# NEW ZEALAND DATA SHEET

**Noradrenaline (Biomed) 0.06 mg/mL, 0.1 mg/mL, 0.12 mg/mL, 0.16 mg/mL**
**Solution for infusion**

## 1 PRODUCT NAME

Noradrenaline 0.06 mg/mL Solution for infusion

Noradrenaline 0.1 mg/mL Solution for infusion

Noradrenaline 0.12 mg/mL Solution for infusion

Noradrenaline 0.16 mg/mL Solution for infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Noradrenaline 0.06 mg/mL contains 0.12 mg noradrenaline acid tartrate.

Each mL of Noradrenaline 0.1 mg/mL contains 0.199 mg noradrenaline acid tartrate.

Each mL of Noradrenaline 0.12 mg/mL contains 0.239 mg noradrenaline acid tartrate.

Each mL of Noradrenaline 0.16 mg/mL contains 0.319 mg noradrenaline acid tartrate.

Excipient(s) with known effect

Sodium metabisulfite

For the full list of excipients, see Section 6.1.

## 3 PHARMACEUTICAL FORM

Noradrenaline is a sterile solution containing noradrenaline acid tartrate available in a range of ready to use strengths in flexible bags and syringes.
The pH range of the infusions is 3.0 – 4.6.

## 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

**Dose**

**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, intra-aortic pressures must be maintained to prevent cerebral or coronary artery ischaemia, noradrenaline can be administered before and concurrently with blood volume replacement.

Administer by slow intravenous infusion, observing the response to an initial dose of 8 – 12 µg noradrenaline base per minute, then adjust the flow rate to establish and maintain a low normal blood pressure (usually 80 – 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 blood pressure.

The average maintenance dose ranges from 2 – 4 µg noradrenaline base per minute. Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of noradrenaline should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg noradrenaline base) may be necessary if the patient remains hypotensive, but occult blood volume depletion should always be suspected and corrected when present. Central venous pressure monitoring is usually helpful in detecting and treating this situation.

### Duration of Therapy

The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. Infusions of noradrenaline should 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 noradrenaline 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. [Noradrenaline'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, noradrenaline is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

### *Special Populations*

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 therapy.

Noradrenaline infusions should not be administered into the veins in the leg in elderly patients (see section 4.4, Site of infusion).

***Paediatric population***

The safety and efficacy of noradrenaline in children has not yet been established.

**Method of administration**

Noradrenaline is intended for use undiluted. It contains no antimicrobial preservatives. Discoloured solutions or those containing a precipitate should not be used.
Avoid contact with iron salts, alkalis, or oxidising agents.

## 4.3 Contraindications

Noradrenaline should not be given to patients who are hypotensive from blood volume deficits except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed. If noradrenaline 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.

Noradrenaline should also 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 noradrenaline is necessary as a life-saving procedure.

Ventricular tachycardia or fibrillation cardiac arrhythmias may result from the use of noradrenaline in patients with profound hypoxia or hypercarbia.

Hypersensitivity to noradrenaline or any of the excipients.

## 4.4 Special warnings and precautions for use

### Warnings

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

Noradrenaline (Biomed) 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.

## Precautions

### General

### Avoid Hypertension

Because of the potency of noradrenaline and because of varying response to pressor substances, the possibility always exists that dangerously high blood pressure may be produced with overdoses of this pressor agent. It is desirable, therefore, to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, then every five minutes if administration is to be continued.

The rate of flow must be watched constantly, and the patient should never be left unattended while receiving noradrenaline. Headache may be a symptom of hypertension due to overdosage.

Similar caution should be observed in patients with hypotension following myocardial infarction, in patients with Prinzemetal's variant angina, and in patients with diabetes, hypertension or hyperthyroidism.

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

### Hypersensitivity

Certain patients may be hypersensitive to the effects of noradrenaline e.g. patients with hyperthyroidism (see Section 4.8).

### Site of Infusion

Whenever possible, infusions of noradrenaline 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. Some authors have indicated that 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. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity. Therefore, one should avoid the veins of the leg in elderly patients or in those suffering from such disorders. Gangrene has been reported in a lower extremity when infusions of noradrenaline 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 noradrenaline 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 also may 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 the advisability of changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

**IMPORTANT -- Antidote for Extravasation Ischaemia**

The antidote for extravasation ischaemia is phentolamine. To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 mL to 15 mL of saline solution containing from 5 mg to 10 mg of phentolamine, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. 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 the extravasation is noted.

**Paediatric population**
Safety and effectiveness in paediatric patients has not been established.

**Elderly**

Clinical studies of noradrenaline 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 therapy.

Noradrenaline infusions should not be administered into the veins in the leg in elderly patients (see Section 4.4 - Site of Infusion).

## 4.5 Interaction with other medicines and other forms of interaction

Ventricular tachycardia or fibrillation cardiac arrhythmias may result from the use of noradrenaline in patients with profound hypoxia or hypercarbia.

Noradrenaline should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result. Linezolid, adrenergic-serotoninergic drugs, or any other cardiac sensitising agents are not recommended as severe prolonged hypertension and possible arrhythmias may result.

**Guanethidine**

The effects of noradrenaline may be enhanced by guanethidine.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Category B3

Noradrenaline should be given to a pregnant woman only if clearly needed.

