

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Noradrenaline (Norepinephrine) 1:1000 Concentrate For Solution For Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre (ml) of concentrate for solution for infusion contains 2 milligram (mg) of noradrenaline (norepinephrine) tartrate, equivalent to 1 mg norepinephrine base. Each 2 ml ampoule contains 4 mg of norepinephrine tartrate equivalent to 2 mg norepinephrine base.

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

Excipient with known effect

Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for Solution for Infusion contains 6.7 mg of sodium in each 2 ml ampoule.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A sterile, clear colourless solution.

The solution has a pH ranging between 3.0 and 4.0 and osmolality ranging between 281- 285 mOsm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Norepinephrine 1:1000 is recommended for use as an emergency measure in the restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration

Route of Administration:

For intravenous use.

Method of Administration:

Norepinephrine 1: 1000 should be administered in a diluted solution and it may be administered 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 instructions on dilution of the product before administration, see section 6.6.

Site of infusion:

If not using a central venous catheter, whenever possible, infusions of norepinephrine tartrate should be administered into a large vein, particularly an antecubital vein. When administered into this vein, the risk of necrosis of the overlying skin from prolonged vasoconstriction is reported to be very slight. Some authors have indicated that the femoral vein is also an acceptable route of administration. A catheter tie-in technique should be avoided if possible, since the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (e.g. atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower extremity than in the upper extremity; therefore, avoid the veins of the leg in elderly patients or in those suffering from such disorders. Gangrene has been reported in a lower extremity when infusions were given in an ankle vein.

Adults:

Add 2 ml of Norepinephrine 1:1000 to 48 ml 5%dextrose for administration by syringe pump.

The final concentration of the infusion solution is 80 mg/litre norepinephrine tartrate, which is equivalent to 40 mg/litre norepinephrine base. If other dilutions are used check the calculation carefully before starting treatment.

Initial rate of infusion:

The initial rate of infusion should be between 10 ml/hour and 20 ml/hour (0.16 ml/min to 0.32 ml/min). This is equivalent to 0.8 mg/hr to 1.6 mg/hr norepinephrine tartrate (or 0.4 mg/hr to 0.8 mg/hr norepinephrine base).

Titration of dose:

Once an infusion of norepinephrine has been established the dose should be titrated 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 80 mm Hg).

Noradrenaline Infusion Solution 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

Duration of treatment and monitoring:

Norepinephrine should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. The patient should be monitored carefully for the duration of norepinephrine therapy.

Noradrenaline should only be administered by healthcare professionals who are familiar with its use and have appropriate facilities to adequately monitor the patient.

Withdrawal of Therapy:

Infusions should be reduced gradually, avoiding abrupt withdrawal which can result in acute hypotension.

Hepatic / renal impairment:

There is no experience in treatment of hepatically or renally impaired patients.

Elderly:

In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range as to reflect the greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Paediatric population:

The safety and efficacy of norepinephrine in children aged less than 18 years old has not yet been established. No data are available.

4.3 Contraindications

Hypersensitivity to the norepinephrine or to any of the excipients listed in section 6.1.

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

Norepinephrine 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.

Norepinephrine should be used only in conjunction with appropriate blood volume replacement.

If norepinephrine 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 systemic 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).

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 norepinephrine tartrate is discontinued or the 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; gangrene of extremities has been rarely reported.

Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because norepinephrine may increase the ischemia and extend the area of infarction, unless in the opinion of the attending physician, the administration of norepinephrine tartrate is necessary as a life-saving procedure. Similar caution should be observed in patients with hypotension following myocardial infarction and in patients with angina, particularly Prinzmetal's variant angina, diabetes, hypertension or hyperthyroidism (see section 4.8).

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

The use of noradrenaline in children is not recommended (see section 4.2 and 5.2).

Norepinephrine should only be used by doctors familiar with the selective indications for its use. Where indicated, appropriate replacement therapy of blood or fluid together with adoption of the supine position with elevation of the legs, must be instituted and maintained prior to and/or during therapy with this product. When infusing norepinephrine, the blood pressure and rate of flow should be checked frequently to avoid hypertension. Therefore, it is desirable to record the blood pressure every two minutes from the time the administration started until the desired blood pressure is obtained and then every five minutes thereafter, if the administration is to be continued. The rate of flow must be watched constantly and the patient should never be left unattended while receiving norepinephrine. Hypertension may eventually lead to acute pulmonary oedema, arrhythmia or cardiac arrest.

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

Extravasation

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of norepinephrine tartrate into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. Blanching along the course of the infused vein, sometimes without obvious extravasation, has been attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. On rare occasions this may progress to superficial slough, particularly during infusion into leg veins in elderly patients or in those suffering from obliterative vascular disease. If blanching occurs, consideration should be given to changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

IMPORTANT — Antidote for extravasation ischaemia: To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of phentolamine, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard and pallid appearance. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Phentolamine should be given as soon as possible after the extravasation is noted and infusion should be stopped.

Excipient information

Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for Solution for Infusion contains 6.7 mg of sodium in each 2 ml ampoule, equivalent to 0.3% 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

Norepinephrine should be used with extreme caution in patients receiving monoamine oxidase inhibitors or within 14 days of cessation of such therapy and in patients receiving tricyclic antidepressants, adrenergic- serotonergic drugs or linezolid because severe, prolonged hypertension may result.

