Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 2 mg noradrenaline tartrate equivalent to 1 mg noradrenaline base.

1 ampoule of 2 ml contains 4 mg noradrenaline tartrate equivalent to 2 mg noradrenaline base.

1 ampoule of 4 ml contains 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base.

1 vial of 20 ml contains 40 mg noradrenaline tartrate equivalent to 20 mg noradrenaline base.

When diluted as recommended, each ml contains 80 micrograms noradrenaline tartrate equivalent to 40 micrograms noradrenaline base.

Excipients:
1 ampoule of 2 ml contains 0.29 mmol (or 6.6 mg) sodium.
1 ampoule of 4 ml contains 0.58 mmol (or 13.2 mg) sodium.
1 vial of 20 ml contains 2.90 mmol (or 66.1 mg) sodium
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion
A clear, colourless or yellowish solution
pH: 3.0 – 4.5
Osmolality: 280 – 320 mosmol/Kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Noradrenaline (Norepinephrine) Concentrate is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration

Route of Administration:
For intravenous use only.

Method of administration:
Administer as a diluted solution via a central venous catheter.
The infusion should be at a controlled rate using either a syringe pump or an infusion pump or a drip counter.

For dilution instructions see section 6.6.

Dosage:

Adults

Initial rate of infusion:

When diluted as recommended in section 6.6 (the concentration of the prepared infusion is 40 mg/litre noradrenaline base (80 mg/litre noradrenaline tartrate)) the initial rate of infusion, at a body weight of 70 kg, should be between 10 ml/hour and 20 ml/hour (0.16 to 0.33 ml/min). This is equivalent to 0.4 mg/hour to 0.8 mg/hour noradrenaline base (0.8 mg/hour to 1.6 mg/hour noradrenaline tartrate). Some clinicians may wish to start at a lower initial infusion rate of 5 ml/hour (0.08 ml/min), equivalent to 0.2 mg/hour noradrenaline base (0.4 mg/hour noradrenaline tartrate).

Titration of dose:
Once an infusion of noradrenaline has been established the dose should be titrated in steps of 0.05 -0.1 µg/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 - 80 mm Hg - depending on the patient's condition).

Noradrenaline (Norepinephrine) Concentrate 40 mg/litre (40 µg/ml) noradrenaline base			
Patient's Weight	Posology (µg/kg/min) noradrenaline base	Posology (mg/hour) noradrenaline base	Infusion Rate (ml/hour)
50 kg	0.05	0.15	3.75
	0.1	0.3	7.5
	0.25	0.75	18.75
	0.5	1.5	37.5
	1	3	75
60 kg	0.05	0.18	4.5
	0.1	0.36	9
	0.25	0.9	22.5
	0.5	1.8	45
	1	3.6	90
70 kg	0.05	0.21	5.25
	0.1	0.42	10.5
	0.25	1.05	26.25
	0.5	2.1	52.5
	1	4.2	105
80 kg	0.05	0.24	6
	0.1	0.48	12
	0.25	1.2	30
	0.5	2.4	60
	1	4.8	120
90 kg	0.05	0.27	6.75
	0.1	0.54	13.5
	0.25	1.35	33.75
	0.5	2.7	67.5
	1	5.4	135

Some clinicians may prefer to dilute to other concentrations. If dilutions other than 40 mg/l are used, check the infusion rate calculation carefully before starting treatment.

Renal or hepatic impairment:
There is no experience in treatment of renally or hepatically impaired patients

Elderly:
As for adults but see section 4.4.

Children:
Not recommended.

Duration of Treatment and Monitoring:

Noradrenaline should be continued for as long as vasoactive drug support is indicated. The patient should be monitored carefully for the duration of therapy. Blood pressure should be carefully monitored for the duration of therapy.

Withdrawal of Therapy:
The noradrenaline infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

4.3 Contraindications

Hypersensitivity to noradrenaline tartrate or to any of the excipients.
Do not use undiluted
Do not use with cyclopropane and halothane anesthetics. For interactions see section 4.5.

4.4 Special warnings and precautions for use

Noradrenaline should only be administered by healthcare professionals who are familiar with its use.

Noradrenaline should not be given to patients who are hypotensive from blood volume deficits except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed.

Elderly patients may be especially sensitive to the effects of noradrenaline due to the greater frequency of hepatic, renal or cardiac function and concomitant disease or other drug therapy.

