Public Assessment Report

Decentralised Procedure

Noradrenaline (norepinephrine) 0.08 mg/ml, solution for infusion

Noradrenaline (norepinephrine) 0.25 mg/ml, solution for infusion

(Noradrenaline tartrate)

Procedure No: UK/H/5538/001-2/DC

UK Licence No: PL 14434/0028-0029

LABORATOIRE AGUETTANT
LAY SUMMARY

Noradrenaline (norepinephrine) 0.08 mg/ml solution for infusion
Noradrenaline (norepinephrine) 0.25 mg/ml solution for infusion
(noradrenaline tartrate, solution for infusion, 0.08 mg/ml and 0.25 mg/ml)

This is a summary of the Public Assessment Report (PAR) for Noradrenaline (norepinephrine) 0.08 mg/ml solution for infusion (PL 14434/0029; UK/H/5538/002/DC) and Noradrenaline (norepinephrine) 0.25 mg/ml solution for infusion (PL 14434/0028; UK/H/5538/001/DC). It explains how Noradrenaline (norepinephrine) 0.08 mg/ml and 0.25 mg/ml solution for infusion were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Noradrenaline (norepinephrine) 0.08 mg/ml and 0.25 mg/ml solution for infusion.

The products will be collectively referred to as Noradrenaline solution for infusion throughout the remainder of this public assessment report.

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 10 years, with recognised efficacy and an acceptable level of safety.

Noradrenaline solution for infusion is used in adults weighing over 50 kg for the on-going treatment of hypotensive (low blood pressure) emergencies with escalating noradrenaline dose requirements. It restores the blood pressure to normal in emergency situations when blood pressure has dropped dangerously low.

How does Noradrenaline solution for infusion work?
The active ingredient, noradrenaline tartrate (also called norepinephrine), belongs to a group of medicines called adrenergic and dopaminergic agents.

Noradrenaline is a hormone that is produced naturally by the body. Noradrenaline produces wide ranging effects on many areas of the body and is often referred to as a 'fight or flight' chemical, as it is responsible for the body's reaction to stressful situations.

Noradrenaline works by stimulating receptors called adrenoceptors, which are found all over the body. When injected into a vein, noradrenaline acts mostly on a type of adrenoceptor known as an alpha receptor. These are found on muscle inside the walls of peripheral blood vessels. Stimulating these alpha receptors causes the muscle to contract, which makes the blood vessels constrict and narrow. By narrowing the blood vessels in the extremities, noradrenaline redirects blood to essential organs such as the heart and brain. It also produces greater resistance for the heart to beat against, and this increases blood pressure.

How is Noradrenaline solution for infusion used?
The pharmaceutical form of this medicine is a solution for infusion. The route of administration of this medicine is into the patient’s vein. It is administered via peripheral cannula and/or peripheral vein.

Noradrenaline solution for infusion will be given to the patient in a hospital by a doctor or nurse.
**Noradrenaline solution for infusion should not be diluted before use:** it is a ready to use solution in a 50 ml vial. Noradrenaline solution for infusion will be administered by intravenous infusion (into a vein) and only via a central venous catheter. A syringe driver pump will be used.

The dose of Noradrenaline solution for infusion will depend on the patient’s condition. The patient’s doctor will know the best dose to use.

Noradrenaline solution for infusion should not be used for initiating vasopressor treatment. It may be considered for use in patients already established on noradrenaline whose dose requirements are clinically confirmed to be escalating, such that Noradrenaline solution for infusion may be commenced at a flow rate of 2 ml/h.

The dose will be adjusted using the syringe driver pump according to the response to treatment, with the aim to establish a normal blood pressure.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Noradrenaline solution for infusion have been shown in studies?**
As noradrenaline tartrate is a well-known substance, and its use in adults weighing over 50 kg for the on-going treatment of hypotensive emergencies with escalating noradrenaline dose requirements 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 MHRA decided that the benefits of Noradrenaline solution for infusion are greater than their risk and recommended that they can be approved for use.

