107882

AGUETTANT Noradrenaline 1 mg/ml, concentrate for solution for infusion

AGUETTANT

1. PRODUCT NAME

AGUETTANT Noradrenaline 1 mg/ml, concentrate for solution for infusion

2. NAME AND STRENGTH OF ACTIVE SUBSTANCE

Noradrenaline tartrate..... 2 mg
(corresponding to Noradrenaline base .....1 mg)

For 1 ml of concentrate for solution for infusion

i.e. 4 mg noradrenaline base (equivalent to 8 mg noradrenaline tartrate) for one 4 ml ampoule.

Excipients: Sodium chloride, hydrochloric acid or sodium hydroxide (qs pH 3.0 to 4.0), water for injection.

Excipient with known effect: sodium.

Each ml of solution contains 3.3 mg of sodium, equivalent to 0.14 mmol.

Each 4ml ampoule contains 13.2 mg of sodium, equivalent to 0.57 mmol.

3. PRODUCT DESCRIPTION

4 ml in a 5 ml clear glass ampoule.

Clear, colourless or slightly yellowish solution.

4. PHARMACODYNAMICS / PHARMACOKINETICS

Pharmacodynamic properties

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. AGUETTANT Noradrenaline 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.

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 monoamine oxidase (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. INDICATION

For blood pressure control in certain acute hypotensive states (e.g. pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion and drug interactions).

As an adjunct in the treatment of cardiac arrest and profound hypotension.

6. RECOMMENDED DOSAGE

AGUETTANT Noradrenaline 1 mg/ml contains noradrenaline as the tartrate. It is a concentrated, potent drug which must be diluted prior to infusion. An infusion of noradrenaline should be given into a large vein (see Warnings and Precautions).

Restoration of Blood Pressure in Acute Hypotensive States: Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intra-aortic pressures must be maintained to prevent cerebral or coronary artery ischaemia, noradrenaline can be administered before and concurrently with blood volume replacement.

Diluent: AGUETTANT Noradrenaline 1 mg/ml should be diluted in glucose 5%, sodium chloride 0.9% or glucose 5% in sodium chloride 0.9%. Whole blood or plasma, if indicated to increase blood volume, should be administered separately (for example, by use of a Y-tube and individual containers if given simultaneously).

Average dosage: Add an ampoule (4mL) of AGUETTANT Noradrenaline 1 mg/ml (4 mg of noradrenaline base) to 1,000 ml of diluent. Each mL of this dilution contains 4 µg of the base of noradrenaline (or 8 µg of the tartrate). Give this solution by intravenous infusion. Insert a plastic intravenous catheter through a suitable bore needle well-advanced centrally into the vein and securely fixed with adhesive tape, avoiding if possible, a catheter tie-in technique as this promotes stasis. An I.V. drip chamber or other suitable metering device is essential to permit an accurate estimation of the rate of flow in drops per minute.

After observing the response to an initial dose of 2 mL to 3 mL (from 8 µg to 12 µg of base) per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 mmHg to 100 mmHg systolic) sufficient to maintain the circulation to vital organs. In previously hypertensive patients, it is recommended that the blood pressure should be raised no higher than 40 mmHg below the pre-existing systolic pressure. The average maintenance dose ranges from 0.5 mL to 1 mL per minute (from 2 µg to 4 µg of base).

High Dosage: Great individual variation occurs in the dose required to obtain and maintain an adequate blood pressure. In all cases, dosage of noradrenaline should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg base or 17 ampoules) may be necessary if the patient remains hypotensive, but occult blood volume depletion should always be suspected and corrected when present. Central venous pressure monitoring is usually helpful in detecting and treating this situation.

Fluid intake: The degree of dilution depends on clinical fluid volume requirements. If large volumes of fluid (dextrose) are needed at a flow rate that would involve an excessive dose of the pressor agent per unit of time, a solution more dilute than 4 µg per mL should be used. On the other hand, when large volumes of fluid are clinically undesirable, a concentration greater than 4 µg per mL may be necessary.

