PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

SINORA 1 mg/1 ml (concentrate for solution for infusion)

SINORA 4 mg/4 ml (concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of the concentrate for solution for infusion contains 2 mg noradrenaline tartrate corresponding to 1 mg noradrenaline base.

Each ampoule containing 1 ml of concentrate for solution for infusion contains 2 mg of noradrenaline tartrate corresponding to 1 mg of noradrenaline base.

Each ampoule containing 4 ml of concentrate for solution for infusion contains 8 mg of noradrenalin tartrate corresponding to 4 mg of noradrenaline base.

When diluted as recommended, each ml contains 80 micrograms noradrenaline tartrate equivalent to 40 micrograms noradrenaline base.

Excipient with known effect

Each ampoule containing 1 ml of concentrate for solution for infusion contains 0,14 mmol (or 3,3 mg) sodium.

Each ampoule containing 4 ml of concentrate for solution for infusion contains 0,57 mmol (or 13,2 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless solution.

pH 3,0 – 4,5.

Osmolarity: 275 – 305 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated in adults for use as an emergency measure in the 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 base (80 mg/litre noradrenaline 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 to 0,33 ml/min). This is equivalent to 0,4 mg/hour to 0,8 mg/hour noradrenaline base (0,8 mg/hour to 1,6 mg/hour noradrenaline 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 base (0,4 mg/hour noradrenaline tartrate).

Titration of dose:

Once an infusion of SINORA has been established, the dose should be titrated in steps of 0,05 - 0,1 µg/kg/min of noradrenaline 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).

SINORA Infusion Solution **40 mg/litre (40 µg/ml) noradrenaline base**			
Patient's weight	**Posology (µg/kg/min) noradrenaline base**	**Posology (mg/hour) noradrenaline 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/l are used, check the infusion rate calculation carefully before starting treatment.

Special populations:

Patients with renal or hepatic impairment:

There is no experience in treatment of renally or hepatically impaired patients.

Elderly patients:

As for adults, but see section 4.4.

Paediatric population:

The safety and efficacy of SINORA in children and adolescents have not been established.

Duration of Treatment and Monitoring:

SINORA 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:

SINORA infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

Method of administration:

For intravenous use.

SINORA 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 or to any of the excipients listed in section 6.1.
- Hypotension due to blood volume deficit (hypovolaemia).
- The use of pressor amines during inhalational anaesthesia with halogenated anaesthetics is contraindicated as this may cause serious cardiac dysrhythmias including ventricular fibrillation.

4.4 Special warnings and precautions for use

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

Warnings

- SINORA 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.
- SINORA should be used only in conjunction with appropriate blood volume replacement.
- When infusing SINORA, the blood pressure and rate of flow should be checked frequently to avoid hypertension.
- SINORA administrated 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 injection. Because of the vasoconstriction of the vein wall with increased permeability, there might be some leakage of noradrenaline 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 ischaemia 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 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. Supportive therapy should be initiated simultaneously with diagnostic evaluation. SINORA should be reserved for patients with cardiogenic shock and refractory hypotension, in particular those without elevated systemic vascular resistance.
- Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because SINORA 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.
- Elderly patients may be especially sensitive to the effects of SINORA.

Perfusion of SINORA 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 SINORA at the same time as total blood or plasma, the latter must be administered in a separate drip.

SINORA contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

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).
- Serotoninergic-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 SINORA with alpha- and beta-blockers, as severe hypertension may result. Caution is required when using SINORA with the following medicines as they may cause increased cardiac effects: thyroid hormones, cardiac glycosides, antidysrhythmic medicines.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established. SINORA 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.

Breastfeeding

The safety of SINORA during breastfeeding has not been established. No information is available on the use of SINORA during lactation.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The frequency of the adverse reactions cannot be estimated from the available data.

System Organ Class	Undesirable effect
Psychiatric disorders	Anxiety, insomnia, confusion, weakness, psychotic state.
Nervous system disorders	Headache, tremor.
Eyes 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, ischaemic injury due to potent vasoconstrictor action may result in coldness and paleness of the members and the face.
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.

