1. NAME OF THE MEDICINAL PRODUCT

Noradrenaline Sintetica 4 mg/4 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Norepinephrine (as bitartrate) 1 mg/ml.

Each ampoule of 4 ml contains 4 mg of norepinephrine (as bitartrate).

This medical product contains 3.2 mg sodium per ml (12.8 mg sodium per 4 ml ampoule).

For the full list of excipients, see section 12.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion. Clear and colorless solution.

4. INDICATIONS AND USAGE

For blood pressure control in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions).

As an adjunct in the treatment of cardiac arrest and profound hypotension.

5. DOSAGE AND ADMINISTRATION

Norepinephrine Bitartrate Injection is a concentrated, potent drug which must be diluted prior to infusion. An infusion of NORADRENALINE SINTETICA should be given into a large vein (see WARNINGS AND PRECAUTIONS).

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, intraaortic pressures must be maintained to prevent cerebral or coronary artery ischemia, NORADRENALINE SINTETICA can be administered before and concurrently with blood volume replacement.

Diluent: NORADRENALINE SINTETICA should be diluted in 5% dextrose injection, 0.9% NaCl or Glucosalin solution. Whole blood or plasma, if indicated to increase blood volume, should be administered separately (for example, by use of a Y-tube and individual containers if given simultaneously).

Average Dosage: Add a 4 mL ampoule (4 mg) of NORADRENALINE SINTETICA to 1,000 mL of a 5% dextrose solution, 0.9% NaCl or Glucosalin solution. Each mL of this dilution contains 4 mcg of the base of NORADRENALINE SINTETICA. 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. An IV drip chamber or other suitable metering device is essential to permit an accurate estimation of the rate of flow in drops per minute. After observing the response to an initial dose of 2 mL to 3 mL (from 8 mcg to 12 mcg 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 preexisting systolic pressure. The average maintenance dose ranges from 0.5 mL to 1 mL per minute (from 2 mcg to 4 mcg of base).

High Dosage: Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of NORADRENALINE SINTETICA should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg base or 17 ampoules) 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.

Fluid Intake: The degree of dilution depends on clinical fluid volume requirements. If large volumes of fluid (dextrose) are needed at a flow rate that would involve an excessive dose of the pressor agent per unit of time, a solution more dilute than 4 mcg per mL should be used. On the other hand, when large volumes of fluid are clinically undesirable, a concentration greater than 4 mcg per mL may be necessary.

Duration of Therapy: The infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. Infusions of NORADRENALINE SINTETICA should 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 SINTETICA 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 SINTETICA's powerful beta-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 SINTETICA is used in the same manner as described under Restoration of Blood Pressure in Acute Hypotensive States.

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

Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

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

6. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 12.

7. WARNINGS AND PRECAUTIONS

7.1 Tissue Ischemia

Administration of NORADRENALINE SINTETICA to patients who are hypotensive from hypovolemia can result in severe peripheral and visceral vasoconstriction, decreased renal perfusion and reduced urine output, tissue hypoxia, lactic acidosis, and reduced systemic blood flow despite "normal" blood pressure. Address hypovolemia prior to initiating NORADRENALINE SINTETICA [see Dosage and Administration (5)]. Avoid NORADRENALINE SINTETICA in patients with mesenteric or peripheral vascular thrombosis, as this may increase ischemia and extend the area of infarction.
Gangrene of the extremities has occurred in patients with occlusive or thrombotic vascular disease or who received prolonged or high dose infusions. Monitor for changes to the skin of the extremities in susceptible patients.
Extravasation of NORADRENALINE SINTETICA may cause necrosis and sloughing of surrounding tissue. To reduce the risk of extravasation, infuse into a large vein, check the infusion site frequently for free flow, and monitor for signs of extravasation.
Emergency Treatment of Extravasation
To prevent sloughing and necrosis in areas in which extravasation has occurred, infiltrate the ischemic area as soon as possible, using a syringe with a fine hypodermic needle with 5 to 10 mg of phentolamine mesylate in 10 to 15 mL of 0.9% Sodium Chloride Injection in adults.
Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours.

7.2 Hypotension after Abrupt Discontinuation

Sudden cessation of the infusion rate may result in marked hypotension. When discontinuing the infusion, gradually reduce the NORADRENALINE SINTETICA infusion rate while expanding blood volume with intravenous fluids.

