Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sinora 1 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 2 mg noradrenaline (norepinephrine) tartrate corresponding to 1 mg noradrenaline (norepinephrine) base.

Each ampoule containing 1 ml of concentrate for solution for infusion contains 2 mg of noradrenaline (norepinephrine) tartrate corresponding to 1 mg of noradrenaline (norepinephrine) base.
Each ampoule containing 4 ml of concentrate for solution for infusion contains 8 mg of noradrenaline (norepinephrine) tartrate corresponding to 4 mg of noradrenaline (norepinephrine) base.
Each ampoule containing 5 ml of concentrate for solution for infusion contains 10 mg of noradrenaline (norepinephrine) tartrate corresponding to 5 mg of noradrenaline (norepinephrine) base.
Each ampoule containing 10 ml of concentrate for solution for infusion contains 20 mg of noradrenaline (norepinephrine) tartrate corresponding to 10 mg of noradrenaline (norepinephrine) base.

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

Excipients:
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.
Each ampoule containing 5 ml of concentrate for solution for infusion contains 0.72 mmol (or 16.5 mg) sodium.
Each ampoule containing 10 ml of concentrate for solution for infusion contains 1.44 mmol (or 33 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

Route of Administration:
For intravenous use.

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 noradrenaline 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).

Noradrenaline 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 clinicians 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.

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 drug 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:
Noradrenaline 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 the active substance or to any of the excipients 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 arrhythmias 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

- Noradrenaline is contra-indicated 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 should be used only in conjunction with appropriate blood volume replacement.
- When infusing noradrenaline, the blood pressure and rate of flow should be checked frequently to avoid hypertension.
- The products 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 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 drug 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. Noradrenaline 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 noradrenaline 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 noradrenaline.

Perfusion of noradrenaline 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 agent whereas the administration of a beta-blocking agent 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 at the same time as total blood or plasma, the latter must be administered in a separate drip.

This medicinal product contains less than1 mmol sodium (23 mg) per 1 ml and 4 ml and 5 ml ampoules, that is to say essentially 'sodium free'.

This medicinal product contains 33 mg sodium per 10 ml ampoule equivalent to 1.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Inadvisable combinations

- Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability.
- Imipramine antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).
- Serotoninergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).

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 with beta-blockers as severe hypertension may result.
Caution is required when using noradrenaline with the following drugs as they may cause increased cardiac effects: thyroid hormones, cardiac glycosides, antiarrhythmic agents.
Ergot alkaloids or oxytocin may enhance the vasopressor and vasoconstrictive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
SINORA may impair placental perfusion and induce fetal bradycardia. It may also exert a contractile effect on the pregnant uterus and lead to fetal asphyxia in late pregnancy. These possible risks to the fetus should therefore be weighed against the potential benefit to the mother.

Breast-feeding
No information is available on the use of SINORA in 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), arrhythmias, 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 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

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

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 noradrenaline 1 mg/ml concentrate for solution for infusion.

Absorption:
- Subcutaneous: poor
- Oral: noradrenaline is rapidly inactivated in the gastrointestinal tract following oral administration
- 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:
- Methylation by catechol-o-methyltransferase
- Deamination by monoamine oxydase (MAO)
- Ultimate metabolites from both is 4-hydroxy-3-methoxymandelic acid
- Intermediate metabolites include 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 fetal bradycardia. It may also exert a contractile effect on the uterus and lead to fetal asphyxia in late pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

SINORA must not be mixed with other medicinal products 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

2 years.

After dilution:
Chemical and physical in-use stability has been demonstrated for 24 hours at 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 at 2 to 8°C.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze.
Store in original package in order to protect from light.

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

6.5 Nature and contents of container

SINORA 1 mg/1 ml
Type I one point cut clear colorless glass 2 ml ampoules one point cut.
Box of 10 ampoules containing 1 ml of concentrate for solution for infusion.

SINORA 4 mg/4 ml
Type I one point cut clear colorless glass 5 ml ampoules one point cut.
Box of 10 ampoules containing 4 ml of concentrate for solution for infusion.

SINORA 5 mg/5 ml
Type I one point cut clear colorless glass 5 ml ampoules one point cut.
Box of 10 ampoules containing 5 ml of concentrate for solution for infusion.

SINORA 10 mg/10 ml
Type I one point cut clear colorless glass 10 ml ampoules one point cut.
Box of 10 ampoules containing 10 ml of concentrate for solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dilution instructions:
Dilute 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 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 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 product is compatible with PVC infusion bags.

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

7 MARKETING AUTHORISATION HOLDER

Sintetica GmbH
Albersloher Weg 11
Münster
48155
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8 MARKETING AUTHORISATION NUMBER

PA22835/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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