

NOREPINEPHRINE



LEVOPHED[®] SF (Sulfite-Free)
1 mg/mL Concentrate for Solution for IV Infusion

1.0 PHARMACOLOGIC CATEGORY

Adrenergic and Dopaminergic Agent

2.0 DESCRIPTION

Norepinephrine (LEVOPHED[®] SF) is a sterile concentrated solution for injection with a clear, colorless or yellowish solution. It has two volumes: 2 mL and 4 mL filled in 2 mL and 5 mL glass ampoules respectively.

3.0 FORMULATION/COMPOSITION

1 mL concentrate for solution for infusion contains 2 mg noradrenaline tartrate equivalent to 1 mg noradrenaline base.

1 ampoule of 2 mL contains 4 mg noradrenaline tartrate equivalent to 2 mg noradrenaline base.

1 ampoule of 4 mL contains 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base.

When diluted as recommended, each mL contains 80 micrograms noradrenaline tartrate equivalent to 40 micrograms noradrenaline base.

Each ampoule also contains the excipients sodium chloride for tonicity and water for injections as diluent. Sodium hydroxide and/or Hydrochloric acid may be used for pH adjustment with pH ranging between 3.0 and 4.0.

4.0 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 Dosage and Method of Administration

Posology

Adults

Initial rate of infusion:

When diluted as recommended in section 6.4 **Special Precautions for Disposal and Other Handling** (the concentration of the prepared infusion is 40 mg/liter noradrenaline base (80

mg/liter noradrenaline tartrate)) 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 noradrenaline base (0.8 mg/hour to 1.6 mg/hour noradrenaline tartrate). 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 noradrenaline base (0.4 mg/hour noradrenaline tartrate).

Titration of dose:

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

Noradrenaline Infusion Solution 40 mg/liter (40 µg/mL) noradrenaline base			
Patient’s Weight	Posology (µg/kg/min) noradrenaline base	Posology (mg/hour) noradrenaline 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 Special Warnings and Precautions for Use.**

Pediatric population:
Not recommended.

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 therapy. Blood pressure should be carefully monitored for the duration of therapy.

Withdrawal of Therapy:

The noradrenaline 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 **6.4 Special Precautions for Disposal and Other Handling**.

4.3 Contraindications

Hypersensitivity to noradrenaline tartrate or to any of the excipients listed in section **3.0 FORMULATION/COMPOSITION**.

4.4 Special Warnings and Precautions for Use

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

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

Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline 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.

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

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.

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 ischemic injury.

Excipient with known effects

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

This medicinal product may be diluted with sodium containing solutions (see sections **4.2 Dosage and Method of Administration** and **6.4 Special Precautions for Disposal and Other Handling**) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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

The effects of noradrenaline may be enhanced by guanethidine.

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

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 sensitizing agents), bradycardia, stress cardiomyopathy
Vascular disorders	Hypertension, peripheral ischemia including gangrene of the extremities, plasma volume depletion with prolonged use
Respiratory, thoracic and mediastinal disorders	Dyspnea
General disorders and administration site conditions	Extravasation necrosis at injection site

4.9 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, pulmonary edema, photophobia, retrosternal pain, pallor, intense sweating and vomiting. In the event of overdosage, treatment should be withdrawn and appropriate corrective treatment initiated.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC code: C01CA03

Noradrenaline exists as 2 enantiomers where the L-form is the active isomer and the D-form is the inactive isomer (see **section 6.1 Shelf-Life**).

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 hemostasis 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.

Noradrenaline 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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

Please see outer package for the expiry date.

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when diluted to 4 mg/L and 40 mg/L noradrenaline 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.

Conversion of the L-isomer to the D-isomer can occur during the shelf life of the product, resulting in a decrease of the biologically active L isomer (see **section 5.1 Pharmacodynamic Properties**).

6.2 Storage Conditions

Store at temperatures not exceeding 25°C.

For storage conditions after dilution of the medicinal product (see section **6.1 Shelf-Life**).

6.3 Availability

Colorless Type I Glass Ampoule in Box of 1 Blister Tray x 5's [2 mL ampoule (w/2 mL filled volume)]

Colorless Type I Glass Ampoule in Box of 1 Blister Tray x 5's [5 mL ampoule (w/4 mL filled volume)]

6.4 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/L noradrenaline base (which is equivalent to 80 mg/liter noradrenaline tartrate). Dilutions other than 40 mg/L noradrenaline base may also be used (see *Titration of dose*). If dilutions other than 40 mg/L noradrenaline 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.

6.5 Incompatibilities

Noradrenaline must not be mixed with other medicinal products except those mentioned in section **6.4 Special Precautions for Disposal and Other Handling**.

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

For compatibility with infusion bags see section **6.4 Special Precautions for Disposal and Other Handling**.

7.0 FDA REGISTRATION NUMBER

Levophed SF (Sulfite-Free) 1 mg/mL Concentrate for Solution for IV Infusion: DR-XY38195

8.0 DATE OF FIRST AUTHORIZATION

Levophed SF (Sulfite-Free) 1 mg/mL Concentrate for Solution for IV Infusion: 07-July-2010

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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Revision No.: 2.1
Revision Date: 11 Jan 2023
Reference: UK SPC/MAH and
manufacturer address update
Reference Date: 29 Oct 2020