Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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.

In this leaflet
1. What Noradrenaline (Norepinephrine) Concentrate is and what it is used for
2. Before you are given Noradrenaline (Norepinephrine) Concentrate
3. How you are given Noradrenaline (Norepinephrine) Concentrate
4. Possible side effects
5. How to store Noradrenaline (Norepinephrine) Concentrate
6. Further information

1. WHAT NORADRENALINE (NOREPINEPHRINE) CONCENTRATE IS AND WHAT IT IS USED FOR
Noradrenaline (Norepinephrine) Concentrate is a drug for solution for infusion, but will be referred as Noradrenaline (Norepinephrine) Concentrate throughout the whole leaflet.

2. BEFORE YOU ARE GIVEN NORADRENALINE (NOREPINEPHRINE) CONCENTRATE

Do not use Noradrenaline (Norepinephrine) Concentrate:

- if you are hypersensitive to noradrenaline or to any of the excipients;
- if you are hypotensive (have low blood pressure) that has been caused by hypovolaemia (low blood volume);
- if you have taken some anaesthetics such as halothane or cyclopropane (this may increase the risk of irregular heart beat).

Take special care with Noradrenaline (Norepinephrine) Concentrate (and inform your doctor):

- 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.

Taking other medicines
Tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription as they may interact with Noradrenaline (Norepinephrine) Concentrate. This is especially important of the following medicines:

- Halothane, cyclopropane: these medicines are anaesthetics, they cause insensitivity 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.
- Amitriptyline, Imipramine, Trimipramine, Moclobemide, Iproniazide, Pheneclizine, 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
Please tell your doctor if you are pregnant, think you may be pregnant or are breast-feeding and your doctor will decide if Noradrenaline is appropriate for you. Ask your doctor or pharmacist for advice before taking any 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.
Important information about some of the ingredients of Noradrenaline (Norepinephrine) Concentrate:

This product contains 13.2 mg of sodium per one 4 ml ampoule.
This product contains 26.4 mg of sodium per one 8 ml ampoule.
Please tell your doctor if you are on a low sodium diet.

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 questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Noradrenaline (Norepinephrine) Concentrate 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, nausea, 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.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NORADRENALINE (NOREPINEPHRINE) CONCENTRATE

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

After dilution:
The physicochemical stability of diluted product (in 5% dextrose or in an isotonic dextrose saline) has been demonstrated for 48 hours at 22°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.

Do not use if you notice any type of coloration.

6. FURTHER INFORMATION

What Noradrenaline (Norepinephrine) Concentrate contains

The active substance is Noradrenaline tartrate 2 mg, equivalent to Noradrenaline base 1 mg.
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 and colourless liquid of pH 3 to 4.0 packaged in a clear glass ampoule of 4 ml or 8 ml.
Each ml of concentrate for solution for infusion contains 2 mg Noradrenaline tartrate equivalent to 1 mg Noradrenaline base.
Each 4 ml ampoule contains 8 mg Noradrenaline tartrate equivalent to 4 mg Noradrenaline base.
Each 8 ml ampoule contains 16 mg Noradrenaline tartrate equivalent to 8 mg Noradrenaline base.

Boxes of 10, 50 or 100 ampoules.

Marketing Authorisation Holder - Manufacturer

Laboratoire AGUETTANT
1, rue Alexander Fleming
69007 LYON
France

Manufacturer

DELPHARM Tours
Rue Paul Langevin
37 170 CHAMBRAY-LÉS-TOURS
France

Distributed by:

AGUETTANT LTD
N°1, Farleigh House - Flax Bourton
BRISTOL - BS48 1UR - United Kingdom

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 September 2013.
Extravasation
Noradrenaline

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

This medicinal product contains sodium.
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.

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear, colourless liquid.

pH = 3.0 – 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).

Titrating 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 nootension. 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

<table>
<thead>
<tr>
<th>Patient’s Weight</th>
<th>Posology (µg/kg/min) Tarrate</th>
<th>Posology (mg/h) Tarrate</th>
<th>Infusion rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 kg</td>
<td>0.2</td>
<td>0.72</td>
<td>9</td>
</tr>
<tr>
<td>0.5</td>
<td>1.8</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.6</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7.2</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>70 kg</td>
<td>0.2</td>
<td>0.84</td>
<td>10.75</td>
</tr>
<tr>
<td>0.5</td>
<td>2.1</td>
<td>26.25</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.2</td>
<td>52.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8.4</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>80 kg</td>
<td>0.2</td>
<td>0.96</td>
<td>12</td>
</tr>
<tr>
<td>0.5</td>
<td>2.4</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.8</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9.6</td>
<td>120</td>
<td></td>
</tr>
</tbody>
</table>

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 minimise the risk of extravasation and subsequent tissue necrosis. Noradrenaline 1 mg/ml concentrate should be diluted prior to intravenous infusion, either with dextrose 5%, 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: Either add 2 ml of Noradrenaline 1 mg/ml to 48 ml 5% dextrose (or isotonic dextrose saline) for administration by syringe pump, or add 20 ml of Noradrenaline 1 mg/ml to 480 ml 5% dextrose (or isotonic dextrose saline) for administration by drip counter.

In the box 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 the desired 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 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 hypertensive
• The products administered 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 of blanching occurs, consideration should be given to changing the infusion site to allow the effects of local vasoconstriction to subside.

Treatment of the ischaemia due to extravasation: During an extravasal 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 15 ml of physiological salt solution containing 5 to 10 mg of phenolamine 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 systemic pressure cannot be maintained at > 90 mm Hg with a dosage of 15 µg/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.

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

4.5 Interaction with other medicinal products and other forms of interaction
Incompatible 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 fibers).
• Sterosominergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and Dopaminergic Agent

Norepinephrine has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. Norepinephrine (Norepinephrine) is not used under severe hypertension. It is recommended to reduce the dosage if possible.

5.2 Pharmacokinetic properties

Norepinephrine is rapidly inactivated in the intravascular tract following oral administration. After intravenous administration it has a half-life of about 1 to 2 minutes.

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.

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.

5.4 Special precautions for storage

Store in the original package to protect from light. After dilution, the physicochemical stability of diluted product (5% dextrose or isotonic dextrose saline) has been demonstrated for 48 hours at 25°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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, hydrochloric acid or sodium hydroxide (ph 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.

6.4 Special precautions for storage

Do not store above 25°C.

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 or isotonic dextrose saline. Please refer to section 4.2.

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 : First MA 02/03/2010

10. DATE OF REVISION OF THE TEXT : September 2013

11. DOSIMETRY : Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS : Not applicable.