

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Noradrenaline (Norepinephrine) 0.1 mg/ml Solution for Infusion in pre-filled syringe.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 0.2mg Noradrenaline Tartrate, equivalent to 0.1mg Noradrenaline. Each 50ml syringe contains 10mg Noradrenaline Tartrate equivalent to 5mg Noradrenaline.

For a full list of excipients see section 6.1

This medicinal product contains approximately 7.4mMol (170mg) Sodium per 50ml syringe. To be taken into consideration by patients on a controlled sodium diet.

This medicinal product contains 12.5mg sodium metabisulphite per 50ml syringe. May rarely cause severe hypersensitivity reaction and bronchospasm.

## 3 PHARMACEUTICAL FORM

Solution for Infusion in pre-filled syringe.

A 50ml pre-filled syringe containing a clear, colourless solution

The pH of the solution is 3.0 – 4.6 and the osmolality is 270-330 mOsmol/kg.

## 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

#### *Route of Administration:*

For intravenous use only.

Noradrenaline should only be administered as an infusion at a controlled rate by a syringe pump. Noradrenaline should not be diluted before use; it is supplied ready for use.

#### Site of injection:

Noradrenaline is used by intravenous infusion only. Infusions of noradrenaline should be given into a large vein via a central venous catheter.

#### 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 flow rate must be controlled constantly, and the patient should never be left unattended during infusion.

#### Initial Rate of Infusion

The initial rate of infusion, at a body weight of 70 kg should be between 4ml/hour and 8ml/hour however some clinicians may wish to start at lower initial infusion rates of 2ml/hour. These initial rates are approximately equal to a dosage of 0.05microgram/kg/min to 0.15microgram/kg/ml. This is equivalent to the following dosage:

Rate	Equivalent Noradrenaline Base / hr	Equivalent Noradrenaline Tartrate / hr	Equivalent Rate / min	Equivalent Noradrenaline Base / min
4ml/hr	0.4 mg/hr	0.8 mg/hr	0.066 ml/min	6.67 µg/min
8ml/hr	0.8 mg/hr	1.6 mg/hr	0.133 ml/min	13.33 µg/min

Initial dosing instruction: Noradrenaline 0.1 mg/ml

	Infusion rate ml/hour								
Body weight	40 kg	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg	110 kg	120 kg
Dose									
0,05 ug/kg/min	1.2	1.5	1.8	2.1	2.4	2.7	3.0	3.3	3.6
0,10 ug/kg/min	2.4	3.0	3.6	4.2	4.8	5.4	6.0	6.6	7.2
0,15 ug/kg/min	3.6	4.5	5.4	6.3	7.2	8.1	9.0	9.9	10.8

Titration of Dose

Once an infusion of Noradrenaline has been established the dose should be titrated in steps of 0.05 – 0.1microgram/kg/min 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 mmHg) or to achieve an adequate mean arterial blood pressure (greater than 65 to 80 mm Hg- depending on the patient’s condition).

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 due to insufficient data on safety and efficacy.

**4.3 Contraindications**

Hypersensitivity to noradrenaline, or any of the excipients (see section 6.1 for details).

Hypotension due to volume deficit.

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, noradrenaline 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

### Extravasation risk:

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation that should 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 can 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 of an injection beside 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 saline 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.

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.

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.

Noradrenaline should be used only in conjunction with the appropriate blood volume replacement.

When infusing noradrenaline, the blood pressure and rate of flow should be checked frequently to avoid hypertension.

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 (see section 4.8).

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 should be used with caution in patients receiving these or any other cardiac sensitising agent or who exhibit profound hypoxia or hypercarbia (see section 4.5)

Noradrenaline should be used with extreme caution in patients receiving monoamine oxidase inhibitors or within 14 days of cessation of such therapy and in patients receiving tricyclic antidepressants because severe, prolonged hypertension may result.

Noradrenaline should only be used by doctors familiar with the selective indications for its use. Where indicated, appropriate replacement therapy of blood or fluid together with adoption of the supine position with elevation of the legs, must be instituted and maintained prior to and/or during therapy with this product. When infusing the blood pressure and rate of flow should be checked frequently to avoid hypertension.

The infusion of Noradrenaline should be stopped gradually as sudden cessation may produce a catastrophic fall in blood pressure

Caution is advised in patients with hyperthyroidism or diabetes mellitus.

The infusion of Noradrenaline should be stopped gradually as sudden cessation may produce a disastrous fall in blood pressure

Each ml of solution contains approximately 0.148 mmol (3.4 mg) of Sodium, 7.4 mmol sodium per 50ml. This may need to be taken into consideration if the patient is on a sodium controlled diet.

The elderly may be especially sensitive to the effects of noradrenaline.

The product contains Sodium Metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

## 4.5 Interaction with other medicinal products and other forms of interaction

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 should be used with caution in patients receiving these or any other cardiac sensitising agent or who exhibit profound hypoxia or hypercarbia (see section 4.4).

Noradrenaline should be used with extreme caution in patients receiving monoamine oxidase inhibitors or within 14 days of cessation of such therapy and in patients receiving tricyclic antidepressants because severe, prolonged hypertension may result.

The effects of Noradrenaline may be enhanced by guanethidine, reserpine, methyldopa or tricyclic antidepressants.

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

Caution is required when using Noradrenaline with alpha and beta blockers as severe hypertension may result. The administration of a  $\beta$ -blocking agent (propranolol) can result in a reduction of the stimulating effect of the product on the heart (coming from a  $\beta_1$  adrenergic action, that is to say cardiac arrhythmias) and result in an increase of the hypertensive effect following the reduction of arteriolar dilatation to the intervention of the  $\beta$  receptor (see section 4.9).