**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 Summaries of Product Characteristics and the package leaflets 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
For Noradrenaline (norepinephrine) 0.08 mg/ml solution for infusion:
Germany, Ireland and the UK agreed to grant a Marketing Authorisation for Noradrenaline
(norepinephrine) 0.08 mg/ml solution for infusion on 04 June 2015. A Marketing Authorisation was
granted in the UK on 30 June 2015.

For Noradrenaline (norepinephrine) 0.25 mg/ml solution for infusion:
Austria, Germany, France, Ireland, Italy, Netherlands Poland, Romania and the UK agreed to grant a
Marketing Authorisation for Noradrenaline (norepinephrine) 0.25 mg/ml solution for infusion on 04
June 2015. A Marketing Authorisation was granted in the UK on 30 June 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 August 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Noradrenaline solution for infusion (PL 14434/0028-0029; UK/H/5538/001-002/DC) could be approved. Noradrenaline solution for infusion is a prescription-only medicine (POM) and is indicated in adults weighing over 50kg for the on-going treatment of hypotensive emergencies with escalating noradrenaline dose requirements.

These applications were submitted under Article 10a of Directive 2001/83/EC, as amended, claiming to be applications for a product containing an active substance of well-established use. The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and:

- Germany and Ireland as Concerned Member States (CMS) for Noradrenaline (norepinephrine) 0.08 mg/ml solution for infusion (PL 14434/0029; UK/H/5538/002/DC).
- Austria, Germany, France, Italy, Poland and Portugal as Concerned Member States (CMS) for Noradrenaline (norepinephrine) 0.25 mg/ml solution for infusion (PL 14434/0028; UK/H/5538/001/DC).

The applicant (LABORATOIRE AGUETTANT), currently markets Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for solution for infusion which requires dilution prior to intravenous infusion. The current approved medicinal product is presented as 4 ml and 8 ml ampoules containing 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base, and 16 mg noradrenaline tartrate equivalent to 8 mg noradrenaline base, respectively. The rationale of the proposed product formulation development was to produce two ready-to-use solutions for intravenous infusion of noradrenaline tartrate (0.08 mg/ml and 0.25 mg/ml) that did not require dilution before administration.

Available concentrations of noradrenaline in clinical use are historically in multiples of 40 mcg/ml. The proposed 0.25 mg/ml strength of this product is therefore a much stronger concentration of noradrenaline than those currently available. In order to minimise the risk of medication error related to the launch of Noradrenaline (norepinephrine) 0.25 mg/ml solution for infusion, the applicant proposes to issue two direct healthcare professional communication (DHPC) letters in addition to the information included in the SmPC and product labelling:

- One direct health care professional communication (DHPC) letter related to Noradrenaline 0.25mg/ml, to be communicated to health care professionals in member states where only Noradrenaline 0.25mg/ml will be launched. This document presents the medicinal product, the vial size, the ‘ready to use’ characteristics, and focuses on the risks of medication error related to the use of Noradrenaline 0.25mg/ml.
- One DHPC letter related to both Noradrenaline 0.25mg/ml and Noradrenaline 0.08mg/ml, to be communicated to health care professionals in member states where both 0.25mg/ml and 0.08mg/ml products will be launched. This document presents the two medicinal products, the vial sizes, the ‘ready to use’ characteristics, focuses on the risks of medication error related to use of Noradrenaline 0.25mg/ml, and also provide comparison between the 0.08mg/ml vials and the 0.25mg/ml vials in order to minimise the risk of confusion between these two presentations.

Furthermore, at the time of validation of the DHPC letters with national authorities, additional information related to noradrenaline products already available locally and highlighting specific risk for medication error will be included, in order to adjust these DHPC letters according to the local situation. The targeted healthcare professionals are intensive care anaesthetists and hospital pharmacists.

Information about the DHPC letters has been incorporated into the Risk Management Plan (also refer to section I.V.6; ‘Risk Management Plan (RMP); Summary table of Risk Minimisation Measures’ on page 14 of this report).
Noradrenaline provides a strong stimulation of alpha receptors in blood vessels at which these are counter-extracted. Noradrenaline also has effect on beta-1 receptors in the heart leading to a positive inotropic and initially positive chronotropic effect. The increase in blood pressure may cause a reflex reduction in heart rate. Vasoconstriction may lead to decreased blood flow in the kidneys, liver, skin and smooth muscle. Local constriction of the vessels may cause hemostasis and/or necrosis. The pressor effect disappears 1-2 minutes after termination of infusion. Development of tolerance to the effects of noradrenaline may occur.

