New Zealand Data Sheet

1 PRODUCT NAME

NORALIN 3 mg/50 mL, 5 mg/50 mL, 6 mg/50 mL and 10 mg/50 mL solution for intravenous infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 3 mg/50 mL vial contains noradrenaline (norepinephrine) 0.06 mg in 1 mL, present as 0.12 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 1 mL.

Each 5 mg/50 mL vial contains noradrenaline (norepinephrine) 0.1 mg in 1 mL, present as 0.2 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 1 mL.

Each 6 mg/50 mL vial contains noradrenaline (norepinephrine) 0.12 mg in 1 mL, present as 0.24 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 1 mL.

Each 10 mg/50 mL vial contains noradrenaline (norepinephrine) 0.2 mg in 1 mL, present as 0.4 mg of noradrenaline (norepinephrine) acid tartrate monohydrate in 1 mL.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Noralin is a sterile, clear colourless solution for intravenous infusion available in vials.

The solution has a pH of 3.0 to 4.5.

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

Noralin should only be administered by healthcare professionals familiar with its use.

Noralin is a ready-to-use solution for intravenous infusion. **The solution should not be diluted before use**.

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 (norepinephrine) can be administered before and concurrently with blood volume replacement.

Average dosage
Several strengths are available and, to ensure accurate patient dosage, it is critical to confirm the correct strength and infusion rate have been selected.

Each 1 mL of solution contains 0.06, 0.1, 0.12 or 0.2 mg of noradrenaline (norepinephrine).

Give this solution by intravenous infusion. Insert a plastic intravenous catheter through a suitable bore needle well advanced centrally into the vein and securely fixed with adhesive tape, avoiding, if possible, a catheter tie-in technique as this promotes stasis.

Administration of Noralin should be controlled by a pump capable of delivering an accurate and consistent volume at a controlled infusion rate in accordance with dosing instructions.

After observing the response to an initial dose of 8 micrograms to 12 micrograms of base per minute, adjust the rate of flow to establish and maintain a low normal blood pressure (usually 80 mm Hg 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 2 micrograms to 4 micrograms of base per minute.

High dosage
Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of noradrenaline (norepinephrine) should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg 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. The infusion rate of noradrenaline (norepinephrine) 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 noradrenaline (norepinephrine) 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 (norepinephrine's) β-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 (norepinephrine) is used in the same manner as described under Restoration of blood pressure in acute hypotensive states above.

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 (norepinephrine) infusions should not be administered into the veins in the leg in elderly patients. (see section 4.4 Special warnings and precautions for use).

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

Method of administration

Noralin contains noradrenaline (norepinephrine) as the acid tartrate monohydrate. An infusion of noradrenaline (norepinephrine) should be given into a large vein (see section 4.4 Special warnings and precautions for use). Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

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

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to use, whenever solution and container permit.

Discoloured solutions or those containing a precipitate should not be used.

Avoid contact with iron salts, alkalis, or oxidising agents.

4.3 Contraindications

Noradrenaline (norepinephrine) 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 (norepinephrine) 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 (norepinephrine) 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 (norepinephrine) is necessary as a lifesaving procedure.

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

4.4 Special warnings and precautions for use

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

Warnings

Noralin 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.

Precautions

General

Avoid hypertension

Because of the potency of noradrenaline (norepinephrine) 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 (norepinephrine). Headache may be a symptom of hypertension due to overdosage.

Hypersensitivity

Certain patients may be hypersensitive to the effects of noradrenaline (norepinephrine), e.g. patients with hyperthyroidism (see section 4.8 Undesirable effects).

Site of infusion

Whenever possible, infusions of noradrenaline (norepinephrine) 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 (norepinephrine). 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 (norepinephrine) 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 (norepinephrine) 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 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 have not been established.

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 (norepinephrine) infusions should not be administered into the veins in the leg in elderly patients (see Site of infusion above).

4.5 Interaction with other medicines and other forms of interaction

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

Noradrenaline (norepinephrine) 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 (see section 4.4 Special warnings and precautions for use).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3
Noralin 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.

Breastfeeding

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 (norepinephrine) 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

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 (norepinephrine) 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, pharyngeal pain, pallor, intense sweating and vomiting (see section 4.9 Overdose).

The following reactions can occur:

Metabolism and nutrition disorders
Hyperglycemia, metabolic acidosis due to reduced tissue oxygenation.

Psychiatric disorders
Insecurity and anxiety, insomnia, confusional state and psychosis, weakness, agitation.

Nervous system disorders
Headache, tremor.

Eye disorders
Acute glaucoma (very common in anatomically disposed patients with angle closure).