Duration of Therapy: The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. Infusions of noradrenaline should be reduced gradually, avoiding abrupt withdrawal. In some of the reported cases of vascular collapse due to acute myocardial infarction, treatment was required for up to six days.

Adjunctive Treatment in Cardiac Arrest: Infusions of noradrenaline are usually administered intravenously during cardiac resuscitation to restore and maintain an adequate blood pressure after an effective heartbeat and ventilation have been established by other means. [Noradrenaline's powerful beta-adrenergic stimulating action is also thought to increase the strength and effectiveness of systolic contractions once they occur.]

Average Dosage: To maintain systemic blood pressure during the management of cardiac arrest, noradrenaline is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

7. ROUTE OF ADMINISTRATION

For intravenous infusion, after dilution.

8. CONTRAINDICATIONS

Use of AGUETTANT 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.

9. WARNINGS AND PRECAUTIONS

AGUETTANT Noradrenaline should only be administered by healthcare professionals who are familiar with its 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 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 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

AGUETTANT
MÉDICAMENTS
ESSENTIELS

N° projet : 24_275_01

Code : 107882	VERSION	COULEURS
PRODUIT : NOT ABT NORADRENALINE 1 mg/ml **PAYS :** MALAISIE (MY)	**INITIALES :** EC- PICTURAL MM **VERSIONS - DATE :** 1 - 01/08/24 - 11h30	**NOIR**
TRACÉ : GER ABT NOT A4 PORTRAIT 01		COULEURS TECHNIQUES
Dimensions : mm = 210 x 297 **Texte : corps =** 8,5 pts	**ANNULE ET REMPLACE :** N/A	**DECOUPE**

Signataire **MKT**	Signataire **AR**	Signataire **DI**
NOM COMPLET : ILYES HANNANE **DATE +** **SIGNATURE :**	**NOM COMPLET :** CÉLINE RIGAUDEAU **DATE +** **SIGNATURE :**	**NOM COMPLET :** ANAÏS JARTIN **DATE +** **SIGNATURE :**

as possible with 10 to 15ml of physiological salt solution containing 5 to 10 mg of phentolamine mesylate. 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 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.

10. INTERACTIONS WITH OTHER MEDICAMENTS

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.

11. STATEMENT ON USAGE DURING 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.

12. ADVERSE EFFECTS / 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 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 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.

13. OVERDOSE AND TREATMENT

Overdosage may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. These may be accompanied by violent headache, photophobia, retrosternal pain, pallor, intense sweating and vomiting. In the event of overdosage, treatment should be withdrawn and appropriate corrective treatment initiated.

14. INCOMPATIBILITIES

AGUETTANT Noradrenaline 1 mg/ml must not be mixed with other medicinal products except those mentioned in "6. Recommended Dosage".

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

15. STORAGE CONDITIONS

Shelf-life: 24 months.

Before dilution: Do not store above 25°C. Store in the original packaging, protected from light.

After dilution: Dilute 1 ampoule of 4 ml in 1,000 ml of glucose 5%, sodium chloride 0.9% or glucose 5% in sodium chloride 0.9% to obtain a solution with a final concentration of 4 µg/ml of noradrenaline base (or 8 µg/ml of noradrenaline tartrate). This solution should be clear, free of particles or precipitate. The physicochemical stability of diluted product 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 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.

Special precautions for disposal and other handling

- Dilute in glucose 5%, sodium chloride 0.9% or glucose 5% in sodium chloride 0.9%.
- 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 colour 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.

16. DOSAGE FORM AND PACKAGING AVAILABLE

Concentrate for solution for infusion.

4 ml in a 5 ml clear glass ampoule: box of 10.

17. MANUFACTURER AND PRODUCT REGISTRATION HOLDER

Manufacturer:

LABORATOIRE AGUETTANT
1 rue Alexander Fleming
69007 LYON
France

Product Registration Holder:

FIRST PHARMACEUTICAL SDN BHD
20, Jalan SS 19/5
47500 Subang Jaya
Selangor
Malaysia

18. DATE OF REVISION OF PACKAGE INSERT

August 2024.