7.3 Cardiac Arrhythmias

NORADRENALINE SINTETICA elevates intracellular calcium concentrations and may cause arrhythmias, particularly in the setting of hypoxia or hypercarbia. Perform continuous cardiac monitoring of patients with arrhythmias.

This medicinal product contains less than 1 mmol (23 mg) sodium per ampoule, i.e. it is essentially “sodium free”.

8. ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Tissue Ischemia *[see Warnings and Precautions (7.1)]*
- Hypotension *[see Warnings and Precautions (7.2)]*
- Cardiac Arrhythmias *[see Warnings and Precautions (7.3)]*

The most common adverse reactions are hypertension and bradycardia.

The following adverse reactions can occur:

Nervous system disorders: Anxiety, headache

Respiratory disorders: Respiratory difficulty, pulmonary edema

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (https://sideeffects.health.gov.il)

9. DRUG INTERACTIONS

9.1 MAO-Inhibiting Drugs

Co-administration of NORADRENALINE SINTETICA with monoamine oxidase (MAO) inhibitors or other drugs with MAO-inhibiting properties (e.g., linezolid) can cause severe, prolonged hypertension.
If administration of NORADRENALINE SINTETICA cannot be avoided in patients who recently have received any of these drugs
and in whom, after discontinuation, MAO activity has not yet sufficiently recovered, monitor for hypertension.

9.2 Tricyclic Antidepressants

Co-administration of NORADRENALINE SINTETICA with tricyclic antidepressants (including amitriptyline, nortriptyline, protriptyline, clomipramine, desipramine, imipramine) can cause severe, prolonged hypertension. If
administration of NORADRENALINE SINTETICA cannot be avoided in these patients, monitor for hypertension.

9.3 Antidiabetics

NORADRENALINE SINTETICA can decrease insulin sensitivity and raise blood glucose. Monitor glucose and consider dosage
adjustment of antidiabetic drugs.

9.4 Halogenated Anesthetics

Concomitant use of NORADRENALINE SINTETICA with halogenated anesthetics (e.g., cyclopropane, desflurane, enflurane, isoflurane, and sevoflurane) may lead to ventricular tachycardia or ventricular fibrillation. Monitor cardiac
rhythm in patients receiving concomitant halogenated anesthetics.

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Limited published data consisting of a small number of case reports and multiple small trials involving the use of norepinephrine in pregnant women at the time of delivery have not identified an increased risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus from hypotension associated with septic shock, myocardial infarction and stroke which are medical emergencies in pregnancy and can be fatal if left untreated. (see Clinical Considerations). In animal reproduction studies, using high doses of intravenous norepinephrine resulted in lowered maternal placental blood flow. Clinical relevance to changes in the human fetus is unknown since the average maintenance dose is ten times lower (see Data).

Increased fetal reabsorptions were observed in pregnant hamsters after receiving daily injections at approximately 2 times the maximum recommended dose on a mg/m3 basis for four days during organogenesis (see Data).

The estimated background risk for major birth defects and miscarriage for the indicated population is unknown.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2-4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypotension associated with septic shock, myocardial infarction, and stroke are medical emergencies in pregnancy which can be fatal if left untreated. Delaying treatment in pregnant women with hypotension associated with septic shock, myocardial infarction and stroke may increase the risk of maternal and fetal morbidity and mortality. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of norepinephrine on the fetus.

Data

Animal Data

A study in pregnant sheep receiving high doses of intravenous norepinephrine (40 mcg/min, at approximately 10 times the average maintenance dose of 2-4 mcg/min in human, on a mg/kg basis) exhibited a significant decrease in maternal placental blood flow. Decreases in fetal oxygenation, urine and lung liquid flow were also observed.

Norepinephrine administration to pregnant rats on Gestation Day 16 or 17 resulted in cataract production in rat fetuses.

In hamsters, an increased number of resorptions (29.1% in study group vs. 3.4% in control group), fetal microscopic liver abnormalities and delayed skeletal ossification were observed at approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day from Gestation Day 7-10).

10.2 Lactation

Risk Summary

There are no data on the presence of norepinephrine in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. Clinically relevant exposure to the infant is not expected based on the short half-life and poor oral bioavailability of norepinephrine.

