Package leaflet: Information for the user

NORADRENALINE (NOREPINEPHRINE) 1 mg/ml
concentrate for solution for infusion

Noradrenaline tartrate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of this medicinal product is NORADRENALINE (NOREPINEPHRINE) 1 mg/ml Concentrate for solution for infusion, but will be referred as Noradrenaline (Norepinephrine) Concentrate throughout the whole leaflet.

What is in this leaflet

1. What NORADRENALINE (NOREPINEPHRINE)Concentrate is and what it is used for?
Noradrenaline (Norepinephrine) Concentrate is a drug that belongs to the group of adrenergic and dopaminergic agent.
Noradrenaline (Norepinephrine) Concentrate is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

2. What you need to know before you are given Noradrenaline (Norepinephrine) Concentrate
You must not be given Noradrenaline (Norepinephrine) Concentrate:
- if you are allergic to noradrenaline or to any of the other ingredients of this medicine (listed in section 6). ;
- if you are hypotensive (have low blood pressure) that has been caused by hypovolaemia (low blood volume) ;
- if you are taking some anaesthetics such as halothane or cyclopropane (this may increase the risk of irregular heart beat).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before you are given Noradrenaline (Norepinephrine) Concentrate:
- if you have extravasation risk ;
- if you have major left ventricular dysfunction (a heart condition) ;
- if you have coronary, mesenteric or peripheral vascular thrombosis ;
- if you have hypotension following myocardial infarction ;
- if you have Prinzmetal’s variant angina ;
- if you have heart rhythm disorders during your treatment – you will need a reduced dose ;

- if you have hyperthyroidism or diabetes mellitus ;
- if you are elderly.
Your blood pressure and heart rate will be checked frequently during your treatment to avoid hypertension.

Other medicines and Noradrenaline (Norepinephrine) Concentrate
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines.
Noradrenaline (Norepinephrine) Concentrate may affect or be affected by other medicines. In particular, tell your doctor if you are taking any of the following:
- Halothane, cyclopropane: these medicines are anaesthetics, they cause insensibility to pain and are used before some operations. If you are taking these medicines as well as Noradrenaline this may increase the risk of irregular heart beat.
- Amitriptiline, Imipramine, Trimipramine, Moclobemide, Iproniazide, Phenelzine, Fluoxetine, Sertraline: these medicines are used for treatment of depression. Taking any of these medicines together with Noradrenaline can dangerously increase its concentration in the blood and therefore its pressor action.
- Linezolid, an antibiotic (drug used to treat infections caused by bacteria and other microorganisms), can dangerously increase Noradrenaline concentration in the blood and therefore its pressor action, when taken together.
- Alpha and beta-blockers: if you are taking these medicines as well as Noradrenaline this may increase the risk of severe hypertension.
- Thyroid hormones, Cardiac glycosides, Anti-arrhythmics: if you are taking these medicines as well as Noradrenaline this may cause increased cardiac effects.
- Ergot alkaloids or oxytocin may enhance the vasopressor and vasoconstrictive effects.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine. Then your doctor will decide if you should be given this medicine.

Driving and using machines
Since Noradrenaline will be given to you in a hospital, your doctor will inform you when you will be able to drive or use machines.

Noradrenaline (Norepinephrine) Concentrate contains sodium:
This medicine contains less than 1 mmol sodium (23 mg) per 4 ml ampoule, that is to say essentially ‘sodium-free’.
This medicine contains 26.4 mg sodium (main component of cooking/table salt) in each 8 ml ampoule. This is equivalent to 1.3 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How you are given Noradrenaline (Norepinephrine) Concentrate
Noradrenaline (Norepinephrine) concentrate will be given to you in a hospital by a doctor or nurse.

Dosage
The dose of Noradrenaline depends on the condition of the patient. Your doctor will know the best dose to use. Noradrenaline is first diluted and then usually infused into a vein. The dose can then be adjusted using a pump according to the response to treatment, with the aim to establish a normal blood pressure. The initial dose is 0.4 to 0.8 milligrams per hour of Noradrenaline (Norepinephrine) base.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Noradrenaline can cause side effects, although not everybody gets them.
The following side effects have been reported:
- skin necrosis (death) if the infusion is not given directly into the vein,
- anxiety, insomnia, confusion, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nauseas, vomiting,
- difficulty in breathing, fast or slow heart rate, pain in the chest or throat,
- retention of urine,
- pallor (loss of skin colour), sweating, sensitivity to light, gangrene (painful and cold extremities that may become purple to very dark/black, with tissue death).