Animal studies indicate noradrenaline 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.

**Breast-feeding**

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 noradrenaline is administered to a nursing woman.

**Fertility**

Studies have not been performed.

### 4.7 Effects on ability to drive and use machines

No information held by the sponsor.

### 4.8 Undesirable effects

The following reactions can occur:

**Body as a whole**

Ischaemic injury due to potent vasoconstrictor action and tissue hypoxia.

**Nervous system disorders**

Anxiety, transient headache.

**Cardiovascular system**

Bradycardia, probably as a reflex of a rise in blood pressure, cardiogenic shock, arrhythmias and stress cardiomyopathy.
Peripheral ischemia, gangrene, hypertension, plasma depletion.

**Respiratory, thoracic and mediastinal disorders**

Respiratory difficulty, dyspnoea.

**Skin and subcutaneous tissue disorders**

Extravasation necrosis at injection site.

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 noradrenaline 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. 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.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

### 4.9 Overdose

Overdosage with noradrenaline may result in headache, 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 should be withdrawn and appropriate corrective measures initiated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Adrenergic and dopaminergic agents
**ATC Code:** C01CA03

**Mechanism of action**

Noradrenaline, (sometimes referred to as norepinephrine or 1-arterenol/levarterenol) a sympathomimetic amine which differs from adrenaline by the absence of a methyl group on the nitrogen atom.
Noradrenaline functions as a peripheral vasoconstrictor (alpha-adrenergic action) and as an inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action).

These actions result in an increase in systemic blood pressure and coronary artery blood flow. In myocardial infarction accompanied by hypertension, Noradrenaline 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 helps raise the blood pressure to an optimal level and establish a more adequate circulation.

## 5.2 Pharmacokinetic properties

### Absorption

Orally ingested noradrenaline is destroyed in the GI tract, and the drug is poorly absorbed after subcutaneous injection. After IV administration, a pressor response occurs rapidly. The drug has a short duration of action, and the pressor action stops within 1-2 minutes after the infusion is discontinued.

### Distribution

Noradrenaline localises mainly in sympathetic nervous tissue. The drug crosses the placenta but not the blood-brain barrier.

### Biotransformation

The pharmacologic actions of noradrenaline are terminated primarily by uptake and metabolism in sympathetic nerve endings. The drug is metabolised in the liver and other tissues by a combination of reactions involving the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). The major metabolites are normetanephrine and 3-methoxyl-4-hydroxy mandelic acid (vanillylmandelic acid, VMA), both of which are inactive.

Other inactive metabolites include 3-methoxy-4-hydroxyphenylglycol, 3,4-dihydroxymandelic acid, and 3,4-dihydroxyphenylglycol.

### Elimination

Noradrenaline metabolites are excreted in urine primarily as sulphate conjugates and, to a lesser extent, as glucuronide conjugates. Only small quantities of noradrenaline are excreted unchanged.

## 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

All strengths of Noradrenaline contain the following excipients:
Glucose, Sodium metabisulfite, Water for injections

## 6.2 Incompatibilities

Noradrenaline should not be mixed with other medicines. Infusion solutions containing noradrenaline acid tartrate monohydrate have been reported to be incompatible with iron salts, alkalis and oxidising agents, barbiturates, chlorphenamine maleate (chlorpheniramine maleate), chlorothiazide, nitrofurantoin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine and sulfafurazole.

## 6.3 Shelf life

The following products have a **12** months shelf life:

Noradrenaline 0.06 mg/mL
Noradrenaline 0.1 mg/mL
Noradrenaline 0.12 mg/mL
Noradrenaline 0.16 mg/mL

## 6.4 Special precautions for storage

**Store at or below 25°C. Do not refrigerate or freeze.**

Noradrenaline 0.1 mg/mL
Noradrenaline 0.12 mg/mL
Noradrenaline 0.16 mg/mL

**Store at 2°C to 8°C. Refrigerate. Do not freeze.**

Noradrenaline 0.06 mg/mL

## 6.5 Nature and contents of container

Noradrenaline is available in 0.1 mg/mL and 0.12 mg/mL strengths in 100 mL IV bags in overwraps.
Noradrenaline is also available in 50 mL polypropylene syringes in the following strengths: 0.06 mg/mL and 0.16 mg/mL.

## 6.6 Special precautions for disposal

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

# 7 MEDICINE SCHEDULE

Prescription medicine

# 8 SPONSOR

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# 9 DATE OF FIRST APPROVAL

15 October 2020

# 10 DATE OF REVISION OF THE TEXT

09 February 2024

**Summary table of changes**

| Section changed | Summary of new information |
|---|---|
| 2.0 | Updated the following sections with information to align with NZ reference product:<br>Addition of Excipients with known effects |
| 4.2 | Addition of Special Populations information |
| 4.3 | Addition of hypersensitivity as a contraindication |
| 4.4 | Addition of general precaution information |
| 4.5 | Addition of further interactions |
| 4.8 | Addition of some more undesirable effects |
| 4.9 | Addition of examples of signs of overdose |
| 5.1 | Addition of Mechanism of action |
| 6.2 | Added incompatibility with iron salts |
| Throughout | Minor editorial changes |