Levophed SF
Concentrate for Solution for Infusion 1 mg/mL
NOREPINEPHRINE IS EQUIVALENT TO NORADRENALINE

1 NAME OF THE MEDICINE
Levophed SF Concentrate for Solution for Infusion 1 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ampoule contains noradrenaline (norepinephrine) 4 mg in 4 mL (1:1000), present as 8 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 4 mL.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
Levophed SF is a sterile, clear colourless, concentrated solution for infusion.

Levophed SF has a pH of 3.0 to 4.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the restoration of blood pressure in certain acute hypotensive states (e.g., phaeochromocytomectomy, sympathectomy, poliomyelitis, spinal anaesthesia, myocardial infarction, septicaemia, blood transfusion and drug reactions). As an adjunct in the treatment of cardiac arrest. To restore and maintain an adequate blood pressure after an effective heartbeat and ventilation have been established by other means.

4.2 Dose and method of administration

Dosage

Add 4 mL of the 1:1000 solution of Levophed SF to 1 L of 5% glucose solution. Each 1 mL of this dilution contains 4 micrograms of norepinephrine (=8 microgram of the acid tartrate monohydrate). Give this dilution intravenously via a catheter well advanced centrally into the vein and securely fixed, if possible, avoiding a catheter tie-in technique as it promotes stasis. A drip bulb is necessary to permit an accurate estimation of the rate of flow in drops per minute. After observing the response to an initial dose of 2 to 3 mL (8 to 12 micrograms of base) per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 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 mm Hg below the pre-existing systolic pressure. The average

maintenance dose ranges from 0.5 to 1 mL per minute (2 to 4 microgram of base). Occasionally much larger daily doses (as high as 68 mg base or 34 ampoules) may be necessary if the patient remains hypotensive, but occult blood volume depletion should always be suspected and corrected when present. Dilution can be varied depending on the clinical fluid volume requirement.

Duration of therapy

The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. The infusion rate should then 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.

Method of administration

Levophed SF should be administered in 5% glucose solution in distilled water or 5% glucose in saline solution. Administration in saline solution alone is not recommended. Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

Levophed SF contains no antimicrobial preservative. It is for single use in one patient only. Discard any residue.

4.3 Contraindications

Levophed SF should not be given to patients who are hypotensive from hypovolaemia except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed. If Levophed SF is continuously administered to maintain blood pressure in the absence of blood volume replacement, the following may occur: severe peripheral and visceral vasoconstriction, decreased renal perfusion and urine output, poor systemic blood flow despite “normal” blood pressure, tissue hypoxia and lactate acidosis. Levophed SF should not be given to patients with mesenteric or peripheral vascular thrombosis (because of the risk of increasing ischaemia and extending the area of infarction) unless, in the opinion of the attending physician, the administration of Levophed SF is necessary as a lifesaving procedure. The use of Levophed SF during cyclopropane and halothane anaesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of Levophed SF in patients with profound hypoxia or hypercarbia.

4.4 Special warnings and precautions for use

Levophed SF should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types because severe, prolonged hypertension may result.

Avoid hypertension

Because of the potency and varying responses to Levophed SF, the possibility exists that hypertension may be produced with overdoses of this pressor agent. Hence it is desirable to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, and then every five minutes if

administration is to be continued. The rate of flow must be watched constantly, and the patient should not be left unattended whilst receiving Levophed SF. Headache may be a symptom of hypertension due to overdose.

Hypersensitivity

Certain patients may be hypersensitive to the effects of Levophed SF, e.g. hyperthyroidism patients (see Section 4.8 Adverse effects (undesirable effects)).

Site of infusion

Levophed SF should be given into a large vein, particularly an antecubital vein, because when administered into this vein, the risk of necrosis of the overlying skin from prolonged vasoconstriction is apparently very slight. The femoral vein is also an acceptable route of administration. A catheter tie in technique should be avoided if possible, since the obstruction to blood flow around the tubing may cause stasis and increased local concentration of noradrenaline (norepinephrine). As occlusive vascular diseases are more likely to occur in the lower rather than in the upper extremity, the leg veins in elderly patients or in those suffering from such disorders should be avoided.