Reporting of side effects
If you get any side effects, talk to your doctor or, your pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Noradrenaline (Norepinephrine) Concentrate
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

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

<u>After dilution:</u>
The physicochemical stability of diluted product (in 5% dextrose, in 0.9% sodium chloride, or in an isotonic dextrose saline) has been demonstrated for 48 hours at 30°C.
However, from a microbiological point of view, the diluted product should be used immediately. If the product is not used immediately, the duration and conditions of use are the sole responsibility of the user.
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. Do not use ampoules with a pink color or darker than pale yellow, or containing a precipitate.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information
What Noradrenaline (Norepinephrine) Concentrate contains
The active substance is Noradrenaline tartrate.
Each ml of concentrate for solution for infusion contains 2 mg Noradrenaline tartrate, equivalent to 1 mg Noradrenaline base
Each 4ml ampoule contains 8mg Noradrenaline tartrate equivalent to 4mg Noradrenaline base.
Each 8ml ampoule contains 16mg Noradrenaline tartrate equivalent to 8mg Noradrenaline base.
The other ingredients are: sodium chloride, sodium hydroxide or hydrochloric acid and water for injections.

What Noradrenaline (Norepinephrine) Concentrate looks like and contents of the pack
Clear,colourless or slightly yellowish solution of pH 3.0 to 4.0 packaged in a clear glass ampoule of 4 ml or 8 ml.

Boxes of 10, 50 or 100 ampoules.
Not all pack sizes may be marketed.

Marketing Authorisation holder - Manufacturer
Laboratoire Aguettant1, rue Alexander Fleming - 69007 LYON - France

Manufacturers
DELPHARM Tours
Rue Paul Langevin
37 170 Chambray-Les-Tours
France
or

HAUPT PHARMA LIVRON
1 rue Comte de Sinard,
26250 LIVRON SUR DROME
France

This medicinal product is authorised in the Member States of the EEA under the following names:
Belgium: Noradrenaline (norepinephrine) Aguettant 1 mg/ml solution à diluer pour perfusion
United kingdom: Noradrenaline (norepinephrine) 1 mg/ml concentrate for solution for infusion

This leaflet was last revised in 08/2022.

THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONAL ONLY

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 tartrate, equivalent to 1 mg Noradrenaline base
Each 4ml ampoule contains 8mg Noradrenaline tartrate equivalent to 4mg Noradrenaline base.
Each 8ml ampoule contains 16mg Noradrenaline tartrate equivalent to 8mg Noradrenaline base.

Excipient with known effect
Each ml of concentrate for solution for infusion contains 3.3 mg equivalent to 0.14 mmol of sodium
Each 4ml ampoule contains 13.2 mg equivalent to 0.57 mmol of sodium
Each 8ml ampoule contains 26.4 mg equivalent to 1.14 mmol of sodium

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
Clear, colourless or slightly yellowish solution
pH = 3.0 to 4.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noradrenaline is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration

Posology

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 0.8 mg/hr to 1.6 mg/hr noradrenaline tartrate (or 0.4 mg/hr to 0.8 mg/hr noradrenaline base).

Titration of dose:
Once an infusion of noradrenaline 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).

Noradrenaline tartrate Infusion solution at 80 mg/L			
Patient's Weight	Posology (µg/kg/min) Tartrate	Posology (mg/h) Tartrate	Infusion rate (ml/h)
60 kg	0.2	0.72	9
	0.5	1.8	22.5
	1	3.6	45
	2	7.2	90
70 kg	0.2	0.84	10.75
	0.5	2.1	26.25
	1	4.2	52.5
	2	8.4	105
80 kg	0.2	0.96	12
	0.5	2.4	30
	1	4.8	60
	2	9.6	120

h: hour

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

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 noradrenaline therapy.

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

Elderly:
As for adults but see Precautions.

Children:
Not recommended

Method of administration
For intravenous use only.
Noradrenaline should be administered through central venous devices to minimize the risk of extravasation and subsequent tissue necrosis.

Noradrenaline 1mg/ml concentrate should be diluted prior to intravenous infusion, either with dextrose 5%, 0.9% sodium chloride, or with isotonic dextrose saline. It should not be mixed with other medicines.
The final concentration of the infusion solution should be 80 mg/litre noradrenaline tartrate, which is equivalent to 40 mg/litre noradrenaline base. If other dilutions are used, check the calculation carefully before starting treatment.

