

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NORADRENALINE (NOREPINEPHRINE) EQUITY, 1 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 2 mg noradrenaline (norepinephrine) tartrate equivalent to 1 mg noradrenaline (norepinephrine) base.

Each 4 mL ampoule contains 8 mg noradrenaline (norepinephrine) tartrate equivalent to 4 mg noradrenaline (norepinephrine) base.

Each 8 mL ampoule contains 16 mg noradrenaline (norepinephrine) tartrate equivalent to 8 mg noradrenaline (norepinephrine) base.

Excipient(s) with known effect:

Each mL of concentrate for solution for infusion contains 3,3 mg equivalent to 0,14 mmol of sodium.

Each 4 mL ampoule contains 13,2 mg equivalent to 0,57 mmol of sodium.

Each 8 mL ampoule contains 26,4 mg equivalent to 1,14 mmol of sodium.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless or slightly yellowish solution, practically free from visible particles.

pH = 3,0 to 4,0

Osmolality: 250 – 320 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NORADRENALINE (NOREPINEPHRINE) EQUITY is indicated in adults for the emergency restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration

Posology

Adults:

Initial rate of infusion:

When diluted as recommended in section 6.6 (the concentration of the prepared infusion is 40 mg/litre noradrenaline (norepinephrine) base (80 mg/litre noradrenaline (norepinephrine) 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 mL/min to 0,33 mL/min). This is equivalent to 0,4 mg/hour to 0,8 mg/hour noradrenaline (norepinephrine) base (0,8 mg/hour to 1,6 mg/hour noradrenaline (norepinephrine) 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 (norepinephrine) base (0,4 mg/hour noradrenaline (norepinephrine) tartrate).

Titration of dose:

Once an infusion of NORADRENALINE (NOREPINEPHRINE) EQUITY has been established the dose should be titrated in steps of 0,05 – 0,1 µg/kg/min of noradrenaline (norepinephrine) 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 (NOREPINEPHRINE) EQUITY infusion solution			
40 mg/litre (40 µg/mL) noradrenaline (norepinephrine) base			
Patient's weight	Posology (µg/kg/min) noradrenaline (norepinephrine) base	Posology (mg/hour) noradrenaline (norepinephrine) 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 medical practitioners may prefer to dilute to other concentrations. If dilutions other than 40 mg/litre are used, check the infusion rate calculation carefully before starting treatment.

Duration of treatment and monitoring:

NORADRENALINE (NOREPINEPHRINE) EQUITY should be continued for as long as vasoactive medicine 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:

NORADRENALINE (NOREPINEPHRINE) EQUITY infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

Special populations

Patients with 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.

Paediatric population:

The safety and efficacy of NORADRENALINE (NOREPINEPHRINE) EQUITY in children and adolescents have not been established.

Method of administration

For intravenous use.

NORADRENALINE (NOREPINEPHRINE) EQUITY solution for infusion is infused as a diluted solution

intravenously. To avoid ischemic necrosis (skin, extremities) a cannula placed in a sufficiently larger vein or a central venous access to the infusion should be used.

The infusion should be at a controlled rate using either a syringe pump or an infusion pump or a drip counter.

For dilution instructions see section 6.6.

4.3 Contraindications

- Hypersensitivity to noradrenaline (norepinephrine) or to any of the excipients of NORADRENALINE (NOREPINEPHRINE) EQUITY as listed in section 6.1.
- Hypotension due to blood volume deficit (hypovolaemia).
- The use of pressor amines during cyclopropane or halothane anaesthesia is contraindicated as this may cause serious cardiac dysrhythmias including ventricular fibrillation.

4.4 Special warnings and precautions for use

NORADRENALINE (NOREPINEPHRINE) EQUITY should only be administered by healthcare professionals who are familiar with its use.

Warning:

- NORADRENALINE (NOREPINEPHRINE) EQUITY is contraindicated in hypotensive patients due to hypovolemia, however, may still be considered as a short-term emergency measure to support blood supply to coronary and cerebral arteries until general blood or solution infusion can be initiated.
- NORADRENALINE (NOREPINEPHRINE) EQUITY should be used only in conjunction with appropriate blood volume replacement.
- When infusing NORADRENALINE (NOREPINEPHRINE) EQUITY, the blood pressure and rate of flow should be checked frequently to avoid hypertension.
- The products administered by injection must always be visually inspected and cannot be used if the

presence of particles or a change of colouring is noted.

- Extravasation risk:

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation that would cause a necrosis of the tissues surrounding the vein used for the injection. Because of the vasoconstriction of the vein wall with increased permeability, there might be some leakage of noradrenaline (norepinephrine) in the tissues surrounding the infused vein causing a blanching of the tissues which is not due to an obvious extravasation. Hence if blanching occurs, consideration should be given to changing the infusion site to allow the effects of local vasoconstriction to subside.