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 "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac 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

Pharmacological classification: 5.1 Adrenomimetics (sympathomimetics)

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC code: C01CA03

Mechanism of action

The vascular effects in the doses normally used clinically result from the simultaneous stimulation of alpha and beta adrenergic receptors in the heart and vascular system. Except in the heart, its action is predominantly on the alpha receptors.

Pharmacodynamic effects

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.

Clinical efficacy and safety

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 exist, the biologically active L-isomer is the one present in SINORA 1 mg/1 ml and SINORA 4 mg/4 ml concentrate for solution for infusion.

Absorption

After intravenous administration noradrenaline has a plasmatic half-life of about 1 to 2 minutes.

Distribution

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

Biotransformation

Noradrenaline undergoes methylation by catechol-o-methyltransferase and deamination by monoamine oxydase (MAO). The main metabolites are 4-hydroxy-3-methoxymandelic acid, normetanephrine and 3,4-dihydroxymandelic acid.

Elimination

Noradrenaline is mainly eliminated as glucuronide or sulphate conjugates of the metabolites in the urine.

5.3 Preclinical safety data

Most of the adverse effects attributable to sympathomimetics result from excessive stimulation of the sympathetic nervous system via the different adrenergic receptors.

Noradrenaline may impair placental perfusion and induce foetal bradycardia. It may also exert a contractile effect on the uterus and lead to foetal asphyxia in late pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride and water for injections.

6.2 Incompatibilities

SINORA must not be mixed with other medicines except those mentioned in section 6.6.

Infusion solutions containing noradrenaline tartrate have been reported to be incompatible with the following substances: alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin. For compatibility with infusion bags see section 6.6.

6.3 Shelf life

24 months

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours when stored at or below 25 °C when diluted to 4 mg/litre and 40 mg/litre noradrenaline base in sodium chloride 9 mg/ml (0,9 %) solution or glucose 5 % solution or sodium chloride 9 mg/ml with glucose 5 % solution. However, from a microbiological point of view, the 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 when stored at 2 to 8 °C.

6.4 Special precautions for storage

Store at or below 30 °C. Do not refrigerate or freeze.

Store in original package in order to protect from light.

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

Keep out of the sight and reach of children.

6.5 Nature and contents of container

SINORA 1 mg/1 ml is presented in 2 ml (1 ml fill) one point cut clear Type I glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10.

SINORA 4 mg/4 ml is presented in 5 ml (4 ml fill) one point cut clear Type I glass ampoules. Ampoules are packed into outer cardboard cartons in pack sizes of 10.

6.6 Special precautions for disposal and other handling

Dilution instructions:

Dilute SINORA 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 SINORA 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 SINORA concentrate to 480 ml glucose 5 % solution (or sodium chloride 9 mg/ml or sodium chloride 9 mg/ml with glucose 5 % solution) for administration by drip counter. In both cases, the final concentration of the infusion solution is 40 mg/litre noradrenaline base (which is equivalent to 80 mg/litre noradrenaline tartrate). Dilutions other than 40 mg/litre noradrenaline base may also be used (see section 4.2). If dilutions other than 40 mg/litre noradrenaline base are used, check the infusion rate calculation carefully before starting treatment.

The SINORA is compatible with PVC infusion bags.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Umsebe Healthcare

506 Sunclare Building

21 Dreyer Street, Claremont

Cape Town

7708

South Africa

8. REGISTRATION NUMBERS

SINORA 1 mg/1 ml: 56/5.1/0111

SINORA 4 mg/4 ml: 56/5.1/0112

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 October 2022

10. DATE OF REVISION OF THE TEXT

19 April 2024

NAMIBIA:

SINORA 1 mg/1 ml (concentrate for solution for infusion): Reg. No.: 22/5.1/0039 NS2

SINORA 4 mg/4 ml (concentrate for solution for infusion): Reg. No.: 22/5.1/0040 NS2