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Direct Healthcare Professional Communication on the association of Noradrenaline (Norepinephrine) 0.08 mg/ml (4 mg in 50 ml) solution for infusion in a vial with potential risk of medication errors

09 March 2016

Dear Healthcare Professional,

Summary

In June 2015 Aguettant Ltd received marketing approval for a new noradrenaline product: Noradrenaline (base) 0.08 mg/ml solution for infusion (equivalent to noradrenaline tartrate 0.16 mg/ml) presented in a 50 ml vial.

This product differs from existing noradrenaline products in both strength and presentation. There is a potential risk of medication errors should healthcare professionals not recognize these new features.

- Noradrenaline 0.08 mg/ml solution for infusion is presented in a **50 ml vial** containing 4 mg noradrenaline base.
- Noradrenaline 0.08 mg/ml solution for infusion is supplied **ready to use** and should **not be diluted before use** nor be mixed with other medicines.
- The other approved noradrenaline products available to date are presented in ampoules as concentrates for solution for infusion and require dilution to give a strength of 0.08 mg/ml noradrenaline base.
- Failure to distinguish the ready to use Noradrenaline 0.08 mg/ml solution for infusion from the concentrates for solution for infusion could lead to inappropriate dilution of Noradrenaline 0.08 mg/ml solution for infusion.
- Inadvertent dilution of Noradrenaline 0.08 mg/ml solution for infusion **could lead to under-dosing of the patient** and persistent life threatening hypotension.

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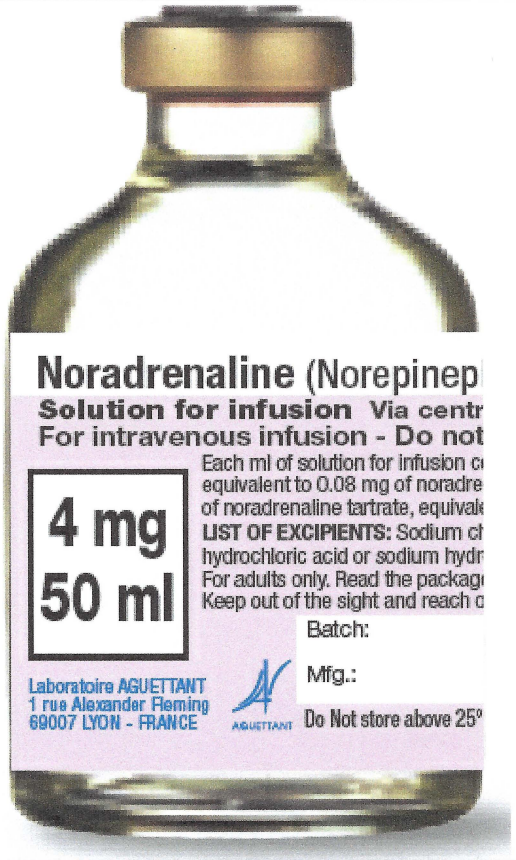
Further information on the safety concern

Noradrenaline (Norepinephrine) **0.08 mg/ml** (4 mg in 50 ml) solution for infusion in a vial
Each 50 ml vial contains 4 mg noradrenaline base.



Noradrenaline 0.08 mg/ml solution for infusion is indicated in adults weighing over 50kg for the on-going treatment of hypotensive emergencies with escalating noradrenaline dose requirements.

It should not be used for initiating vasopressor treatment. It may be considered for use in patients already established on noradrenaline therapy whose dose requirements are clinically confirmed to be escalating, such that Noradrenaline 0.08 mg/ml solution for infusion may be commenced at a flow rate of 2 ml/hour.

Blood pressure should be monitored carefully for the duration of therapy and preferably controlled by arterial blood pressure monitoring.

Noradrenaline should only be administered as an intravenous infusion via a central venous catheter to minimize the risk of extravasation and subsequent tissue necrosis. Noradrenaline 0.08 mg/ml solution for infusion should be infused at a controlled rate using a syringe driver pump.

Noradrenaline 0.08 mg/ml solution for infusion is not approved for use in children.

Please read the enclosed Summary of Product Characteristics for full details.

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Call for reporting

Please report suspected adverse drug reactions including medication errors to the MHRA through the Yellow Card Scheme.

Please report:

- All suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.
- All suspected ADRs associated with new drugs and vaccines identified by the black triangle.

It is easiest and quickest to report ADRs online via the Yellow Cards website –

https://yellowcard.mhra.gov.uk/ .

Alternatively, prepaid Yellow Cards for reporting are available:

- By writing to FREEPOST YELLOW CARD (no other address details necessary)
- By emailing yellowcard@mhra.gsi.gov.uk
- At the back of the British National Formulary (BNF)
- By telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- Or by downloading and printing a form from the website https://yellowcard.mhra.gov.uk/

Adverse reactions should also be reported to Aguettant Ltd on 01275 463 691.

Company contact details

If you have any questions please contact Aguettant Ltd by phone on 01275 463 691 or via email at info@aguettant.co.uk .

