

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

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

Each ampoule of 4 ml contains 8 mg noradrenaline (norepinephrine) tartrate, equivalent to 4 mg noradrenaline (norepinephrine).

Each ampoule of 8 ml contains 16 mg noradrenaline (norepinephrine) tartrate, equivalent to 8 mg noradrenaline (norepinephrine).

Excipient with known effect

Each ml of concentrate for solution for infusion contains 3.3 mg sodium.

Each 4 ml ampoule contains 13.2 mg sodium

Each 8 ml ampoule contains 26.4 mg sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear, colourless or slightly yellowish solution

pH = 3.0 to 4.0

Osmolality = 250 – 320 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Noradrenaline (Norepinephrine) should be diluted before use. When diluted, the final concentration of the infusion solution is usually 40 mg/l noradrenaline (norepinephrine) (equivalent to 80 mg/l noradrenaline (norepinephrine) tartrate). If other dilutions are used check the calculation carefully before starting treatment.

See section 6.6 for dilution instructions.

Adults:

Initial rate of infusion:

The initial rate of infusion should be between 10 ml/hour and 20 ml/hour (0.16 ml/min to 0.33 ml/min).

This is equivalent to 0.4 mg/h to 0.8 mg/h noradrenaline (norepinephrine) (equivalent to 0.8 mg/h to 1.6 mg/h noradrenaline (norepinephrine) tartrate).

Titration of dose:

Once an infusion of noradrenaline (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 65 to 80 mm Hg – depending on the patient's condition).

Posology instructions:

The posology per patient's weight is detailed in the table hereafter.

- **Table 1** : posology expressed in Noradrenaline,

Table 1: Posology table (expressed in Noradrenaline)

	Noradrenaline (Norepinephrine) Infusion solution at 40 mg/L		
Patient's Weight	Posology (µg/kg/min) (Noradrenaline)	Posology (mg/h) (Noradrenaline)	Infusion rate (ml/h)
40 kg	0.05	0.12	3
	0.1	0.24	6
	0.25	0.6	15
	0.5	1.2	30
	1	2.4	60
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:

Noradrenaline (Norepinephrine) should be continued for as long as vasoactive drug support is indicated. The patient should be monitored carefully for the duration of noradrenaline (norepinephrine) therapy.

Blood pressure control:

Measure blood pressure every two minutes at the beginning of the infusion until the desired blood pressure is obtained. Then every five minutes when desired the blood pressure is obtained, if the administration has to be continued. The infusion should be at a control rate and the patient should be monitored carefully for the duration of noradrenaline (norepinephrine) therapy.

Withdrawal of therapy

The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure.

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 (refer to Section 4.4).

Paediatric population:

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

Patients with renal and hepatic impairment

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

Method of administration

For intravenous use only after dilution.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Noradrenaline (Norepinephrine) should be administered through central venous devices to minimize the risk of extravasation and subsequent tissue necrosis.

The infusion should be at a controlled rate using either a syringe pump or an infusion pump or a drip counter.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypotension due to blood volume deficit (Hypovolaemia).
- Do not use with cyclopropane and halothane anaesthetics as this may cause serious cardiac arrhythmias including ventricular fibrillation. For interactions see section 4.5.

4.4 Special warnings and precautions for use

Warning:

- Do not use undiluted.
- Noradrenaline (Norepinephrine) should be used only in conjunction with appropriate blood volume replacement.
- When infusing noradrenaline (norepinephrine), the blood pressure and rate of flow should be checked frequently to avoid hypertension.
- The patients receiving noradrenaline (norepinephrine) should be closely monitored in order to identify early symptoms of vasopressor-induced limb ischaemia and implement the appropriate measures (e.g. elevation of the extremity, splinting, warming of affected limb with ad hoc device, use of vasodilating agents) to prevent progression and minimize the risks associated with necrosis of the extremities.
- Extravasation risk:

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation that would cause a necrosis of the tissues surrounding the vein used for the injection. Because of the vasoconstriction of the vein wall with increased permeability, there might be some leakage of noradrenaline (norepinephrine) in the tissues surrounding the infused vein causing a blanching of the tissues which is not due to an obvious extravasation. Hence if blanching occurs, consideration should be given to changing the infusion site to allow the effects of local vasoconstriction to subside.

