



## Norepinephrine Tartrate Injection USP 4mg/2ml, 4mg/4ml

### 1. Name of the medicinal product

**Norepinephrine Tartrate Injection USP  
4mg/2ml Taj Pharma**

Norepinephrine Tartrate Injection USP 4mg/4ml  
Taj Pharma

### 2. Qualitative and quantitative composition

**a)Norepinephrine Tartrate Injection USP  
4mg/2ml**

**Each ml of Contains:**

**Norepinephrine tartrate, equivalent to  
Norepinephrine base** 2mg  
**Sodium metabisulfide** 2mg  
**Sodium Chloride** q.s

**b)Norepinephrine Tartrate Injection USP  
4mg/4ml**

**Each ml of Contains:**

**Norepinephrine tartrate, equivalent to  
Norepinephrine base** 1mg  
**Sodium metabisulfide** 2mg  
**Sodium Chloride** q.s

For full list of excipients, see section 6.1.

### 3. Pharmaceutical form

Concentrate for solution for infusion

Clear, colourless liquid

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The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure.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

+ **Serotonergic-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.

- **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 and chronotrope), acute cardiac insufficiency, stress cardiomyopathy.

- **Central nervous system:** anxiety, insomnia, confusion, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nausea 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  $\alpha$ -blocking agent (phentolamine mesilate) whereas the administration of a  $\beta$ -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  $\beta_1$  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.

#### 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, (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 monoamine 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

### **6.4 Special precautions for storage**

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 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.

### **6.5 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 “Posology and method of administration”.

- Do not use an opened ampoule.

- Do not use if you notice any type of coloration

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

**7.Manufactured in India by:**

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