PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

SINORA 0,08 mg/ml (solution for infusion)

SINORA 0,16 mg/ml (solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SINORA 0,08 mg/ml

Each 1 ml contains 0,16 mg noradrenaline tartrate equivalent to 0,08 mg noradrenaline base.

Each 50 ml vial contains 8 mg of noradrenaline tartrate corresponding to 4 mg of noradrenaline base.

SINORA 0,16 mg/ml

Each 1 ml contains 0,32 mg noradrenaline tartrate equivalent to 0,16 mg noradrenaline base.

Each 50 ml vial contains 16 mg of noradrenaline tartrate corresponding to 8 mg of noradrenaline base.

Excipient with known effect

Each ml of solution for infusion contains 0,14 mmol (or 3,3 mg) sodium. Each 50 ml vial contains 7,19 mmol (or 165,3 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless solution.

pH 3,0 – 4,0.

Osmolarity: 250 – 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sinora solution for infusion is indicated in adults weighing over 50 kg for the on-going treatment of hypotensive emergencies.

4.2 Posology and method of administration

Blood pressure control:

Blood pressure should be monitored carefully for the duration of therapy, and preferably controlled by direct arterial blood pressure monitoring. The patient should be monitored carefully for the duration of SINORA therapy.

Posology:

SINORA solution for infusion should not be used for initiating vasopressor treatment. It may be considered for use in patients already established on noradrenaline therapy, whose dose requirements are clinically confirmed to be escalating, such that SINORA 0,08 mg/ml, solution for infusion may be commenced at a flow rate of 1,5 ml/h and SINORA 0,16 mg/ml, solution for infusion may be commenced at a flow rate of 0,75 ml/h.

Adults

Initial dose:

The initial dose of noradrenaline base is usually between 0,05 and 0,15 micrograms/kg/min. This initial posology should be administered using a less concentrated noradrenaline solution that permits better titration by 0,05 and 0,1 micrograms/kg/min steps.

Maintenance dose range:

The recommended maintenance range of noradrenaline base is between 0,05 and 1 micrograms/kg/min.

Infusion rates and relative adjustments must be determined according to the required posology, as detailed in the Tables below.

Titration of dose:

SINORA solution for infusion, should be used with a suitable syringe pump capable of accurately and consistently delivering the minimum specified volume at a strictly controlled rate of infusion in line with the dose titration instructions.

Once an infusion of noradrenaline has been established the dose should be titrated in steps of 0,05 and 0,1 micrograms/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 mm Hg – depending on the patient’s condition).

Manual bolus for priming when initiating an infusion is not recommended.

Caution is required during syringe relay (replacement of the used syringe with a new one) to avoid haemodynamic instability.

Continuous SINORA infusion through a double pump system and an extension set reducing dead-space volume should be encouraged.

SINORA 0,08 mg/ml solution for infusion **50 ml vial containing 4 mg of 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	1,9
	0,1	0,3	3,8
	0,25	0,75	9,4
	0,5	1,5	18,8
	1	3	37,5
60 kg	0,05	0,18	2,3
	0,1	0,36	4,5
	0,25	0,9	11,3
	0,5	1,8	22,5
	1	3,6	45,0
70 kg	0,05	0,21	2,6
	0,1	0,42	5,3
	0,25	1,05	13,1
	0,5	2,1	26,3
	1	4,2	52,5
80 kg	0,05	0,24	3,0
	0,1	0,48	6,0
	0,25	1,2	15,0
	0,5	2,4	30,0
	1	4,8	60,0
90 kg	0,05	0,27	3,4

	0,1	0,54	6,8
	0,25	1,35	16,9
	0,5	2,7	33,8
	1	5,4	67,5

SINORA 0,16 mg/ml solution for infusion **50 ml vial containing 8 mg of 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	1,0
	0,1	0,3	1,9
	0,25	0,75	4,7
	0,5	1,5	9,4
	1	3	18,8
60 kg	0,05	0,18	1,2
	0,1	0,36	2,3
	0,25	0,9	5,7
	0,5	1,8	11,3
	1	3,6	22,5
70 kg	0,05	0,21	1,3
	0,1	0,42	2,7
	0,25	1,05	6,6
	0,5	2,1	13,2
	1	4,2	26,3
80 kg	0,05	0,24	1,5