Extravasation

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of Levophed SF into the tissues as local necrosis might ensue due to the vasoconstrictive action of the drug. Blanching along the course of the infused vein, sometimes without obvious extravasation, has been attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage. This may also progress on rare occasions to superficial slough, particularly during infusion into leg veins in elderly patients or in those suffering from obliterative vascular disease. Hence, if blanching occurs, consideration should be given to changing the infusion site at intervals to allow the effects of local vasoconstriction to subside. The antidote for extravasation ischaemia is phentolamine. To prevent sloughing and necrosis in areas in which extravasation has occurred, the area should be infiltrated as soon as possible with 10 mL to 15 mL of saline solution containing 5 mg to 10 mg of phentolamine. Using a syringe with a fine hypodermic needle, the solution is infiltrated liberally throughout the area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperaemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after extravasation is noted.

Use in the elderly

No data available.

Paediatric use

No data available.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Extreme caution should be exercised in patients receiving monoamine oxidase (MAO) inhibitors and antidepressants of the triptyline or imipramine types (see Section 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category B3

No data available.

Use in lactation

No data available.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

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 Levophed SF is discontinued, or blood pressure may be maintained at the risk of severe peripheral vasoconstriction with diminution in blood flow and tissue perfusion. Bradycardia sometimes occurs, probably as a reflex result of a rise in blood pressure. Overdoses or conventional doses in hypersensitive persons (e.g., hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating and vomiting.

The following reactions can occur:

Body as a Whole
Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.

Cardiovascular System
Bradycardia, probably as a reflex of a rise in blood pressure, arrhythmias and stress cardiomyopathy.

Nervous System
Anxiety, transient headache.

Respiratory System
Respiratory difficulty.

Skin and Appendages
Extravasation necrosis at injection site.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

4.9 Overdose

Overdosage with Levophed SF may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. Headache may indicate severe hypertension.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Noradrenaline (norepinephrine), a sympathomimetic amine, acts predominantly on α receptors and on β receptors in the heart. It therefore causes peripheral vasoconstriction (α-adrenergic action), and a positive inotropic effect on the heart and dilation of coronary arteries (β-adrenergic action). These actions result in an increase in systemic blood pressure and coronary artery blood flow. In myocardial infarction accompanied by hypotension, noradrenaline (norepinephrine) usually increases aortic blood pressure, coronary artery blood flow, and myocardial oxygenation, thereby helping to limit the area of myocardial ischaemia and infarction. Venous return is increased and the heart tends to resume a more normal rate and rhythm than in the hypotensive state. In hypotension that persists after correction of blood volume deficits, noradrenaline (norepinephrine) helps raise the blood pressure to an optimal level and establish a more adequate circulation.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

No data available.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections

6.2 Incompatibilities

Levophed SF should not be mixed with other medicines. Infusion solutions containing norepinephrine acid tartrate monohydrate have been reported to be incompatible with alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine and sulfafurazole.

6.3 Shelf life

Please refer to outer carton for expiry date.

6.4 Special precautions for storage

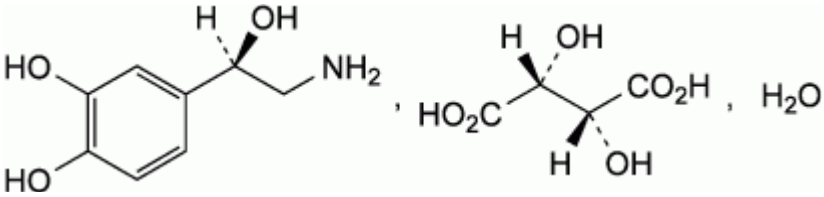
Please refer to outer carton for storage condition.

6.5 Nature and contents of container

Levophed SF is available as a single use ampoule, 4 mg/4 mL. It is supplied in packs of 5 ampoules per carton.

6.6 Physicochemical properties

Chemical structure



Chemical Name: (1R)-2-Amino-1-(3,4-dihydroxyphenyl) ethanol hydrogen (2R,3R)-2,3-dihydroxybutanedioate monohydrate

Molecular Formula: $C_{12}H_{17}NO_9$, H_2O

Molecular Weight: 337.3

Noradrenaline (norepinephrine) Acid Tartrate Monohydrate, is a white or almost white crystalline powder. It is freely soluble in water, and slightly soluble in ethanol (96%).

CAS Registry No.:

69815-49-2

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