Bibliographic data on noradrenaline have been submitted to support these applications. No new non-clinical or clinical studies were conducted for these applications, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place 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.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 04 June 2015. After a subsequent national phase, licences were granted in the UK on 30 June 2015.
II QUALITY ASPECTS

II.1 Introduction
Each ml of solution contains 0.16 mg or 0.5 mg noradrenaline tartrate, equivalent to 0.08 mg or 0.25 mg noradrenaline base respectively.

Each 50 ml vial contains 8 mg or 25 mg noradrenaline tartrate equivalent to 4 mg or 12.5 mg noradrenaline base respectively.

Other ingredients consist of the pharmaceutical excipients sodium chloride, disodium edetate dehydrate, hydrochloric acid or sodium hydroxide (pH adjustment) and water for injections. Both strengths of the finished product (0.08 mg/ml and 0.25 mg/ml) are packed into clear glass vials closed with a type I bromobutyl stopper and an aluminium cap containing 50 ml of solution for infusion in pack size of 1, 10, and 25 vials. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

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

Structural formula:

![Structural formula image]

Molecular formula: C_{12}H_{17}NO_9H_2O
Molecular mass: 337.3
Appearance: A white to almost white crystalline powder.
Solubility: Freely soluble in water, slightly soluble in ethanol (96%).

Noradrenaline tartrate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, noradrenaline tartrate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate two, safe, efficacious, ready-to-use solutions for intravenous infusion of noradrenaline tartrate (0.08 mg/ml and 0.25 mg/ml) that did not require dilution before administration, were sulphites-free and are stable over time. A satisfactory account of the pharmaceutical development has been provided.
All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**
The 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 at commercial-scale batch size and shown satisfactory results.

**Finished Product Specification**
The finished product specification proposed is acceptable. 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:

Noradrenaline (norepinephrine) 0.08 mg/ml, solution for infusion:
- 18 months for the unopened vial with the storage conditions “Do not store above 25° C. Store the vial in the outer carton to protect from light.”

Noradrenaline (norepinephrine) 0.25 mg/ml, solution for infusion:
- 12 months for the unopened vial with the storage conditions “Do not store above 25° C. Store the vial in the outer carton to protect from light.”

After first opening, the product should be used immediately. For single use only. Discard any unused contents.

**This medicinal product must not be mixed with other medicinal products.**

Noradrenaline solution for infusion is already diluted and ready to use. It should be used without prior dilution. It should be used with a suitable syringe driver pump capable of accurately and consistently delivering the minimum specified volume at a strictly controlled rate of infusion in line with the dose titration instructions specified in Section 4.2 of the SmPC. This medicine should not be used if the solution is darker than slightly yellow or pink in colour or if it contains a precipitate.

The sterile solution should not be used if it is not clear and contains particles, or if the tamper evident sealed vial is not intact.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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 these applications from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of noradrenaline are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics 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.

Impurities
The active substance and all excipients are of pharmacopoeial grade and there are no issues in respect of their inclusion in the proposed product. The proposed limits for all related substances and residual solvents within the drug substance and/or drug product comply with the limits as outlined by ICHQ3A(R2), ICH Q3B(R2) and ICH Q3(R5) and are therefore considered to be acceptable from a toxicological point of view.

III.5 Ecotoxicity/environmental risk assessment (ERA)
The applicant has not conducted an in depth environmental risk assessment in accordance with regulatory guidelines (EMEA/CHMP/SWP/4447/00). The non-clinical assessor concurs that the risks to the environment are not expected to increase as the proposed product will be used to substitute other currently marketed forms of noradrenaline.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that these are bibliographic applications for a product containing an active ingredient of well-established use.

There are no objections to the approval of these applications from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
No new clinical pharmacology data, efficacy data or safety 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.

The applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new pharmacokinetic data were submitted and none were required for an application of this type.
IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type. The clinical efficacy of noradrenaline is well-established. Efficacy is adequately reviewed in the clinical overview.

IV.5 Clinical safety
No new safety data were submitted and none were required for these bibliographic applications. Safety is adequately reviewed in the clinical overview. The safety profile of noradrenaline is well-known.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 solution for infusion.

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

Summary table of safety concerns:

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<tr>
<th>Important identified risks</th>
<th>Hypersensitivity</th>
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<td></td>
<td>Extravasation</td>
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<td></td>
<td>Hypertension</td>
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<td></td>
<td>Reflex bradycardia</td>
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<td>Arrhythmia</td>
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<td></td>
<td>Acute glaucoma in patients anatomically predisposed</td>
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<tr>
<td>Drug interaction increasing the risk of hypertension or arrhythmia</td>
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</table>

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<tr>
<th>Important potential risks</th>
<th>Medication error / risk of medication error</th>
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<tr>
<td></td>
<td>Adverse foetal events in pregnancy</td>
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<table>
<thead>
<tr>
<th>Missing information</th>
<th>Use in children and adolescents</th>
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<tbody>
<tr>
<td></td>
<td>Use during breastfeeding</td>
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<tr>
<td></td>
<td>Use in patients with renal and hepatic impairment</td>
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</tbody>
</table>
Summary table of Risk Minimisation Measures:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identified Risk</strong></td>
<td>Proposed text in SmPC:</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Section 4.3: Contraindications in case of hypersensitivity to noradrenaline or to any of the excipients listed in section 6.1</td>
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<tr>
<td></td>
<td>Section 4.3: Contraindication via peripheral cannula and/or peripheral vein.</td>
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<td></td>
<td>Section 4.4: - As noradrenaline solution should be infused only via a central venous catheter, the risk of extravasation and subsequent tissue necrosis is very limited. The infusion site should be checked frequently. However, if extravasation occurs, the infusion should be stopped immediately and the area should be infiltrated with phenolamine without delay</td>
<td></td>
</tr>
<tr>
<td><strong>Identified Risk</strong></td>
<td>Proposed text in SmPC:</td>
<td>None proposed</td>
</tr>
<tr>
<td>Extravasation</td>
<td>Section 4.2: Noradrenaline should only be administered as an intravenous infusion via a central venous catheter to minimize the risk of extravasation and subsequent tissue necrosis.</td>
<td></td>
</tr>
<tr>
<td><strong>Identified Risk</strong></td>
<td>Proposed text in SmPC:</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Section 4.8: Vascular system: arterial hypertension and tissue hypoxia; ischemic injury due to potent vasoconstrictor action may result in coldness and paleness of the members and the face</td>
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<tr>
<td>Reflex bradycardia</td>
<td>Proposed text in SmPC:</td>
<td>None proposed</td>
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<tr>
<td></td>
<td>Section 4.8: bradycardia (probably as a reflex result of blood pressure rising)</td>
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<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td><strong>Identified Risk</strong>&lt;br&gt;Arhythmia</td>
<td>Proposed text in SmPC:&lt;br&gt;Section 4.4: In general, cautious evaluation is recommended in the following cases of hypotension and hypoperfusion, in which a reduction in the dose of noradrenaline may be required:&lt;br&gt;- Major left ventricular dysfunction associated with acute hypotension. Supportive therapy should be initiated simultaneously with diagnostic evaluation. Noradrenaline should be reserved for patients with cardiogenic shock and refractory hypotension, in particular those without elevated systemic vascular resistance.&lt;br&gt;- Hypotensive patients diagnosed with coronary, mesenteric or peripheral vascular thrombosis; myocardial infarction or Prinzmetal’s variant angina. Particular caution should be observed as noradrenaline may increase the associated ischaemia and extend the area of infarction.&lt;br&gt;- Occurrence of heart rhythm disorders during noradrenaline therapy.&lt;br&gt;Section 4.8: arrhythmia</td>
<td>None proposed</td>
</tr>
<tr>
<td><strong>Identified Risk</strong>&lt;br&gt;Acute glaucoma in patients anatomically pre-disposed</td>