	0,1	0,48	3,0
	0,25	1,2	7,5
	0,5	2,4	15,0
	1	4,8	30,0
90 kg	0,05	0,27	1,7
	0,1	0,54	3,4
	0,25	1,35	8,5
	0,5	2,7	16,9
	1	5,4	33,8

Duration of Treatment:

SINORA solution for infusion should be continued until high-dose vasoactive drug support is no longer indicated, at which point, the infusion should be gradually decreased, then switched to an infusion of lower concentration. Abrupt withdrawal can result in acute hypotension.

Special populations:

Patients with renal or hepatic impairment:

There is no experience of treatment in patients with renal- and hepatic impairment.

Elderly patients:

See section 4.4 Special warnings and precautions for use.

Paediatric population:

SINORA solution for infusion is indicated for adults only.

The efficacy and safety of SINORA solution for infusion in children and adolescents has not been established.

Method of administration:

For intravenous use only.

SINORA solution for infusion is administered intravenously. To avoid ischemic necrosis (skin, extremities) SINORA solution for infusion should be infused via a cannula placed in a central vein.

SINORA solution for infusion should be infused at a controlled rate using a syringe pump.

SINORA solution for infusion should not be diluted before use: it is supplied ready to use. It should not be mixed with other medicines.

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 may cause serious cardiac dysrhythmias. Because of the possibility of increasing risk of ventricular fibrillation, SINORA solution for infusion should be used with caution in patients receiving these or any other cardiac sensitising medicine or who exhibit profound hypoxia or hypercarbia.

4.4 Special warnings and precautions for use

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

Warnings

- 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 SINORA solution for infusion or an injection besides the vein, a tissue destruction can appear, resulting from the vasoconstrictive action of SINORA solution for infusion 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 solution for infusion 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 solution for infusion 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 solution for infusion.

Perfusion of SINORA solution for infusion 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 medicines whereas the administration of a beta-blocking medicines 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 solution for infusion at the same time as total blood or plasma, the latter must be administered in a separate drip.

SINORA solution for infusion contains 165,3 mg sodium per 50 ml vial, equivalent to 8,3 % 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).
- 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 solution for infusion with alpha- and beta-blockers, as severe hypertension may result. Caution is required when using SINORA solution for

infusion 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 solution for infusion 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 solution for infusion 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 (including gangrene of the extremities) 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 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 oxidase (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

Hydrochloric acid, sodium chloride and water for injections.

6.2 Incompatibilities

SINORA must not be mixed with other medicines.

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.

6.3 Shelf life

18 months

After the first opening, SINORA should be used immediately.

6.4 Special precautions for storage

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

Store in original package in order to protect from light.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

SINORA 0,08 mg/ml is presented in Type I clear, colourless glass vials closed with bromobutyl stoppers and an aluminium flip-off caps, containing 50 ml of solution for infusion. Each 50 ml vial is packed into a cardboard carton.

SINORA 0,16 mg/ml is presented in Type I clear, colourless glass vials closed with bromobutyl stoppers and an aluminium flip-off caps, containing 50 ml of solution for infusion. Each 50 ml vial is packed into a cardboard carton.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

SINORA solution for infusion is already diluted and ready to use. It should be used without prior dilution. It should be used with a suitable syringe either a syringe pump or an infusion pump or a drip counter capable of accurately and consistently delivering the minimum specified volume at a strictly controlled rate of infusion in line with the dose titration instructions specified in Section 4.2.

SINORA solution for infusion should not be used if the solution is darker than slightly yellow or pink in colour or if it contains a precipitate.

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

Name of Manufacturer: Sintetica SA

8. REGISTRATION NUMBERS

SINORA 0,08 mg/ml: 56/5.1/0109

SINORA 0,16 mg/ml: 56/5.1/0110

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 October 2022

10. DATE OF REVISION OF THE TEXT

23 April 2024

NAMIBIA:

SINORA 0,08 mg/ml (solution for infusion): Reg. No.: 22/5.1/0012 NS2

SINORA 0,16 mg/ml (solution for infusion): Reg. No.: 22/5.1/0013 NS2