10.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

10.4 Geriatric Use

Clinical studies of NORADRENALINE SINTETICA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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 drug therapy.

Avoid administration of NORADRENALINE SINTETICA into the veins in the leg in elderly patients *[see Warnings and Precautions (7.1)]*.

11. OVERDOSAGE

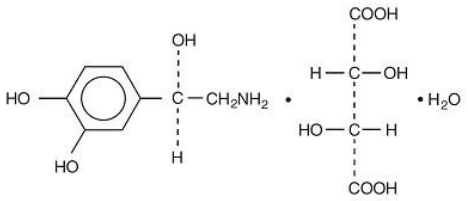
Overdosage with NORADRENALINE SINTETICA may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output.

In case of overdosage, discontinue NORADRENALINE SINTETICA until the condition of the patient stabilizes.

12. DESCRIPTION

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

Norepinephrine Bitartrate is (-)-α-(aminomethyl)-3,4-dihydroxybenzyl alcohol tartrate (1:1) (salt) monohydrate and has the following structural formula:



NORADRENALINE SINTETICA is supplied in sterile aqueous solution in the form of the bitartrate salt to be administered by intravenous infusion following dilution. Norepinephrine is sparingly soluble in water, very slightly soluble in alcohol and ether, and readily soluble in acids. Each mL contains 2 mg noradrenaline bitartrate, the equivalent of 1 mg base of noradrenaline, sodium chloride for isotonicity, and water for injection. It has a pH of 3 to 4.5. The air in the ampoules has been displaced by nitrogen gas.

13. CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Norepinephrine is a peripheral vasoconstrictor (alpha-adrenergic action) and an inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action).

13.2 Pharmacodynamics

The primary pharmacodynamic effects of norepinephrine are cardiac stimulation and vasoconstriction. Cardiac output is generally unaffected, although it can be decreased, and total peripheral resistance is also elevated. The elevation in resistance and pressure result in reflex vagal activity, which slows the heart rate and increases stroke volume. The elevation in vascular tone or resistance reduces blood flow to the major abdominal organs as well as to skeletal muscle. Coronary blood flow is substantially increased secondary to the indirect effects of alpha stimulation. After intravenous administration, a pressor response occurs rapidly and reaches steady state within 5 minutes. The pharmacologic actions of norepinephrine are terminated primarily by uptake and metabolism in sympathetic nerve endings. The pressor action stops within 1-2 minutes after the infusion is discontinued.

13.3 Pharmacokinetics

Absorption

Following initiation of intravenous infusion, the steady state plasma concentration is achieved in 5 min.

Distribution

Plasma protein binding of norepinephrine is approximately 25%. It is mainly bound to plasma albumin and to a smaller extent to prealbumin and alpha 1-acid glycoprotein. The volume of distribution is 8.8 L. Norepinephrine localizes mainly in sympathetic nervous tissue. It crosses the placenta but not the blood-brain barrier.

Elimination

The mean half-life of norepinephrine is approximately 2.4 min. The average metabolic clearance is 3.1 L/min.

Metabolism

Norepinephrine is metabolized in the liver and other tissues by a combination of reactions involving the enzymes catechol-O-methyltransferase (COMT) and 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.

Excretion

Noradrenaline metabolites are excreted in urine primarily as sulphate conjugates and, to a lesser extent, as glucuronide conjugates. Only small quantities of norepinephrine are excreted unchanged.

14. NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Studies have not been performed.

15. SHELF-LIFE

The expiry date is indicated on the packaging materials.

Use immediately after opening. Discard any residual solution.

Stability after opening

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. 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, unless dilution has taken place in controlled and validated aseptic conditions.

16. HOW SUPPLIED

NORADRENALINE SINTETICA contains the equivalent of 4 mg base of NORADRENALINE per each 4 mL ampoule (1 mg/mL).

Supplied as:

Ampoules of 4 mL in boxes of 10.

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

Manufacturer: Sintetica SA, Via Penate 5, CH-6850 Mendrisio, Switzerland

Registration holder: CTS Ltd., 4 Haharash St., Hod-Hasharon, 4524075.

Marketing authorization number: 158-56-34555-00

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