Yours sincerely

Kind regards,

Alice DIDIER

Claire BROOMFIELD

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UK

SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

NORADRENALINE (NOREPINEPHRINE) 0.08 mg/ml, solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 0.16 mg Noradrenaline tartrate, equivalent to 0.08 mg Noradrenaline base. Each 50 ml vial contains 8 mg Noradrenaline tartrate, equivalent to 4 mg Noradrenaline base.

Excipients:

Each ml of solution for infusion contains 3.546 mg equivalent to 0.1542 mmol of sodium. Each 50 ml vial contains approximately 177.3 mg equivalent to 7.71 mmol of sodium. For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless or slightly yellow solution
pH = 3.2 – 3.8
Osmolality: 260 - 320 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Noradrenaline 0.08 mg/ml, solution for infusion is indicated in adults weighing over 50kg for the on-going treatment of hypotensive emergencies with escalating noradrenaline dose requirements.

4.2 Posology and method of administration

For intravenous use only.

Noradrenaline 0.08mg/ml solution for infusion should not be used for initiating vasopressor treatment. It may be considered for use in patients already established on noradrenaline therapy whose dose requirements are clinically confirmed to be escalating, such that Noradrenaline 0.08 mg/ml, solution for infusion may be commenced at a flow rate of 2 ml/hr.

Noradrenaline should only be administered as an intravenous infusion via a central venous catheter to minimize the risk of extravasation and subsequent tissue necrosis. Noradrenaline (Norepinephrine) 0.08 mg/ml, solution for infusion should be infused at a controlled rate using a syringe driver pump.

Noradrenaline (Norepinephrine) 0.08 mg/ml, solution for infusion should not be diluted before use: it is supplied ready to use. It should not be mixed with other medicines.

Blood pressure control:

Blood pressure should be monitored carefully for the duration of therapy, and preferably controlled by arterial blood pressure monitoring. The patient should be monitored carefully for the duration of noradrenaline therapy.

Posology

Initial dose:

The initial dose of noradrenaline base is usually between 0.05 and 0.15 micrograms/kg/min.

Maintenance dose range:

The recommended maintenance range of noradrenaline base is between 0.05 and 1.5 micrograms/kg/min.

Titration of dose:

Noradrenaline (Norepinephrine) 0.08 mg/ml, solution for infusion, should be used with a suitable syringe driver pump capable of accurately and consistently delivering the minimum specified volume at a strictly controlled rate of infusion in line with the dose titration instructions.

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

Manual bolus for priming when initiating an infusion is not recommended.

Caution is required during syringe relay to avoid haemodynamic instability. Continuous noradrenaline infusion through a double pump system and an extension set reducing dead-space volume should be encouraged.

Patient's Weight (kg)	Posology (µg/kg/min) noradrenaline base	Posology (mg/h) noradrenaline base	Infusion rate (ml/h)
50	0.05	0.15	1,9
	0.1	0.3	3,8
	0.25	0.75	9,4
	0.5	1.5	18,8
	1	3	37,5
	1.5	4.5	56,3
60	0.05	0.18	2,3
	0.1	0.36	4,5
	0.25	0.9	11,3
	0.5	1.8	22,5
	1	3.6	45,0
	1.5	5.4	67,5
70	0.05	0.21	2,6
	0.1	0.42	5,3
	0.25	1.05	13,1
	0.5	2.1	26,3
	1	4.2	52,5
	1.5	6.3	78,8

Patient's Weight (kg)	Posology (µg/kg/min) noradrenaline base	Posology (mg/h) noradrenaline base	Infusion rate (ml/h)
80	0.05	0.24	3,0
	0.1	0.48	6,0
	0.25	1.2	15,0
	0.5	2.4	30,0
	1	4.8	60,0
	1.5	7.2	90,0
90	0.05	0.27	3,4
	0.1	0.54	6,8
	0.25	1.35	16,9
	0.5	2.7	33,8
	1	5.4	67,5
	1.5	8.1	101,3
100	0.05	0.3	3,8
	0.1	0.6	7,5
	0.25	1.5	18,8
	0.5	3	37,5
	1	6	75,0
	1.5	9	112,5

Duration of Treatment:

Noradrenaline 0.08mg/ml, solution for infusion should be continued until high-dose vasoactive drug support is no longer indicated, at which point, the infusion should be gradually decreased, then switched to an infusion of lower concentration. Abrupt withdrawal can result in acute hypotension.

Elderly patients

See section 4.4 Special warnings and precautions for use.

Paediatric population

Noradrenaline 0.08 mg/ml, solution for infusion is indicated for adults only.

The efficacy and safety of Noradrenaline 0.08mg/ml, solution for infusion in children and adolescents has not been established.

Patients with renal and hepatic impairment

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

4.3 Contraindications

Administration via peripheral cannula and/or peripheral vein.