Treatment of the ischemia due to extravasation:

During an extravascular leak of the product or an injection besides the vein, tissue destruction can appear resulting from the vasoconstrictive action of the drug on the blood vessels. The area should be infiltrated as quickly as possible with 10 to 15ml of physiological salt solution containing 5 to 10 mg of phentolamine mesilate, an adrenergic blocking agent. For this purpose, it is necessary to use a syringe provided with a fine needle and to inject locally throughout the area, which is easily identified by its cold, hard and pallid appearance.

Precautions for use:

Caution and respect of the strict indication must be retained in case of:

- Major left ventricular dysfunction associated with acute hypotension, a careful evaluation of patient's blood pressure is needed. Supportive therapy should be initiated simultaneously with diagnostic evaluation. Noradrenaline (Norepinephrine) should be reserved for patients with cardiogenic shock and refractory hypotension, in particular those without elevated systemic vascular resistance.
- Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline (norepinephrine) may increase the ischaemia and extend the area of infarction. Similar caution should be observed in patients with hypotension following myocardial infarction and in patients with Prinzmetal's variant angina.
- Occurrence of heart rhythm disorders during the treatment must lead to a reduction in the dosage.
- Caution is advised in patients with hyperthyroidism or diabetes mellitus.
- The elderly may be especially sensitive to the effects of noradrenaline (norepinephrine) due to the greater frequency of hepatic, renal or cardiac function and concomitant disease or other drug therapy.
- The use of noradrenaline (norepinephrine) in children is not recommended (see section 4.2).

The vasopressor effect (resulting from the adrenergic action on the vessels) can be reduced by the concomitant administration of an α -blocking agent (phentolamine mesilate) whereas the administration of a β -blocking agent (propranolol) may result in a reduction of the stimulating effect of the product on the heart and in an increase of the hypertensor effect (through reduction of arteriolar dilatation), resulting from β_1 adrenergic stimulation.

Excipient:

This medicinal product contains 3.3 mg sodium per ml, equivalent to 0.16 % 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**Contraindicated combinations**

- **Volatile halogen anaesthetics:** severe ventricular arrhythmia (increase in cardiac excitability).

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. Noradrenaline is contraindicated in combination with these medicines. See section 4.3.

Inadvisable combinations

- **Imipramine antidepressants:** paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

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

- **Desipramine:** significantly increase the toxicity of noradrenaline (norepinephrine).

- **Digitalis glycosides:** may occasionally cause arrhythmia.

- **Levodopa:** may enhance the effects of noradrenaline (norepinephrine).

- **Antihistamines,** as some may block the intake of catecholamines by peripheral tissues and increase the toxicity of injected noradrenaline (norepinephrine).

- **Chlorpheniramine hydrochloride, tripeleminamine hydrochloride:** significantly increase the toxicity of noradrenaline (norepinephrine).

Combinations requiring precautions for use

- **Non-selective MAO inhibitors (or within 14 days of cessation of such therapy):** increase in the pressor action of the sympathomimetic which is usually moderate. Should only be used under close medical supervision.

- **Selective MAO-A inhibitors:** by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. Should only be used under close medical supervision.
- **Linezolid:** by extrapolation from non-selective MAO inhibitors: risk of increase in the pressor action. Should only be used under close medical supervision.
- **Alpha and beta blockers:** Caution is required as severe hypertension may result.
- **Thyroid hormones, Cardiac glycosides, Anti-arrhythmics:** Caution is required as they may cause increased cardiac effects.
- **Ergot alkaloids or oxytocin:** may enhance the vasopressor and vasoconstrictive effects.
- **Desmopressin or vasopressin:** its antidiuretic effect is diminished.
- **Lithium** decreases the effect of noradrenaline (norepinephrine)
- **Guanethidine, guanadrel, reserpine, methyldopa or tricyclic antidepressants, amphetamine, doxapram, mazindol, rauwolfia alkaloids** : may enhance the effects of noradrenaline (norepinephrine) .
- **Propofol:** Concomitant administration may lead to propofol infusion syndrome (PRIS).

4.6 Fertility, pregnancy and lactation

Pregnancy

Noradrenaline (Norepinephrine) 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.

