Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity Extravasation Hypertension Reflex bradycardia Arrhythmia Acute glaucoma in patients anatomically pre-disposed Drug interaction increasing the risk of hypertension or arrhythmia
Important potential risks	Medication error / risk of medication error Adverse foetal events in pregnancy
Missing information	Use in children and adolescents Use during breastfeeding Use in patients with renal and hepatic impairment

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Identified Risk Hypersensitivity	Proposed text in SmPC: Section 4.3: Contraindications in case of hypersensitivity to noradrenaline or to any of the excipients listed in section 6.1	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risk Extravasation	Proposed text in SmPC: 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. Section 4.3: Contraindication: administration via peripheral cannula and/or peripheral vein. 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 phentolamine without delay	None proposed
Identified Risk Hypertension	Proposed text in SmPC: 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	None proposed
Identified Risk Reflex bradycardia	Proposed text in SmPC: Section 4.8: bradycardia (probably as a reflex result of blood pressure rising)	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risk Arrhythmia	Proposed text in SmPC: 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: - 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. - 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. - Occurrence of heart rhythm disorders during noradrenaline therapy. Section 4.8: arrhythmia	None proposed
Identified Risk Acute glaucoma in patients anatomically pre-disposed	Proposed text in SmPC: Section 4.8: acute glaucoma; very frequent in patients anatomically predisposed with the closing of the iridocorn angle	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified Risk Drug interaction increasing the risk of hypertension or arrhythmia	Proposed text in SmPC: Section 4.5: Inadvisable combinations + Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability). + Imipramine antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers). + Serotoninergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).	None proposed
Potential Risk Medication error / risk of medication error	Labelling Item under close monitoring - Laboratoire Aguettant 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 SVI.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.	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.
Potential Risk Adverse foetal events in pregnancy	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.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Interaction Halogenated inhalational anaesthetics	Proposed text in SmPC Section 4.5: Inadvisable combinations: Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability).	None proposed
Interaction Imipramine antidepressants	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).	None proposed
Interaction Serotoninergic-adrenergic antidepressants	Proposed text in SmPC Section 4.5: Inadvisable combinations: Serotoninergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).	None proposed
Interaction Non-selective MAO Inhibitors	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	None proposed
Interaction Selective MAO-A Inhibitors, Linezolid and Methylene Blue	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.	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology (Maximum 150 words per indication)

Hypotension / Collapse

Noradrenaline is indicated for the emergency restoration of blood pressure in cases of suddenly decreased blood pressure (acute hypotension). A collapse of blood pressure (cardiovascular collapse) is observed in situations of circulatory medical emergency named "shock". Shock may be due to:

- a decrease in circulating blood volume (hypovolemic shock, haemorrhagic shock),
- a widening of blood vessels (vasodilation). This may happen in situation of serious allergic reaction (anaphylactic shock) or severe infection (septic shock),
- a decrease of the volume of blood being pumped by the heart (primary decrease in cardiac output),
- a combination of these situations.

VI.2.2 Summary of treatment benefits

Noradrenaline is a well-established use product and its benefits are widely described in the scientific literature. In current practice, noradrenaline is used in emergency to increase blood pressure to normal levels. The immediate rise in blood pressure which results from its administration is 1.5-fold more intense than the rise induced by adrenaline.

VI.2.3 Unknowns relating to treatment benefits (1 short paragraph per indication of 50 words maximum)

No extended information is available regarding the use of noradrenaline in paediatric population, in patients with hepatic or renal failure and during lactation.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Allergy (Hypersensitivity)	Noradrenaline may cause allergic reaction	Noradrenaline must not be administered in patients with allergy to noradrenaline or to other ingredients of this medicine
Accidental administration of the medicine outside the vein (Extravasation)	Accidental administration of the medicine outside the vein (Extravasation) may cause a death of cells (necrosis) in the tissue surrounding the vein used for the injection	Noradrenaline solution should be infused only via a central venous catheter

Risk	What is known	Preventability
High blood pressure (Hypertension)	Administration of Noradrenaline may lead to high blood pressure (hypertension)	Blood pressure should be continuously checked during administration of Noradrenaline, and dose administered should be adjusted accordingly
Slow hear rate (Reflex bradycardia)	Administration of Noradrenaline may decrease heart rate	Heart rate should be continuously checked during administration of Noradrenaline, and dose administered should be adjusted accordingly
Heart rhythm disorders (Arrhythmia)	Administration of Noradrenaline may cause heart rhythm disorders	Noradrenaline should be used with care in case of heart condition. Heart rate should be continuously checked during administration of Noradrenaline
Acute glaucoma (Acute glaucoma)	Administration of Noradrenaline may cause acute glaucoma	Noradrenaline should be used with care in patients with specific risk factors (anatomically pre-disposed patients)
Combination of drugs that may lead to high blood pressure or heart rhythm disorders (Drug interaction increasing the risk of hypertension or arrhythmia)	Concomitant use of some specific medications such as anaesthetic gas and antidepressants may lead to high blood pressure or heart rhythm disorders	Concomitant use of these medications is not recommended

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Medication error / risk of medication error	Despite measures taken to prevent the risk of medication error, a potential risk remains.
Harm of unborn babies during pregnancy (Adverse foetal events in pregnancy)	Receiving Noradrenaline during pregnancy may harm the unborn babies.

Missing information

Risk	What is known
Use in children and adolescents	The efficacy and safety in children and adolescents have not been established.
Use during breastfeeding	No information is available on the use of noradrenaline in lactation.
Use in Patients with kidney (renal) and liver (hepatic) impairment	There is no experience of treatment in patients with kidney (rena)l and liver (hepatic) impairment.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). There is additional risk minimisation measure for the following risk:

Medication error / risk of medication error – Direct Healthcare Professional Communication (DHPC)
Objective and rationale: Information of concerned healthcare professionals (intensive care anaesthetists and hospital pharmacists) about the risks of medication error related to the launch of Noradrenaline 0.25 mg/mL via a DHPC letter.
Summary description of additional risk minimisation measure: In order to minimise the risk of medication error related to launch of Noradrenaline 0.25 ml/mL, the applicant proposes to issue two DHPC letters: - One direct healthcare professional communication (DHPC) letter related to Noradrenaline 0.25 mg/mL, to be communicated to health care professionals in member states where only Noradrenaline 0.25 mg/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 0.25 mg/mL. - One DHPC letter related to both Noradrenaline 0.25 mg/mL and Noradrenaline 0.08 mg/mL, to be communicated to healthcare professionals in member states where both 0.25 mg/mL and 0.08 mg/mL products will be launched. This document presents the 2 medicinal products, the vial sizes, the "ready to use" characteristics, focuses on the risks of medication error related to the use of Noradrenaline 0.25 mg/mL, and also provide comparison between the 0.08 mg/mL vials and 0.25 mg/mL vials in order to minimize the risk of confusion between these two presentations.

VI.2.6 Planned post authorisation development plan

None.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time: not applicable.