<td>Proposed text in SmPC:&lt;br&gt;Section 4.8: acute glaucoma; very frequent in patients anatomically predisposed with the closing of the iridocorneal angle</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td>--------------------------------------</td>
</tr>
<tr>
<td><strong>Identified Risk</strong></td>
<td>Proposed text in SmPC: Section 4.5: Inadvisable combinations:</td>
<td>None proposed</td>
</tr>
<tr>
<td>Drug interaction increasing the risk of hypertension or arrhythmia</td>
<td>+ Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability).</td>
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<td></td>
<td>+ Imipramine antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).</td>
<td></td>
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<tr>
<td></td>
<td>+ Serotonergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).</td>
<td></td>
</tr>
<tr>
<td><strong>Potential Risk</strong></td>
<td>Labelling</td>
<td></td>
</tr>
<tr>
<td>Medication error / risk of medication error</td>
<td>Item under dose monitoring - Laboratoire Aguetant already has noradrenaline products in its portfolio and the risk of medication error is already closely monitored. The current risk of medication error is very low, corresponding to residual risk (see Part II – Module SVL.4.4). Any evolution of this current risk would so be early detected. An emergent safety signal related to medication error would be detected and managed without delay.</td>
<td>Noradrenaline 0.08 mg/mL: none. Noradrenaline 0.25 mg/mL: DHPC letters to be sent to intensive care anaesthetists and hospital pharmacists. See annex 10 for details concerning this proposed additional risk minimisation measure and annex 11 for the proposed templates of DHPC letters.</td>
</tr>
<tr>
<td><strong>Potential Risk</strong></td>
<td>Proposed text in SmPC: Section 4.6: Because of its indications, noradrenaline may be administered if necessary during pregnancy. However, pharmacodynamics properties of the substance have to be considered. 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.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<tr>
<td>--------------------------------------------</td>
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</tr>
<tr>
<td>Interaction</td>
<td>Proposed text in SmPC Section 4.5: Inadvisable combinations: Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability).</td>
<td>None proposed</td>
</tr>
<tr>
<td>Halogenated inhalational anaesthetics</td>
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<tr>
<td>Interaction</td>
<td>Proposed text in SmPC Section 4.5: Inadvisable combinations: Imipramine antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).</td>
<td>None proposed</td>
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<tr>
<td>Imipramine antidepressants</td>
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<td></td>
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<tr>
<td>Interaction</td>
<td>Proposed text in SmPC Section 4.5: Inadvisable combinations: Serotoninergic-adrnergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).</td>
<td>None proposed</td>
</tr>
<tr>
<td>Serotoninergic-adrenergic antidepressants</td>
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<tr>
<td>Interaction</td>
<td>Proposed text in SmPC Section 4.5: Combinations requiring precautions for use: Non-selective MAO inhibitors: increase in the pressor action of the sympathomimetic which is usually moderate. Should only be used under close medical supervision.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Non-selective MAO Inhibitors</td>
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<tr>
<td>Interaction</td>
<td>Proposed text in SmPC Section 4.5: Combinations requiring precautions for use: Selective MAO-A inhibitors, Linezolid and Methylene Blue: by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. Should only be used under close medical supervision.</td>
<td>None proposed</td>
</tr>
<tr>
<td>Selective MAO-A Inhibitors, Linezolid and Methylene Blue</td>
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</tbody>
</table>

Templates for the DHCP letters are included in the RMP; the final content and format and methods of distribution will need to be agreed nationally with CMS’s prior to the marketing of the product.

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

The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

The bibliographic data submitted for these applications does support the claim of well-established use for the sought indication for the on-going treatment of hypotensive emergencies with escalating
noradrenaline dose requirements in adults weighing over 50kg.

The grant of marketing authorisations is recommended for these applications.

V  **User consultation**
The package leaflets have 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 PILs was English.

The results show that the package leaflets meet 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 safety concerns have been identified. Extensive clinical experience with noradrenaline is considered to have demonstrated the therapeutic value of the compound. The benefit-risk 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 solution for infusion is presented below: