AUSTRALIAN PRODUCT INFORMATION LEVOPHED™ 1:1000 (Noradrenaline (norepinephrine) as acid tartrate monohydrate)

1. NAME OF THE MEDICINE

Noradrenaline (norepinephrine) acid tartrate monohydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains noradrenaline (norepinephrine) 4 mg in 4 mL (1:1000), present as 8 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 4 mL.

Excipient(s) with known effect:

Sodium metabisulfite

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

3. PHARMACEUTICAL FORM

LEVOPHED™ 1:1000 is a sterile, clear colourless solution, concentrated solution for injection available in vials.

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

LEVOPHED™ 1:1000 is a concentrated solution for injection which must be diluted in glucose containing solutions prior to infusion. An infusion of LEVOPHED™ 1:1000 should be given into a large vein (see Section 4.4 Special warnings and precautions for use)

LEVOPHED™ 1:1000 must be administered in 5% glucose solution in distilled water or 5% glucose in saline solution, and must not be administered in saline solution alone. Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

This product contains no antimicrobial preservative, to reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2 to 8 °C for not more than 24 hours.

LEVOPHED™ 1:1000 is for single use in one patient only. Discard any residue. Discoloured solutions or those containing a precipitate should not be used. Avoid contact with iron salts, alkalis or oxidising agents.

Restoration of blood pressure in Acute Hypotensive States

Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischaemia, LEVOPHED™ 1:1000 can be administered before and concurrently with blood volume replacement.

Average Dosage

Add 2 mL of the 1:1000 solution of LEVOPHED™ 1:1000 to 500 mL, (or 4 mL LEVOPHED™ 1:1000 to 1 litre) of 5% glucose solution. Each 1 mL of this dilution contains 4 micrograms of noradrenaline (norepinephrine) (= 8 microgram of noradrenaline (norepinephrine) 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 mm Hg 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). Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of LEVOPHED™ 1:1000 should be titrated according to the response of the patient. Occasionally much larger daily doses (as high as 68 mg base or 17 vials) 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.

Adjunctive Treatment in Cardiac Arrest

Infusions of LEVOPHED™ 1:1000 are usually administered intravenously during cardiac resuscitation to restore and maintain an adequate blood pressure after an effective heartbeat and ventilation have been established by other means. LEVOPHED™ 1:1000's beta-adrenergic stimulating action is also thought to increase the strength and effectiveness of systolic contractions once they occur.

Average Dosage: To maintain systemic blood pressure during the management of cardiac arrest, LEVOPHED™ 1:1000 is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

Paediatric Use

Safety and effectiveness in paediatric patients has not been established.

Use in the elderly

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

LEVOPHED™ 1:1000 infusion solutions should not be administered into the veins in the leg in elderly patients.

4.3 Contraindications

LEVOPHED™ 1:1000 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™ 1:1000 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™ 1:1000 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™ 1:1000 is necessary as a lifesaving procedure. Ventricular tachycardia or fibrillation cardiac arrythmias may result from the use of noradrenaline (norepinephrine) in patients with profound hypoxia or hypercarbia.

Hypersensitivity to noradrenaline (norepinephrine) or any of the excipients.

4.4 Special warnings and precautions for use

LEVOPHED™ 1:1000 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. LEVOPHED™ 1:1000 contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

General

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

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

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

Avoid Hypertension

Because of the potency and varying responses to LEVOPHED™ 1:1000, 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™ 1:1000. Headache may be a symptom of hypertension due to overdose.

Hypersensitivity

Certain patients may be hypersensitive to the effects of LEVOPHED™ 1:1000, e.g. patients with hyperthyroidism (see Section 4.8 Adverse effects (undesirable effects)).

Site of Infusion

LEVOPHED™ 1:1000 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. Gangrene has been reported in a lower extremity when infusions of LEVOPHED™ 1:1000 were given in an ankle vein.

Extravasation

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of LEVOPHED™ 1:1000 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.

Fluid Replacement

Noradrenaline (norepinephrine) should be used only in conjunction with appropriate blood volume replacement. When infusing noradrenaline (norepinephrine), 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 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 (eg, decreased renal perfusion) with reduced blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis, and possible ischemic injury.

Use in the elderly

Clinical studies of LEVOPHED™ 1:1000 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection

for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

LEVOPHED™ 1:1000 infusion solutions should not be administered into the veins in the leg in elderly patients.