Hypersensitivity to noradrenaline or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Warning:

Noradrenaline is contraindicated in hypotensive patients in whom circulatory collapse is associated with hypovolaemia except as an emergency measure to maintain supply to the coronary and cerebral arteries until blood volume replacement therapy can be instituted.

Noradrenaline solution is intended for infusion via a central venous catheter only. As such, the risk of extravasation and subsequent tissue necrosis is very limited. The infusion site should be checked frequently. However, if extravasation occurs, the infusion should be stopped immediately and the area should be infiltrated with phentolamine without delay, monitored closely for improvement and re-assessed for further treatment to reverse the ischemic effect.

Precautions for use:

Noradrenaline 0.08 mg/ml, solution for infusion should not be used for initiating vasopressor treatment.

In general, cautious evaluation is recommended in the following cases of hypotension and hypoperfusion, in which a reduction in the dose of noradrenaline may be required:

- Major left ventricular dysfunction associated with acute hypotension. 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.

- Hypotensive patients diagnosed with coronary, mesenteric or peripheral vascular thrombosis, myocardial infarction or Prinzmetal's variant angina. Particular caution should be observed as noradrenaline may increase the associated ischaemia and extend the area of infarction.

- Occurrence of heart rhythm disorders during noradrenaline therapy.

Caution is advised in patients with hyperthyroidism or diabetes mellitus.

In cases where it is necessary to administer Noradrenaline at the same time as total blood or plasma, the latter must be administered in a separate drip.

This medicinal product contains sodium. To be taken into consideration by patients on a controlled sodium diet, see section 2.

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, Linezolid and Methylene Blue : by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. Should only be used under close medical supervision.

4.6 Fertility, pregnancy and lactation

Pregnancy

Because of its indications, noradrenaline may be administered if necessary during pregnancy.

However, pharmacodynamics properties of the substance have to be considered. 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.

Lactation

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

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Psychiatric disorders: Anxiety.

Nervous system disorders: Headache, tremor.

Eyes disorders: Acute glaucoma (very frequent in patients anatomically predisposed with closing of the iridocorneal angle).

Cardiac disorders: Tachycardia, bradycardia (probably as a reflex result of blood pressure rising), arrhythmia, palpitations, increase in the contractility of the cardiac muscle resulting from the ß adrenergic effect on the heart (inotrope and chronotrope), acute cardiac insufficiency.

Vascular disorders: Arterial hypertension and tissue hypoxia; ischemic injury due to potent vasoconstrictor action (may result in coldness and paleness of the members limbs and the face).

Respiratory, thoracic and mediastinal disorders: Respiratory insufficiency or difficulty, dyspnea.

Gastrointestinal disorders: Vomiting.

Renal and urinary disorders: Retention of urine.

General disorders and administration site conditions: Locally: possibility of irritation and necrosis at the injection site.

The continuous administration of vasopressor to maintain blood pressure in the 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.

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.

4.9 Overdose

In the event of overdose, the following may be observed: cutaneous vasoconstriction, bed sores, circulatory collapse, and 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 agents, ATC code: C01CA03

Noradrenaline provides a strong stimulation of alpha receptors in blood vessels at which these are counter- extracted. Noradrenaline also has an effect on beta-1 receptors in the heart leading to a positive inotropic and initially positive chronotropic effect. The increase in blood pressure may cause a reflex reduction in heart rate. Vasoconstriction may lead to decreased blood flow in the kidneys, liver, skin and smooth muscle. Local constriction of the vessels may cause hemostasis and/or necrosis.

The pressor effect disappears 1-2 min after termination of infusion. Development of tolerance to the effects of noradrenaline may occur.

5.2 Pharmacokinetic properties

Two stereoisomers of noradrenaline exist, the biologically active L-isomer is the one present in Noradrenaline 0.08 mg/ml, 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 undesirable effects can be derived from sympathomimetic results from excessive stimulation of the sympathetic nervous system through the various adrenergic receptors.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Disodium edetate dihydrate

Hydrochloric acid or Sodium hydroxide (pH adjustment)

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months.

After the first opening, the product should be used immediately.

6.4 Special precautions for storage

Do not store above 25° C. Store the vial in the outer carton to protect from light.

6.5 Nature and contents of container

Clear glass vial closed with a type I bromobutyl stopper and an aluminum cap containing 50 ml of solution for infusion in pack size of 1, 10, and 25 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused contents.

Noradrenaline 0.08 mg/ml, solution for infusion is already diluted and ready to use. It should be used without prior dilution .It should be used with a suitable syringe driver pump capable of accurately and consistently delivering the minimum specified volume at a strictly controlled rate of infusion in line with the dose titration instructions specified in Section 4.2. This medicine should not be used if the solution is darker than slightly yellow or pink in colour or if it contains a precipitate.

The sterile solution should not be used if it is not clear and contains particles, or if the tamper evident sealed vial is not intact.

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

69007 LYON

FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

PL 14434/0029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 June 2015

10. DATE OF REVISION OF THE TEXT

06/2015

AGUETTANT

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