Treatment of the ischemia due to extravasation:

During an extravascular leak of the product or an injection besides the vein, a tissue destruction can appear resulting from the vasoconstrictive action of the medicine on the blood vessels. The injection zone must be then irrigated as quickly as possible with 10 to 15 mL of physiological salt solution containing 5 to 10 mg of phentolamine mesilate. For this purpose, it is necessary to use a syringe provided with a fine needle and to inject locally.

Precautions for use:

Caution and respect of the strict indication must be retained in case of:

- Major left ventricular dysfunction associated with acute hypotension; a careful evaluation of patient's blood pressure is needed. Supportive therapy should be initiated simultaneously with diagnostic evaluation. NORADRENALINE (NOREPINEPHRINE) EQUITY should be reserved for patients with cardiogenic shock and refractory hypotension, in particular those without elevated systemic vascular resistance. It should be started at a dosage of 2 to 4 µg/min and titrated upwards and titrated as necessary. If systemic perfusion or systolic pressure cannot be maintained at > 90 mm Hg with a dosage of 15 µg/min, it is unlikely that a further increase will be beneficial.
- Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline (norepinephrine) may increase the ischaemia and extend the area of

infarction. Similar caution should be observed in patients with hypotension following myocardial infarction and in patients with Prinzmetal's variant angina.

- Occurrence of heart rhythm disorders during the treatment must lead to a reduction in the dosage.
- Caution is advised in patients with hyperthyroidism or diabetes mellitus.
- The elderly may be especially sensitive to the effects of noradrenaline (norepinephrine) e.g.,
NORADRENALINE (NOREPINEPHRINE) EQUITY.

Perfusion of NORADRENALINE (NOREPINEPHRINE) EQUITY must be performed with continuous monitoring of blood pressure and cardiac frequency.

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 ischaemic injury.

The vasopressor effect (resulting from the adrenergic action in the vessels) can be reduced by the concomitant administration of an alpha-blocking medicine whereas the administration of a beta-blocking medicine may result in a reduction of the stimulating effect of the product on the heart and in an increase of the hypertensive effect (through reduction of arteriolar dilatation), resulting from beta-1-adrenergic stimulation.

In cases where it is necessary to administer NORADRENALINE (NOREPINEPHRINE) EQUITY at the same time as total blood or plasma, the latter must be administered in a separate drip.

NORADRENALINE (NOREPINEPHRINE) EQUITY contains sodium.

NORADRENALINE (NOREPINEPHRINE) EQUITY contains 26,4 mg sodium per 8 mL ampoule, equivalent to 1,3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Inadvisable combinations

- *Volatile halogen anaesthetics*: severe ventricular dysrhythmia (increase in cardiac excitability).
- *Tricyclic antidepressants*: paroxysmal hypertension with the possibility of dysrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).
- *Serotonergic-adrenergic antidepressants*: paroxysmal hypertension with the possibility of dysrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

Combinations requiring precautions for use

- *Non-selective MAO inhibitors*: increase in the pressor action of the sympathomimetic which is usually moderate. Should only be used under close medical supervision.
- *Selective MAO-A inhibitors*: by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. Should only be used under close medical supervision.
- *Linezolid*: by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. Should only be used under close medical supervision.

Caution is required when using NORADRENALINE (NOREPINEPHRINE) EQUITY with alpha and beta blockers as severe hypertension may result.

Caution is required when using NORADRENALINE (NOREPINEPHRINE) EQUITY with the following medicines as they may cause increased cardiac effects: thyroid hormones, cardiac glycosides, anti-dysrhythmics.

Ergot alkaloids or oxytocin may enhance the vasopressor and vasoconstrictive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

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.

Safety has not been established in pregnant woman.

Breastfeeding

No information is available on the use of NORADRENALINE (NOREPINEPHRINE) EQUITY in lactation. The safety of NORADRENALINE (NOREPINEPHRINE) EQUITY during breastfeeding has not been established.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Tabulated list of adverse reactions

System organ class	<i>Frequency unknown</i>
Psychiatric disorders	Anxiety, insomnia, confusion, weakness, psychotic state, lower vigilance, anorexia.
Nervous system disorders	Headache, tremor.
Eye disorders	Acute glaucoma (very frequent in patients anatomically predisposed with the closing of the iridocorneal angle).
Cardiac disorders	Tachycardia, bradycardia (probably as a reflex result of blood pressure rising), dysrhythmias, palpitations, increase in the contractility of the cardiac muscle resulting from the beta-adrenergic effect on the heart (inotrope and chronotrope), acute cardiac insufficiency, stress cardiomyopathy.
Vascular disorders	Arterial hypertension and tissue hypoxia; ischemic injury due to potent vasoconstrictor action may

	result in coldness and paleness of the members and the face, and gangrene of the extremities.
Respiratory, thoracic and mediastinal disorders	Respiratory insufficiency or difficulty, dyspnoea.
Gastrointestinal disorders	Nausea, vomiting.
Renal and urinary disorders	Retention of urine.
General disorders and administration site conditions	Possibility of irritation, sloughing and necrosis at the injection site.