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 administrated 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).

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.

Noradrenaline should be used with caution in patients who exhibit profound hypoxia or hypercarbia.

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 hypertension.

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.

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.

The infusion of noradrenaline should be stopped gradually as sudden cessation may produce a catastrophic fall in blood pressure.

To be taken into consideration by patients on a controlled sodium diet.

The product administrated must always be visually inspected and cannot be used if the presence of particles or a change of colouring is noted.

4.5 Interaction with other medicinal products and other forms of interactions

The use of noradrenaline with volatile halogenated anesthetic agents, monoamine oxidase inhibitors, linezolid, tricyclic antidepressants, adrenergic-serotoninergic drugs or any other cardiac sensitizing agents is not recommended because severe, prolonged hypertension and possible arrhythmias may result.

4.6 Fertility, pregnancy and lactation

Pregnancy

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. These possible risks to the fetus should therefore be weighed against the potential benefit to the mother.

Lactation

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

4.7 Effects on ability to drive and use machines

None state

4.8 Undesirable effects

Systemic Organ Class	**Undesirable effect**
Psychiatric disorders	Anxiety
Nervous system disorders	Headache
Cardiac disorders	Arrythmias (when used in conjunction with cardiac sensitizing agents), bradycardia, stress cardiomyopathy
Vascular disorders	Hypertension, peripheral ischaemia including gangrene of the extremities, plasma volume depletion with prolonged use
Respiratory, thoracic and mediastinal disorders	Dyspnoea
General disorders and administration site conditions	Extravasation necrosis at injection site

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;
Fax: +353 1 6762517. Website: www.hpra.ie, E-mail: medsafety@hpra.ie.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC code: C01CA03

The vascular effects in the doses normally used clinically result from the simultaneous stimulation of alpha and beta adrenergic receptors in the heart and vascular system. Except in the heart, its action is predominantly on the alpha receptors. This results in an increase in the force (and in the absence of vagal inhibition, in the rate) of myocardial contraction. Peripheral resistance increases and diastolic and systolic pressures are raised.

The increase in blood pressure may cause a reflex decrease in heart rate. Vasoconstriction may result in decreased blood flow in kidneys, liver, skin and smooth muscles. Local vasoconstriction may cause haemostasis and/or necrosis.

The effect on blood pressure disappears 1-2 minutes after stopping the infusion.

5.2 Pharmacokinetic properties

Two stereoisomers of Noradrenaline exist, the biologically active L-isomer is the one present in Noradrenaline (Norepinephrine) Concentrate.
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 adverse effects attributable to sympathomimetics result from excessive stimulation of the sympathetic nervous system via the different adrenergic receptors.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

List of excipients
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicinal products except those mentioned in the section 6.6

Infusion solutions containing noradrenaline tartrate have been reported to be incompatible with the following substances: alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin.

For compatibility with infusion bags see section 6.6

6.3 Shelf life

15 months.
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.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

2 ml and 4 ml colourless glass ampoules and 20 ml vials containing sterile concentrate for solution for infusion.
5 ampoules of 2 ml in a pack
5 ampoules of 4 ml in a pack
5 vials of 20 ml in a pack

6.6 Special precautions for disposal and other handling

Dilution instructions:

Dilute before use with glucose 5% solution or sodium chloride 9 mg/ml (0.9%) with glucose 5 % solution.

Either add 2 ml concentrate to 48 ml glucose 5% solution (or sodium chloride 9 mg/ml (0.9%) with glucose 5% solution) for administration by syringe pump, or add 20 ml of concentrate to 480 ml glucose 5 % solution (or sodium chloride 9 mg/ml (0.9%) with glucose 5% solution) for administration by drip counter. In both cases the final concentration of the infusion solution is 40 mg/litre noradrenaline base (which is equivalent to 80 mg/litre noradrenaline tartrate). Dilutions other than 40 mg/litre noradrenaline base may also be used (see section 4.2). If dilutions other than 40 mg/litre noradrenaline base are used, check the infusion rate calculation carefully before starting treatment.

The product is compatible with PVC infusion bags.

This medicine should not be used if the solution is brown in colour.

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

For single use only.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/245/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of lastest renewal: 11th March 2020

10 DATE OF REVISION OF THE TEXT

January 2021