Withdrawal of Therapy

The noradrenaline (norepinephrine) infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

Paediatric use

Safety and effectiveness in paediatric patients has not been established. The use of noradrenaline (norepinephrine) in children is not recommended.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

LEVOPHED™ 1:1000 infusion solutions should not be mixed with other medicines. Extreme caution should be exercised in patients receiving monoamine oxidase (MAO) inhibitors and tricyclic antidepressants of the triptyline or imipramine types (see Section 4.4 Special warnings and precautions for use). Linezolid, adrenergic-serotoninergic drugs or any other cardiac sensitizing agents are not recommended because severe, prolonged hypertension and possible arrhythmias may result.

Guanethidine

The effects of noradrenaline (norepinephrine) may be enhanced by guanethidine.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available

Use in pregnancy

Pregnancy Category B3

LEVOPHED™ 1:1000 should be given to a pregnant woman only if clearly needed.

Animal studies indicate noradrenaline (norepinephrine) may impair placental perfusion and induce foetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to foetal asphyxia in late pregnancy. However, the clinical significance of these changes to a human foetus is unknown. These possible risks to the foetus should therefore be weighed against the potential benefit to the mother.

Use in lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LEVOPHED™ 1:1000 is administered to a nursing woman.

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. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

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™ 1:1000 is discontinued, or blood pressure may be maintained at the risk of severe peripheral and visceral vasoconstriction (eg decreased renal perfusion) with diminution in blood flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischaemic injury. Gangrene of extremities has been rarely reported. 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

Ischaemic injury due to potent vasoconstrictor action and tissue hypoxia. Gangrene, hypertension, plasma depletion

Cardiovascular System

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

Nervous System

Anxiety, transient headache.

Respiratory System

Respiratory difficulty, Dyspnea

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. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Overdosage with LEVOPHED™ 1:1000 may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. Headache may indicate severe hypertension. Pulmonary oedema, photophobia, retrosternal pain, pallor, intense sweating and vomiting may occur. In the event of overdose, treatment with noradrenaline (norepinephrine) should be withdrawn and appropriate corrective measures initiated.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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

Studies have not been performed.

Carcinogenicity

Studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite

Sodium chloride

Water for injections

6.2 Incompatibilities

Infusion solutions containing noradrenaline (norepinephrine) acid tartrate monohydrate have been reported to be incompatible with iron salts, alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine and sulfafurazole (see Section 4.2 Dose and method of administration).

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Do not freeze. Protect from light.

6.5 Nature and contents of container

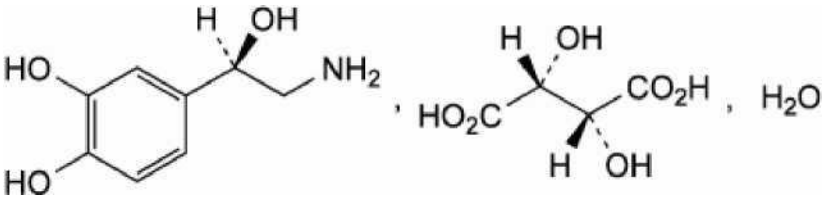
LEVOPHED™ 1:1000 is available as a single use glass vial (4 mg/4 mL). It is supplied in packs of 10 vials per carton.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



Molecular Formula: $C_8H_{11}NO_3,C_4H_6O_6,H_2O$

Molecular Weight: 337.3

Chemically, noradrenaline (norepinephrine) acid tartrate monohydrate, (1*R*)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol hydrogen (2*R*,3*R*)-2,3-dihydroxybutanedioate monohydrate, is a white or almost white crystalline powder. It is freely soluble in water, and slightly soluble in ethanol (96%).

LEVOPHED™ 1:1000 concentrate for intravenous injection has a pH of 3.0 to 4.5.

CAS number

69815-49-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 22
www.pfizermedinfo.com.au

9. DATE OF FIRST APPROVAL

29 November 2012

10. DATE OF REVISION

04 August 2022

Summary Table of Changes

Section changed	Summary of new information
4.3	Removal of references to two anaesthetic medicinal products – cyclopropane and halothane - as these products are not currently on the ARTG as requested by TGA on 31 March 2022.
8	Update of website address