Cardiac disorders
Tachycardia, bradycardia (probably a reflex reaction to the increase in blood pressure), arrhythmias, stress cardiomyopathy, palpitations, increased contractility of the heart muscle resulting from the beta-adrenergic effect on the heart (inotropic and chronotropic), acute heart failure, angina pain, myocardial ischaemia, myocardial lesions. An overdose or too-fast intravenous administration may trigger an increase in blood pressure, reflex bradycardia and cardiac arrhythmias, and in extreme cases ventricular fibrillation.

Vascular disorders
Generalised vasoconstriction, particularly in the skin, mucosa and kidneys with a risk of decreased perfusion of vital organs leading to ischaemia. These effects particularly occur in hypovolaemic patients. Hypertension and tissue hypoxia, ischaemic lesions caused by the potent vasoconstrictor action which may cause cold and pallor of the limbs and face, undue risk of cerebral haemorrhage.

Respiratory, thoracic and mediastinal disorders
Respiratory failure or shortness of breath, 7etabol, pulmonary oedema in the event of a substantial increase in blood pressure.

Gastrointestinal disorders
Hypersalivation, nausea, vomiting.

Skin and subcutaneous tissue disorders
Pallor, sweating.

Renal and urinary disorders
Oliguria, anuria, dysuria.

General disorders and administration site conditions
Ischaemic necrosis at the site of application (e.g. skin), particularly with para- or perivascular administration.

Continuous administration of vasopressors to maintain blood pressure without volume expansion may cause the following symptoms:

- serious peripheral and visceral vasoconstriction
- reduced renal blood flow
- reduced production of urine
- hypoxia
- elevated serum lactate concentrations.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Overdosage with noradrenaline (norepinephrine) may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output (see section 4.8 Undesirable effects). Headache may indicate severe hypertension. In case of accidental overdosage, as evidenced by excessive blood pressure elevation, discontinue noradrenaline (norepinephrine) until the condition of the patient 8etabolize.

In case of overdose, immediately contact the New Zealand Poisons Information Centre for advice on 0800 764 766.

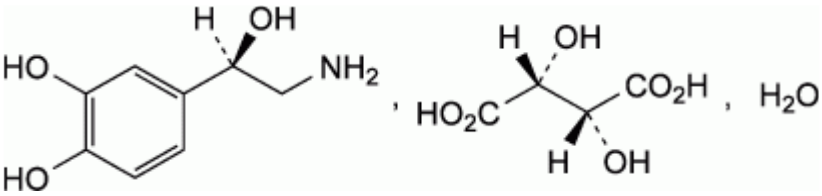
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents
ATC code: C01CA03

Chemistry information

The chemical structure for noradrenaline (norepinephrine) acid tartrate monohydrate is shown below:



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%).

Molecular formula: $C_8H_{11}NO_3,C_4H_6O_6,H_2O$
Molecular weight: 337.3 g/mol
CAS registry no.: 69815-49-2

Mechanism of action

Noradrenaline (sometimes referred to as norepinephrine or l-arterenol/levarterenol), a sympathomimetic amine which differs from adrenaline by the absence of a methyl group on the nitrogen atom.

Noradrenaline (norepinephrine) functions as a peripheral vasoconstrictor (α-adrenergic action) and as an inotropic stimulator of the heart and dilator 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.

5.2 Pharmacokinetic properties

Absorption

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 (norepinephrine) 10etaboliz mainly in sympathetic nervous tissue. The drug crosses the placenta but not the blood-brain barrier.

Metabolism

The pharmacologic actions of noradrenaline (norepinephrine) are terminated primarily by uptake and metabolism in sympathetic nerve endings. The drug is 10etabolized 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 (norepinephrine) metabolites are excreted in urine primarily as the sulfate conjugates and, to a lesser extent, as the glucuronide conjugates. Only small quantities of noradrenaline (norepinephrine) are excreted unchanged.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Noralin contains the following excipients: sodium chloride, hydrochloric acid for pH adjustment, and water for injections.

6.2 Incompatibilities

Noralin infusion solutions should not be mixed with other medicines. Infusion solutions containing noradrenaline (norepinephrine) acid tartrate monohydrate have been reported to be incompatible with iron salts, alkalis and oxidising agents, barbituates, chlorphenamine maleate (chlorpheniramine maleate), chlorothiazide, nitrofurantoin, phenytoin, sodium

bicarbonate, sodium iodide, streptomycin, sulfadiazine and sulfafurazole.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store below 25ºC. Do not refrigerate or freeze. Protect from light.

6.5 Nature and contents of container

Noralin is supplied in clear glass vials with a rubber stopper and aluminium flip-off cap. It is available in packs of 1 vial.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

BNM Group
39 Anzac Road
Browns Bay
Auckland 0753

Phone 0800 565 633

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
06 August 2020

10 DATE OF REVISION OF TEXT

14 October 2022

Summary table of changes

Section changed	Summary of new information
4.3 and 4.5	Updated to remove the reference to two anaesthetic medicinal products – cyclopropane and halothane