Breastfeeding

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

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Table 3: Tabulated summary of adverse reactions

Very common: $\geq 1/10$; Common : $\geq 1/100$, $< 1/10$; Uncommon: $\geq 1/1,000$, $< 1/100$; Rare: $\geq 1/10,000$, $< 1/1,000$; Very rare: $< 1/10,000$; Not known: cannot be estimated from the available data

System Organ Class (SOC)	Adverse Reactions (<i>Frequency: not known</i>)
Metabolism and nutrition disorders	anorexia.
Psychiatric disorders	anxiety, insomnia, confusion, psychotic state, weakness.
Nervous system disorders	headaches, tremor, lower vigilance,
Eyedisorders	acute glaucoma; very frequent in patients anatomically predisposed with the closing of the iridocorn angle.
Cardiac disorders	tachycardia, bradycardia (probably as a reflex result of blood pressure rising), arrhythmias, palpitations, increase in the contractility of the cardiac muscle resulting from the β 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 skin, members (peripheries) and the face, and gangrene of the extremities; cyanosis; hot flushes or skin redness.
Respiratory, thoracic and mediastinal disorders	respiratory insufficiency or difficulty, dyspnoea
Skin and subcutaneous tissue disorders	Scarification of the skin, skin rash, hives or itching.
Gastrointestinal disorders	nauseas and vomiting.
Renal and urinary disorders	retention of urine.
General disorders and administration site conditions	possibility of irritation and necrosis at the injection site.

Additional information regarding the safety of Noradrenaline (Norepinephrine)

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

- severe peripheral and visceral vasoconstriction
- decrease in renal blood flow
- decrease in urine production
- tissue hypoxia
- lactic acidosis.

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

Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate water and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when the noradrenaline (norepinephrine) infusion is discontinued, or blood pressure may be maintained with 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.

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

Symptoms

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.

The following may also be observed: cutaneous vasoconstriction, bed sores.

Treatment

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 Agent; ATC Code: C01CA03 (C: Cardiovascular system)

Mechanism of action

Noradrenaline (Norepinephrine) has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors.

Pharmacodynamic effects

Noradrenaline (Norepinephrine) causes generalised vasoconstriction, except for the coronary vessels which it dilates indirectly by increasing the oxygen consumption. 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

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

Absorption

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

Distribution

- Noradrenaline (Norepinephrine) 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 monoamine oxydase (MAO)
- Ultimate metabolites from both is 4- hydroxy-3-methoxymandelic acid
- Intermediate metabolites include normetanephrine and 3,4- dihydroxymandelic acid.

Elimination

- Noradrenaline (Norepinephrine) 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 (Norepinephrine) 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After dilution:

Chemical and physical in-use stability of diluted product (in 5% dextrose, sodium chloride 9 mg/ml (0.9%), or isotonic dextrose saline) has been demonstrated for 48 hours at 30°C.

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 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the ampoule in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass ampoule containing 4 ml or 8 ml of concentrate for solution for infusion. Each pack contains 10, 50 or 100 ampoules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use.

Noradrenaline (Norepinephrine) should be diluted prior to intravenous infusion, either with dextrose 5%, sodium chloride 9 mg/ml (0.9%), or with isotonic dextrose saline. It should not be mixed with other medicines.

Dilution instructions:

Add 2 ml of Noradrenaline (Norepinephrine) to 48 ml 5% dextrose (or sodium chloride 9 mg/ml (0.9%), or isotonic dextrose saline) for administration by syringe pump,
or add 20 ml of Noradrenaline (Norepinephrine) to 480 ml 5% dextrose (or sodium chloride 9 mg/ml (0.9%), or isotonic dextrose saline) for administration by drip counter.

In both cases the final concentration of the infusion solution is usually 40 mg/litre noradrenaline (norepinephrine) (80 mg/l noradrenaline (norepinephrine) tartrate).

If other dilutions are used check the calculation carefully before starting treatment.

This product should be visually inspected prior to administration. Only a clear, colourless or slightly yellowish solution, free of particles or precipitates should be used. The ampoules with a pink colour or darker than pale yellow, or containing a precipitate should not be administered.

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

7 MARKETING AUTHORISATION HOLDER

Laboratoire Aguettant
1 Rue Alexander Fleming
Lyon
69007
France

8 MARKETING AUTHORISATION NUMBER

PA1968/023/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th April 2025

10 DATE OF REVISION OF THE TEXT

April 2025