NOREPINEPHRINE BITARTRATE
INJECTION USP
4MG/2ML
TAJ PHARMA

1. NAME OF THE MEDICINAL PRODUCT

Norepinephrine Bitartrate Injection USP 4mg/2ml Taj Pharma

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ampoule of 2 ml contains:

Norepinephrine bitartrate equivalent to

Norepinephrine…….....4mg

when diluted as recommended, each ml contains 80 micrograms Norepinephrine bitartrate equivalent to 40 micrograms Norepinephrine base.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion
A clear colourless or yellowish solution
pH: 3.0 – 4.0
Osmolarity: approximately 280 mOsm/l

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for use as an emergency measure in the restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration

Adults:

Initial rate of infusion:

When diluted as recommended in section 6.6 (the concentration of the prepared infusion is 40 mg/litre Norepinephrine base (80 mg/litre Norepinephrine bitartrate) the initial rate of infusion, at a body weight of 70 kg, should be between 10 ml/hour and 20 ml/hour (0.16 to 0.33 ml/min). This is equivalent to 0.4 mg/hour to 0.8 mg/hour Norepinephrine base (0.8 mg/hour to 1.6 mg/hour Norepinephrine bitartrate). Some clinicians may wish to start at a lower initial infusion rate of 5 ml/hour (0.08 ml/min), equivalent to 0.2 mg/hour Norepinephrine base (0.4 mg/hour Norepinephrine bitartrate).

Titration of dose:

Once an infusion of Norepinephrine has been established the dose should be titrated in steps of 0.05 -0.1 µg/kg/min of Norepinephrine 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 - 80 mm Hg – depending on the patient's condition).

Norepinephrine Infusion Solution 40 mg/litre (40 µg /ml) Norepinephrine base			
Patient's Weight	Posology (µg/kg/min) Norepinephrine base	Posology (mg/hour) Norepinephrine base	Infusion Rate (ml/hour)

50 kg	0.05	0.15	3.75
	0.1	0.3	7.5
	0.25	0.75	18.75
	0.5	1.5	37.5
	1	3	75
60 kg	0.05	0.18	4.5
	0.1	0.36	9
	0.25	0.9	22.5
	0.5	1.8	45
	1	3.6	90
70 kg	0.05	0.21	5.25
	0.1	0.42	10.5
	0.25	1.05	26.25
	0.5	2.1	52.5
	1	4.2	105
80 kg	0.05	0.24	6
	0.1	0.48	12
	0.25	1.2	30
	0.5	2.4	60
	1	4.8	120
90 kg	0.05	0.27	6.75
	0.1	0.54	13.5
	0.25	1.35	33.75
	0.5	2.7	67.5
	1	5.4	135

Some clinicians may prefer to dilute to other concentrations. If dilutions other than 40 mg/l are used, check the infusion rate calculation carefully before starting treatment.

Renal or hepatic impairment:

There is no experience in treatment of renally or hepatically impaired patients

Elderly:
As for adults but see section 4.4.

Paediatric population

Not recommended.

Duration of Treatment and Monitoring:

Norepinephrine should be continued for as long as vasoactive drug support is indicated. The patient should be monitored carefully for the duration of therapy. Blood pressure should be carefully monitored for the duration of therapy.

Withdrawal of Therapy:

The Norepinephrine infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

Route of Administration:

For intravenous use.

Method of administration:

Administer as a diluted solution via a central venous catheter.
The infusion should be at a controlled rate using either a syringe pump or an infusion pump or a drip counter.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to Norepinephrine bitartrate or to any of the excipients listed in section 6.1.

4.4 Special Warnings and precautions for use

Norepinephrine should only be administered by healthcare professionals who are familiar with its use.

Elderly patients may be especially sensitive to the effects of Norepinephrine.

Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because Norepinephrine may increase the ischemia and extend the area of infarction. Similar caution should be observed in patients with hypotension following myocardial infarction, in patients with Prinzmetal's variant angina and in patients with diabetes, hypertension or hyperthyroidism.

Norepinephrine should be used with caution in patients who exhibit profound hypoxia or hypercarbia.

Norepinephrine should be used only in conjunction with appropriate blood volume replacement. When infusing Norepinephrine, the blood pressure and rate of flow should be checked frequently to avoid hypertension.

Extravasation of the solution may cause local tissue necrosis. The infusion site should be checked frequently. If extravasation occurs, the infusion should be stopped and the area should be infiltrated with phentolamine without delay.

Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when the infusion is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (e.g., decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischaemic injury.

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

The use of Norepinephrine with volatile halogenated anaesthetic agents, monoamine oxidase inhibitors, linezolid, tricyclic antidepressants, adrenergic-serotoninergic drugs or any other cardiac sensitising agents is not recommended because severe, prolonged hypertension and possible arrhythmias may result.

4.6 Fertility, Pregnancy and lactation

Pregnancy

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. 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 Norepinephrine in lactation.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable Effects

System Organ Class	Undesirable effect
Psychiatric disorders	Anxiety
Nervous system disorders	Headache
Cardiac disorders	Arrhythmias (when used in conjunction with cardiac sensitising agents), bradycardia, stress cardiomyopathy
Vascular disorders	Hypertension, peripheral ischaemia including gangrene of the extremities, plasma volume depletion with prolonged use
Respiratory, thoracic and mediastinal disorders	Dyspnoea
General disorders and administration site conditions	Extravasation necrosis at injection site

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents

The vascular effects in the doses normally 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.

The increase in blood pressure may cause a reflex decrease in heart rate. Vasoconstriction may result in decreased blood flow in kidneys, liver, skin and smooth muscles. Local vasoconstriction may cause haemostasis and/or necrosis**.**

The effect on blood pressure disappears 1-2 minutes after stopping the infusion.

5.2 Pharmacokinetic properties

Up to 16% of an intravenous dose is excreted unchanged in the urine with methylated and deaminated metabolites in free and conjugated forms.

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 uterus and lead to fetal asphyxia in late pregnancy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment), Water for Injections

6.2 Incompatibilities

Norepinephrine must not be mixed with other medicinal products except those mentioned in section 6.6.

Infusion solutions containing Norepinephrine bitartrate 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.

For compatibility with infusion bags see section 6.6.

6.3 Shelf life

18 months.

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when diluted to 4 mg/litre and 40 mg/litre Norepinephrine base in sodium chloride 9 mg/ml (0.9%) solution or glucose 5% solution. However, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

Do not store above 25°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ampoules containing 2 ml of concentrate.

Pack size of 5 ampoules.

6.6 Special precautions for disposal and other handling

Dilution instructions:

Dilute before use with glucose 5% solution or sodium chloride 9 mg/ml (0.9%) with glucose 5 % solution.

Either add 2 ml concentrate to 48 ml glucose 5% solution (or sodium chloride 9 mg/ml (0.9%) with glucose 5% solution) for administration by syringe pump, or add 20 ml of concentrate to 480 ml glucose 5 % solution (or sodium chloride 9 mg/ml (0.9%) with glucose 5% solution) for administration by drip counter. In both cases the final concentration of the infusion solution is 40 mg/litre Norepinephrine base (which is equivalent to 80 mg/litre Norepinephrine bitartrate). Dilutions other than 40 mg/litre Norepinephrine base may also be used (see

section 4.2). If dilutions other than 40 mg/litre Norepinephrine base are used, check the infusion rate calculation carefully before starting treatment.

The product is compatible with PVC infusion bags.

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

7. MANUFACTURED IN INDIA BY:

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