Dilution instructions:
Add 2 ml of Noradrenaline 1 mg/ml to 48 ml 5% dextrose (or 0.9% sodium chloride, or isotonic dextrose saline) for administration by syringe pump, or add 20 ml of Noradrenaline 1 mg/ml to 480 ml 5% dextrose (or 0.9% sodium chloride, or isotonic dextrose saline) for administration by drip counter. In both cases the final concentration of the infusion solution is 80 mg/litre noradrenaline tartrate, which is equivalent to 40 mg/litre noradrenaline base. If other dilutions are used check the calculation carefully before starting treatment.

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.

4.3 Contraindications

Use of Noradrenaline 1 mg/ml concentrate for solution for infusion is contraindicated in patients with known hypersensitivity to noradrenaline or to any of the excipients.
Hypotension due to blood volume deficit (Hypovolaemia).

The use of pressor amines during cyclopropane or halothane anaesthesia 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.

4.4 Special warnings and precautions for use

Warning:

- 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.
- The products administrated by injection must always be visually inspected and cannot be used if the presence of particles or a change of colouring is noted.
- 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 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, a tissue destruction can appear resulting from the vasoconstrictive action of the drug on the blood vessels. The injection zone must be then irrigated as quickly as possible with 10 to 15ml of physiological salt solution containing 5 to 10 mg of phentolamine mesilate. For this purpose, it is necessary to use a syringe provided with a fine needle and to inject locally.

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 should be reserved for patients with cardiogenic shock and refractory hypotension, in particular those without elevated systemic vascular resistance. It should be started at a dosage of 2 to 4 µg/min and titrated upwards and titrated as necessary. If systemic perfusion or systolic pressure cannot be maintained at >90mmHg with a dosage of 15µg/min, it is unlikely that a further increase will be beneficial.
- Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline 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.

This medicinal product contains sodium.
This medicinal product contains 26.4 mg sodium per 8 ml ampoule, equivalent to 1.3 % 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

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: 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.

Caution is required when using Noradrenaline with alpha and beta blockers as severe hypertension may result.

Caution is required when using Noradrenaline with the following drugs as they may cause increased cardiac effects: Thyroid hormones, Cardiac glycosides, Anti-arrhythmics.

Ergot alkaloids or oxytocin may enhance the vasopressor and vasoconstrictive effects.

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.

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

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

- **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, and gangrene of the extremities.
- **Cardiac system:** tachycardia, bradycardia (probably as a reflex result of blood pressure rising), arrhythmias, 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.
- **Central nervous system:** anxiety, insomnia, confusion, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nauseas and vomiting.
- **Urinary system:** retention of urine.
- **Respiratory system:** respiratory insufficiency or difficulty, dyspnoea.
- **Locally:** possibility of irritation and necrosis at the injection site.
- **Eyes:** acute glaucoma; very frequent in patients anatomically predisposed with the closing of the iridocorn angle.

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
- 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.

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 ß-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 ß1 adrenergic stimulation.

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 infusion is discontinued, or

blood pressure may be maintained with the risk of severe peripheral and visceral vasoconstriction with diminution in blood flow.

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 the national reporting system :

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdose, the following may be observed: cutaneous vasoconstriction, bed sores, circulatory collapse, 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 Agent; ATC Code: C01CA03 (C: Cardiovascular system)

Noradrenaline has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. NORADRENALINE (NOREPINEPHRINE) 1 mg / ml 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 exist, the biologically active L-isomer is the one present in Noradrenaline (Norepinephrine) 1mg/ml Concentrate for solution for infusion.

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 pregnant uterus and lead to fetal asphyxia in late pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, hydrochloric acid or sodium hydroxide (qs pH 3.0 to 4.0) and water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years
After dilution:
Chemical and physical in-use stability of diluted product (in 5% dextrose, 0.9% sodium chloride, or isotonic dextrose saline) has been demonstrated for 48 hours at 30°C.
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°C to 8°C, unless manipulation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

4 ml and 8 ml clear glass ampoules packed in boxes of 10, 50 or 100 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Dilute in 5% dextrose, 0.9% sodium chloride, or isotonic dextrose saline. Please refer to section 4.2 “Posology and method of administration”.
- Do not use an opened ampoule.
- 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 color or darker than pale yellow, or containing a precipitate should not be administered

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

7. MARKETING AUTHORISATION HOLDER

Laboratoire Aguettant
1, rue Alexander Fleming - 69007 LYON - France

8. MARKETING AUTHORISATION NUMBER(S)

PL 14434/0017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02/03/2010
Date of latest renewal: 31/08/2013

10. DATE OF REVISION OF THE TEXT

08/2022