The use of pressor amines with cyclopropane, halothane, chloroform, enflurane or other halogenated anaesthetics may cause serious cardiac arrhythmias, because of the possibility of increasing the risk of ventricular fibrillation, Norepinephrine should be used with caution in patients receiving these or any other cardiac sensitising agent or who exhibit profound hypoxia or hypercarbia.

The effects of Norepinephrine 1:1000 may be enhanced by guanethidine, reserpine, methyldopa or tricyclic antidepressants. Concomitant administration of propofol and noradrenaline may lead to propofol infusion syndrome (PRIS).

Norepinephrine infusion solutions should not be mixed with other medications.

4.6 Fertility, pregnancy and lactationPregnancy

Norepinephrine 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.

Breastfeeding

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when norepinephrine is administered to a nursing woman.

Fertility

No studies have been performed to collect fertility data for norepinephrine.

4.7 Effects on ability to drive and use machines

No information is available; therefore, driving or operating machinery is not recommended.

4.8 Undesirable effects

Table 1 lists adverse reactions that have been experienced following treatment with norepinephrine. This data has largely been collected from spontaneous reporting, and due to the problems in calculating reporting frequencies from spontaneous

reporting, the frequency of the listed adverse reactions is not known (cannot be estimated from the available data). The adverse reactions are reported in decreasing order of frequency within each system order class (SOC).

Table 1 : Adverse Reactions Reported With Norepinephrine Through Spontaneous Reporting

System Organ Class (SOC)	Adverse Reactions
Psychiatric disorders	Anxiety
Nervous system disorders	Transient headache
Cardiac disorders	Bradycardia ¹ , Arrhythmia, Electrocardiogram change, Tachycardia, Cardiogenic shock, stress cardiomyopathy
Vascular disorders	Hypertension, Peripheral ischaemia ² including gangrene of the extremities, plasma volume depletion with prolonged use
Respiratory, thoracic and mediastinal disorders	Dyspnoea
General disorders and administration site conditions	Extravasation, Injection site necrosis

¹Bradycardia, probably as a reflex result of a rise in blood pressure.

²Ischaemia, due to potent vasoconstrictor action and tissue hypoxia

Hypertension may occur, which may be associated with bradycardia as well as headache and peripheral ischemia, including gangrene of the extremities.

Cardiac arrhythmias may arise when norepinephrine is used in conjunction with cardiac sensitizing agents, and may be more likely in patients with hypoxia or hypercarbia.

Norepinephrine should be used only in conjunction with appropriate blood volume replacement. Prolonged administration may result in plasma volume depletion. When infusing norepinephrine, the blood pressure and rate of flow should be checked frequently to avoid hypertension, which may be associated with bradycardia as well as headache and peripheral ischemia, including rarely gangrene of the extremities. Extravasation may cause local tissue necrosis.

Special caution should be used for patients with liver failure, severe renal dysfunction, ischemic heart diseases and elevated intracranial pressure. Overdoses or conventional doses in hypersensitive persons (e.g., hyperthyroid patients) may cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating and vomiting. Hypertension may eventually lead to acute pulmonary edema, arrhythmia or cardiac arrest.

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

Overdosage may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output. These may be accompanied by violent headache, cerebral haemorrhage, photophobia, retrosternal pain, pallor, fever, intense sweating, pulmonary oedema and vomiting. In case of accidental overdose, as evidenced by excessive blood pressure elevation, discontinue the drug until the condition of the patient stabilises.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents.

ATC code: C01CA03

The vascular effects of norepinephrine in the doses usually 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.

5.2 Pharmacokinetic properties

Up to 16% of an intravenous dose is excreted unchanged in the urine with methylated and deaminated metabolites in free and conjugated forms.

Paediatric population

No data on experience of pharmacokinetic studies in paediatric age groups is available.

5.3 Preclinical safety data

No preclinical safety data is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Hydrochloric acid (for pH-adjustment)

Sodium hydroxide (for pH-adjustment)

Water for Injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened: 2 years

Once opened, the diluted solution should be prepared immediately and it should be used immediately following preparation. Any unused contents remaining in the ampoule should be discarded.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

The product is supplied in a pack containing 5 x 2ml glass ampoules. Each ampoule contains 2 ml of concentrate for solution for infusion.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

This medicine should not be used if the solution is slightly pink, yellow or brown in colour or if it is cloudy or contains visible particles/solids.

Dilute before use with glucose 5% solution or sodium chloride 9 mg/ml (0.9%) with glucose 5 % solution. These dextrose containing fluids are protection against significant loss of potency due to oxidation. Administration in saline solution alone is

not recommended as deterioration occurs more rapidly in normal saline than in dextrose 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 norepinephrine base (which is equivalent to 80 mg/litre norepinephrine tartrate). Dilutions other than 40 mg/litre norepinephrine base may also be used (see section 4.2). If dilutions other than 40 mg/litre norepinephrine base are used, check the infusion rate calculation carefully before starting treatment.

The diluted solution should be used immediately after preparation.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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