Description of selected adverse reactions

The continuous administration of vasopressor to maintain blood pressure in absence of blood volume replacement may cause the following symptoms:

- severe peripheral and visceral vasoconstriction
- decrease in renal blood flow
- decrease in urine production
- hypoxia
- increase in lactate serum levels.

In case of hypersensitivity or overdose, the following effects may appear more frequently: hypertension, photophobia, retrosternal pain, pharyngeal 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 providers are asked to report any suspected adverse reactions to SAHPRA via the “**Adverse drug reaction and quality problem reporting form**”, found online under SAHPRA’s publications:

<https://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/>.

4.9 Overdose

In the event of overdose, the following may be observed: cutaneous vasoconstriction, bed sores, circulatory collapse, severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased output. These may be accompanied by violent headache, photophobia, retrosternal pain, pallor, intense sweating and vomiting.

In the event of overdosage, treatment should be withdrawn, and appropriate corrective treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.1 Adrenomimetics (sympathomimetics)

Pharmacotherapeutic group: Adrenergic and Dopaminergic Agent; ATC Code: C01CA03 (C: Cardiovascular system)

Noradrenaline (norepinephrine) has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. NORADRENALINE (NOREPINEPHRINE) EQUITY causes generalised vasoconstriction, except for the coronary vessels which it dilates indirectly by increasing the oxygen consumption. 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 haemostasis and/or necrosis.

The effect on blood pressure disappears 1 – 2 minutes after stopping the infusion.

5.2 Pharmacokinetic properties

Two stereoisomers of noradrenaline (norepinephrine) exist, the biologically active L-isomer is the one present in NORADRENALINE (NOREPINEPHRINE) EQUITY.

Absorption

- After intravenous administration noradrenaline (norepinephrine) has a plasmatic half-life of about 1 to

2 minutes.

Distribution

- Noradrenaline (norepinephrine) is rapidly cleared from plasma by a combination of cellular reuptake and metabolism. It does not readily cross the blood-brain barrier.

Biotransformation

- Methylation by catechol-o-methyltransferase
- Deamination by monoamine oxidase (MAO)
- Ultimate metabolites from both is 4-hydroxy-3-methoxymandelic acid
- Intermediate metabolites include normetanephrine and 3,4- dihydroxymandelic acid.

Elimination

- Noradrenaline (norepinephrine) is mainly eliminated as glucuronide or sulphate conjugates of the metabolites in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid or sodium hydroxide (qs pH 3,0 to 4,0)

Water for injections

6.2 Incompatibilities

NORADRENALINE (NOREPINEPHRINE) EQUITY must not be mixed with other medicines except those mentioned in the section 6.6.

6.3 Shelf life

24 months

After dilution:

Chemical and physical in-use stability of diluted product (in glucose 5 %, sodium chloride 9 mg/mL (0,9 %), or sodium chloride 9 mg/mL with glucose 5 % solution) has been demonstrated for 48 hours at 30 °C.

However, from a microbiological point of view, the diluted 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 °C to 8 °C, unless manipulation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

NORADRENALINE (NOREPINEPHRINE) EQUITY is packaged in type I clear glass, self-breaking (one point cut) ampoules of 5 mL and 10 mL, filled to 4 mL and 8 mL, respectively.

The glass ampoules are packed into carton boxes containing 10, 50 or 100 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- *Dilution instructions:*

Dilute NORADRENALINE (NOREPINEPHRINE) EQUITY before use with glucose 5 % solution or sodium chloride 9 mg/mL (0,9 %) or sodium chloride 9 mg/mL with glucose 5 % solution.

Either add 2 mL of NORADRENALINE (NOREPINEPHRINE) EQUITY concentrate to 48 mL glucose 5 % solution (or sodium chloride 9 mg/mL, or sodium chloride 9 mg/mL with glucose 5 % solution) for administration by syringe pump, or add 20 mL of NORADRENALINE (NOREPINEPHRINE) EQUITY concentrate to 480 mL glucose 5 % (or sodium chloride 9 mg/mL, or

sodium chloride 9 mg/mL with glucose 5 % solution) for administration by drip counter.

In both the cases, the final concentration of the infusion solution is 40 mg/litre noradrenaline (norepinephrine) base (which is equivalent to 80 mg/litre noradrenaline (norepinephrine) tartrate). Dilutions other than 40 mg/litre noradrenaline (norepinephrine) base may also be used (see section 4.2). If dilutions other than 40 mg/litre noradrenaline (norepinephrine) base are used, check the infusion rate calculation carefully before starting treatment.

NORADRENALINE (NOREPINEPHRINE) EQUITY is compatible with PVC infusion bags.

- Do not use an opened ampoule.
- This product should be visually inspected prior to administration. Only a clear, colourless or slightly yellowish solution, free of particles or precipitates should be used. The ampoules with a pink colour or darker than pale yellow, or containing a precipitate should not be administered.
- Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene, Pretoria

8. REGISTRATION NUMBER(S)

57/5.1/0871

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 February 2024

10. DATE OF REVISION OF THE TEXT