Ergot alkaloids or oxytocin may enhance the vasoconstrictor 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 be weighed against the potential benefit to the mother.

### Lactation

No information is available on use of noradrenaline in lactation.

## 4.7 Effects on ability to drive and use machines

None stated.

## 4.8 Undesirable effects

- Vascular system: Arterial hypertension and tissue hypoxia: Ischemic injury due to potent vasoconstrictor action which can result in coldness and paleness on the members and the face.
- 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  $\beta$  adrenergic effect on the heart (inotrope + chronotrope), acute cardiac insufficiency.
- Central nervous system: anxiety, insomnia, confusion, cephalgia, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nausea and vomiting.
- Eyes: acute glaucoma: very frequent with the persons anatomically predisposed with the closing of the iridocorneal angle.
- Urinary system: retention of urine.
- Respiratory system: respiratory insufficiency or difficulty, dyspnoea.
- Locally: possibility of irritation and necrosis at the injection site.

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

- severe peripheral and visceral vasoconstriction (see section 4.4)
- decrease in renal blood output
- decrease in urine production
- insufficient level of oxygen in tissues

- increase of the lactic acid level in blood.

In case of hypersensitivity or overdosage, the following effects may appear more frequently : hypertension, photophobia, retrosternal pain, pharyngeal pain, pallor, intense sweating and vomiting (see section 4.9).

## 4.9 Overdose

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 (see section 4.8).

The vasopressor effect (resulting from an adrenergic action on the vessels, that is to say hypertension) can be reduced by the concomitant administration of an  $\alpha$ -blocking agent (phentolamine mesilate). Whereas the administration of a  $\beta$ -blocking agent (propranolol) can result in a reduction of the stimulating effect of the product on the heart (coming from a  $\beta_1$  adrenergic action, that is to say cardiac arrhythmias) and result in an increase of the hypertensive effect following the reduction of arteriolar dilatation to the intervention of the  $\beta$  receptor (see section 4.5).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

ATC Code: C01CA03

Mechanism of Action

The vascular effects of noradrenaline in the doses usually used clinically result from the simultaneous stimulation of alpha and beta adrenergic receptors in the heart and vascular system. Except in the heart, its action is predominantly on the alpha receptors. 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.

Pharmacodynamic Effects

Noradrenaline (NA) is a catecholamine sympathomimetic. It is an endogenous compound with a short duration of action and is the neurotransmitter for most sympathetic post ganglionic fibres. It is stored in granules in the nerve axons and is released with adrenaline from the adrenal medulla. Exogenous administration of NA results in an increase in total peripheral resistance due to vasoconstriction of skin and mucosal blood vessels. This causes a resultant increase in systolic and diastolic blood pressure. There is little change in cardiac output, although cardiac blood flow is generally increased as a result of coronary dilation. These cardiovascular changes are generally accompanied by a bradycardia that is the result of a compensatory mechanisms mediated by the carotid aortic baroreceptor system. Blood flow to the kidneys is reduced, as is hepatic and splanchnic flow. The latter most likely as a result of constriction of the mesenteric vasculature.

### 5.2 Pharmacokinetic properties

The pharmacokinetic behaviour of Noradrenaline has been studied in critically ill head injured patients.

Noradrenaline plasma clearance was found to be independent of infusion rate. Furthermore steady state plasma concentrations of Noradrenaline correlated with infusion rates. These observations suggest that Noradrenaline has linear pharmacokinetics over the dose range studied.

An observation in this study was the lack of a discernible relationship between Noradrenaline plasma concentrations and pharmacodynamic effects namely mean arterial pressure, cardiac index and systemic vascular resistance.

Following intravenous administration Noradrenaline is rapidly inactivated, particularly in the liver which is abundant in the enzymes responsible for its metabolism namely monamine oxidase (MAO) and catechol-O-methyl transferase (COMT).

A small amount of Noradrenaline is excreted unchanged in the urine, in addition to the methylated and deaminated metabolites in free and conjugated forms.

In patients with phaeochromocytoma the excretion rate may be markedly increased.

### 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 Metabisulphite (E223)

Disodium Edetate (E386)

Sodium Chloride

Water for Injections

Hydrochloric Acid (pH adjuster)

Sodium Hydroxide (pH adjuster)

### 6.2 Incompatibilities

Solutions containing Noradrenaline Tartrate have been reported to be incompatible with the following: Alkalis and oxidising agents, barbituates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium, iodide, streptomycin.

### 6.3 Shelf life

6 Months (unopened)

Once opened the product should be used immediately.

### 6.4 Special precautions for storage

Store between 2-8°C Keep in the outer carton. Do not freeze.

Check the appearance before use. Do not use if the solution is discoloured or brown.

### 6.5 Nature and contents of container

Sterile 50ml COC plastic pre-filled syringe fitted with bromobutyl rubber tip cap and plunger. The syringe is supplied in a sealed pouch also containing a sachet of oxygen scavenger. The pouched syringes are supplied individually in cartons.

### 6.6 Special precautions for disposal

Any unused product should be discarded appropriately.

For single use only. Discard any unused contents.

The solution should not be used if it is brown in colour.

## **7 MARKETING AUTHORISATION HOLDER**

Martindale Pharmacueticals Ltd  
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Harold Hill  
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United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA 361/34/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 7th October 2011

## **10 DATE OF REVISION OF THE TEXT**