Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Noradrenaline (Norepinephrine) 0.08 mg/mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for infusion contains 0.16 mg noradrenaline tartrate, equivalent to 0.08 mg noradrenaline base.
Each 50 mL vial contains 8 mg noradrenaline tartrate, equivalent to 4 mg noradrenaline base.

Excipient with known effect:
Each mL of solution for infusion contains 3.5 mg equivalent to 0.2 mmol of sodium.
Each 50 mL vial contains approximately 177.3 mg equivalent to 7.7 mmol of sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless or slightly yellow solution
pH = 3.2 – 3.8
Osmolality: 260 - 320 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Noradrenaline (Norepinephrine) is indicated in adults weighing over 50kg for the treatment of hypotensive emergencies.

4.2 Posology and method of administration

For intravenous use only.
Noradrenaline (Norepinephrine)

Noradrenaline (Norepinephrine) should only be administered as an intravenous infusion via a central venous catheter to minimize the risk of extravasation and subsequent tissue necrosis. Noradrenaline (Norepinephrine) should be infused at a controlled rate using an infusion pump or a syringe pump.
Noradrenaline (Norepinephrine) should not be diluted before use: it is supplied ready to use. It should not be mixed with other medicines.

Blood pressure control:
Blood pressure should be monitored carefully for the duration of therapy, and preferably controlled by arterial blood pressure monitoring. The patient should be monitored carefully for the duration of noradrenaline (norepinephrine) therapy.

Posology
Initial dose:
The initial dose of noradrenaline base is usually between 0.05-0.15 micrograms/kg/min.

Maintenance dose range:
The recommended maintenance range of noradrenaline base is between 0.05-1.5 micrograms/kg/min.

Titration of dose:
Noradrenaline (Norepinephrine) should be used with a suitable infusion pump or syringe 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.
Once an infusion of noradrenaline has been established the dose should be titrated in steps of 0.05 -0.1 micrograms/kg/min of noradrenaline base according to the pressor effect observed. There is great individual variation in the dose required to attain

and maintain normotension. The aim should be to establish a low normal systolic blood pressure (100 - 120 mm Hg) or to achieve an adequate mean arterial blood pressure (greater than 65 mm Hg – depending on the patient's condition).
Manual bolus for priming when initiating an infusion is not recommended.
Caution is required during infusion relay to avoid hemodynamic instability. Continuous noradrenaline infusion through a double pump system and an extension set reducing dead-space volume should be encouraged.

Noradrenaline (Norepinephrine) 0.08 mg/ mL solution for infusion			
Patient's Weight (kg)	Posology (µg/kg/min) noradrenaline base	Posology (mg/h) noradrenaline base	Infusion rate (mL/h)
50	0.05	0.15	1.9
	0.1	0.3	3.8
	0.25	0.75	9.4
	0.5	1.5	18.8
	1	3	37.5
	1.5	4.5	56.3
60	0.05	0.18	2.3
	0.1	0.36	4.5
	0.25	0.9	11.3
	0.5	1.8	22.5
	1	3.6	45.0
	1.5	5.4	67.5
70	0.05	0.21	2.6
	0.1	0.42	5.3
	0.25	1.05	13.1
	0.5	2.1	26.3
	1	4.2	52.5
	1.5	6.3	78.8
80	0.05	0.24	3.0
	0.1	0.48	6.0
	0.25	1.2	15.0
	0.5	2.4	30.0
	1	4.8	60.0
	1.5	7.2	90.0
90	0.05	0.27	3.4
	0.1	0.54	6.8
	0.25	1.35	16.9
	0.5	2.7	33.8
	1	5.4	67.5
	1.5	8.1	101.3
100	0.05	0.3	3.8
	0.1	0.6	7.5
	0.25	1.5	18.8
	0.5	3	37.5
	1	6	75.0
	1.5	9	112.5

h: hour

Duration of Treatment:
The treatment should be continued until high-dose vasoactive drug support is no longer indicated, at which point, the infusion should be gradually decreased, then switched to an infusion of lower concentration. Abrupt withdrawal can result in acute hypotension.

Elderly patients
See section 4.4 Special warnings and precautions for use.

Paediatric population
Noradrenaline (Norepinephrine) is indicated for adults only.

The efficacy and safety of Noradrenaline (Norepinephrine) in 50 mL ready to use solution for infusion in children and adolescents has not been established.

Patients with renal- and hepatic impairment.
There is no experience of treatment in patients with renal- and hepatic impairment.

4.3 Contraindications

Administration via peripheral cannula and/or peripheral vein.
Hypersensitivity to noradrenaline or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Warning:

Noradrenaline is contraindicated in hypotensive patients in whom circulatory collapse is associated with hypovolaemia except as an emergency measure to maintain supply to the coronary and cerebral arteries until blood volume replacement therapy can be instituted.
Noradrenaline (Norepinephrine) is intended for infusion via a central venous catheter only. As such, 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, monitored closely for improvement and re-assessed for further treatment to reverse the ischemic effect.

Precautions for use:

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.

Caution is advised in patients with hyperthyroidism or diabetes mellitus.

In cases where it is necessary to administer noradrenaline at the same time as total blood or plasma, the latter must be administered in a separate drip.

This medicinal product contains 177.3 mg sodium per vial, equivalent to 8.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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 fibres).
+ Serotoninergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

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.
+ 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Lactation
No information is available on the use of noradrenaline in lactation.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

- *Psychiatric disorders*
Anxiety.
- *Nervous system disorders*
Headache, tremor.
- *Eyes disorders*
Acute glaucoma (very frequent in patients anatomically predisposed with closing of the iridocorneal angle).
- *Cardiac disorders*
Tachycardia, bradycardia (probably as a reflex result of blood pressure rising), arrhythmia, palpitations, increase in the contractility of the cardiac muscle resulting from the ß adrenergic effect on the heart (inotrope and chronotrope), acute cardiac insufficiency, stress cardiomyopathy.
- *Vascular disorders*
Arterial hypertension and tissue hypoxia; ischemic injury due to potent vasoconstrictor action (may result in coldness and paleness of the members limbs and the face), gangrene of the extremities.
- *Respiratory, thoracic and mediastinal disorders*
Respiratory insufficiency or difficulty, dyspnea.
- *Gastrointestinal disorders*
Vomiting.
- *Renal and urinary disorders*
Retention of urine.
- *General disorders and administration site conditions*
Locally: possibility of irritation and necrosis at the injection site.

The continuous administration of vasopressor to maintain blood pressure in the absence of blood volume replacement may cause the following symptoms:

- severe peripheral and visceral vasoconstriction,
- decrease in renal blood flow,
- decrease in urine production,
- hypoxia,
- increase in lactate serum levels.

In case of hypersensitivity or overdose, the following effects may appear more frequently: hypertension, photophobia, retrosternal pain, pharyngeal pain, pallor, intense sweating and vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the event of overdose, the following may be observed: cutaneous vasoconstriction, bed sores, circulatory collapse, and hypertension.
In the event of adverse reactions linked to an excessive dosage, it is recommended to reduce the dosage if possible.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC code: C01CA03
Noradrenaline provides a strong stimulation of alpha receptors in blood vessels at which these are counter-extracted. Noradrenaline also has an 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 min after termination of infusion. Development of tolerance to the effects of noradrenaline may occur.

5.2 Pharmacokinetic properties

Two stereoisomers of noradrenaline exist, the biologically active L-isomer is the one present in Noradrenaline (Norepinephrine).

Absorption:

- Subcutaneous: Poor
- Oral: Noradrenaline is rapidly inactivated in the gastro-intestinal tract following oral administration.
- After intravenous administration, noradrenaline has a plasmatic half-life of about 1 to 2 minutes.

Distribution:

- Noradrenaline is rapidly cleared from plasma by a combination of cellular reuptake and metabolism. It does not readily cross the blood-brain barrier.

Biotransformation:

- Methylation by catechol-o-methyltransferase,
- Deamination by manoamine oxydase (MAO),
- Ultimate metabolites from both is 4- hydroxy-3-methoxymandelic acid,
- Intermediate metabolites include normetanephrine and 3,4- dihydroxymandelic acid.

Elimination:

- Noradrenaline is mainly eliminated as glucuronide or sulphate conjugates of the metabolites in the urine.

5.3 Preclinical safety data

Most of the undesirable effects can be derived from sympathomimetic results from excessive stimulation of the sympathetic nervous system through the various adrenergic receptors.

Noradrenaline may impair placental perfusion and induce fatal fetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to fatal fetal asphyxia in late pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium edetate
Hydrochloric acid or Sodium hydroxide (pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

18 months.
After the first opening, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25° C. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear type II glass vial closed with a type I bromobutyl stopper and an aluminum cap containing 50ml of solution for infusion in pack size of 1, 10, and 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.
Noradrenaline (Norepinephrine) is already diluted and ready to use. It should be used without prior dilution. It should be used with a suitable infusion 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. 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.

7 MARKETING AUTHORISATION HOLDER

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1 Rue Alexander Fleming
69007 LYON
France

8 MARKETING AUTHORISATION NUMBER

PA1968/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 5th February 2016
Date of last renewal: 4th June 2020

10 DATE OF REVISION OF THE TEXT

February 2023