium chloride 9 mg/ml (0.9%) solution or glucose 5% solution. However, 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 and would normally not be longer than 24 hours at 2 to 8°C.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical point of view.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of noradrenaline tartrate are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetic and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since this product is intended for substitution of an originator product, 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
There are no objections to the approval of this application from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
This application has been made under Article 10a, well established use application, of Directive 2001/83/EC, as amended. As per the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), “bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.”

No new clinical data have been submitted and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of noradrenaline tartrate.

IV.2 Pharmacokinetics
In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none are required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none are required for applications of this type.
IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The Marketing Authorisation Holder (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 (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Summary table of risk minimisation measures:

<table>
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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe left ventricular dysfunction associated with acute hypotension</td>
<td><strong>SmPC 4.4 Special warnings and precaution for use</strong>&lt;br&gt;Noradrenaline should be used only in conjunction with appropriate blood volume replacement. When infusing noradrenaline, the blood pressure and rate of flow should be checked frequently to avoid hypotension.&lt;br&gt;Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when the infusion is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (e.g., decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischemic injury.</td>
<td><strong>SmPC 4.8 Unconsiderable effects</strong>&lt;br&gt;<em>Cardiac disorders</em>&lt;br&gt;Arrhythmias (when used in conjunction with cardiac sensitizing agents), bradycardia&lt;br&gt;<em>Vascular disorders</em>&lt;br&gt;Hypertension, peripheral ischaemia including gangrene of the extremities, plasma volume</td>
</tr>
<tr>
<td>Condition</td>
<td>SmPC 4.4 Special warnings and precaution for use</td>
<td>N/A</td>
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<td>------------------------------------------</td>
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</tbody>
</table>
| Coronary vascular thrombosis, mesenteric or peripheral because. | - Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline may increase the ischemia and extend the area of infarction.  
  **SmPC 4.8 Uniderable effects**  
  *Cardiac disorders*  
  Arrhythmias (when used in conjunction with cardiac sensitizing agents), bradycardia  
  *Vascular disorders*  
  Hypertension, peripheral ischaemia including gangrene of the extremities, plasma volume depletion with prolonged use | N/A |
| Heart rhythm disorders                   | - Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline may increase the ischemia and extend the area of infarction.  
  **SmPC 4.8 Uniderable effects**  
  *Cardiac disorders*  
  Arrhythmias (when used in conjunction with cardiac sensitizing agents), bradycardia  
  *Vascular disorders*  
  Hypertension, peripheral ischaemia including gangrene of the extremities, plasma volume depletion with prolonged use | N/A |
<p>| Hyperthyroidism or diabetes mellitus     | - Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline may increase the ischemia and extend the area of infarction. Similar caution should be observed in patients with hypotension following myocardial infarction, in patients with Prinzmetal's variant angina and in patients with diabetes, hypertension or hyperthyroidism. | N/A |
| Plasma volume depletion with prolonged   | - Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline may increase the ischemia and extend the area of infarction. | N/A |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
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<tr>
<td>administration</td>
<td>If noradrenaline is continuously administered to maintain blood pressure in the absence of blood volume replacement, the following may occur: severe peripheral and visceral vasoconstriction decreased renal perfusion and urine output, poor system blood flow despite “normal” blood pressure, tissue hypoxia and lactic acidosis. Blood volume replacement can be administered before and/or concurrently with this agent; however, if whole blood or blood plasma is indicated to increase blood volume, administer separately (e.g. if given simultaneously, use Y-tubing and individual containers).</td>
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</tbody>
</table>
| Peripheral ischaemia including gangrene of the extremities | **SmPC 4.4 Special warnings and precaution for use**  
Extravasation of the solution may cause local tissue necrosis. The infusion site should be checked frequently. If extravasation occurs, the infusion should be stopped and the area should be infiltrated with phentolamine without delay.                                                                                                      | N/A                                                                                           |
| Impaired placental perfusion and foetal bradycardia:  
- Severe, prolonged hypertension and possible arrhythmias when used concomitantly with cardiac sensitising agents. | **SmPC 4.6 Pregnancy and lactation**  
Noradrenaline may impair placental perfusion and induce foetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to foetal asphyxia in late pregnancy. These possible risks to the foetus should therefore be weighed against the potential benefit to the mother. | None                                                                                         |
| Medication error/overdose                    | **SmPC 4.9 Overdose**  
Overdose may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. These may be accompanied by violent headache, photophobia, retrosternal pain, pallor, intense sweating and vomiting. In the event of overdose, treatment should be withdrawn and appropriate corrective treatment initiated. | None                                                                                         |
| Use in lactation                             | **SmPC 4.6 Pregnancy and lactation**  
No information is available on the use of noradrenaline in lactation. | None                                                                                         |
The RMP for Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion adequately documents the safety concerns for the product. Routine pharmacovigilance and risk minimisation are sufficient for the safety concerns in the RMP, given the established benefit-risk profile of noradrenaline tartrate and the information available to inform decisions on the balance of benefits and risks when it is used in clinical practice.

**IV.7 Discussion on the clinical aspects**

No new clinical data were submitted and none are required for applications of this type.

The published literature supports the efficacy of this product in the proposed indication. The efficacy of noradrenaline tartrate is well-known. The presented evidence for well-established use of the active substance is sufficient.

The safety profile of noradrenaline tartrate is well-known. The literature review identified no new or unexpected safety issues or concerns.

The grant of a Marketing Authorisation is recommended for this application.

**V User consultation**

The package leaflet 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 patient information leaflet (PIL) was English.

The package leaflet 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**

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with noradrenaline tartrate is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for Infusion is presented below:

1. NAME OF THE MEDICINAL PRODUCT

Noradrenaline (Norepinephrine) 1 mg/ml concentrate for solution for infusion. Noradrenaline (as noradrenaline tartrate).

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2.0 mg of Noradrenaline tartrate equivalent to 1 mg noradrenaline base.

3. LIST OF EXCIPIENTS

The other ingredients are sodium chloride, hydrochloric acid, sodium hydroxide, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Ampoules of 2 and 4 ml containing sterile solution
Vials of 20 ml containing sterile solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.
Dilute before use
Read the package leaflet before use.

After dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when diluted to 4 mg/litre and 40 mg/litre noradrenaline base in sodium chloride 9 mg/ml (0.9%) solution or glucose 5% solution. However, 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 and would normally not be longer than 24 hours at 2 to 8°C.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

This medicinal product contains sodium

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Store in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF NECESSARY

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

**NOVOCAT FARMA, S.A**  
Avenida de las Flores 29. L7  
08191. Rubí. Barcelona. Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Intravenous route.  
For single use.  
Read carefully the package leaflet before use

16. INFORMATION IN BRAILLE

NORADRENALINE (Norepinephrine) 1 mg/ml CONCENTRATE FOR SOLUTION FOR INFUSION
Table of content of the PAR update for MRP and DCP
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<th>Product information affected</th>
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<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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