1. NAME OF THE MEDICINAL PRODUCT

Noradrenaline Kalceks

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Noradrenaline (as tartrate) 1 mg/ml.

Each ampoule of 4 ml contains 4 mg of noradrenaline (as tartrate).

This medical product contains 3.3 mg sodium per ml (13.2 mg sodium per 4 ml ampoule).

For the full list of excipients, see section 5.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear, colourless or yellowish solution, practically free from visible particles.
pH ranges between 3.0 and 4.0. Osmolality 260-310 mOsm/kg.

4. INDICATIONS AND USAGE

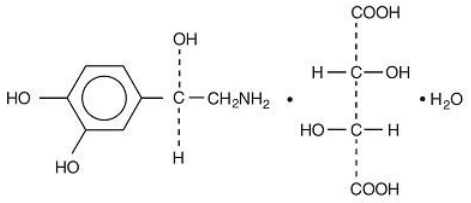
For blood pressure control in certain acute hypotensive states (e.g., pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, myocardial infarction, septicemia, blood transfusion, and drug reactions).

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

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



Noradrenaline Kalceks is supplied in sterile aqueous solution in the form of the tartrate salt to be administered by intravenous infusion following dilution. Noradrenaline is sparingly soluble in water, very slightly soluble in alcohol and ether, and readily soluble in acids. Each ml contains 2 mg noradrenaline tartrate, the equivalent of 1 mg base of noradrenaline, sodium chloride for isotonicity, hydrochloric acid and water for injections. It has a pH of 3.0 to 4.0. The air in the ampoules has been displaced by nitrogen gas.

CLINICAL PHARMACOLOGY

Noradrenaline Kalceks functions as a peripheral vasoconstrictor (alpha-adrenergic action) and as an inotropic stimulator of the heart and dilator of coronary arteries (beta-adrenergic action).

6. CONTRAINDICATIONS

Noradrenaline Kalceks should not be given to patients with hypersensitivity to the active substance or to any of the excipients listed in section 5.

Noradrenaline Kalceks should not be given to patients who are hypotensive from blood volume deficits except as an emergency measure to maintain coronary and cerebral artery perfusion until blood volume replacement therapy can be completed. If Noradrenaline Kalceks is continuously administered to maintain blood pressure in the absence of blood volume replacement, the following may occur: severe peripheral and visceral vasoconstriction, decreased renal perfusion and urine output, poor systemic blood flow despite “normal” blood pressure, tissue hypoxia, and lactate acidosis.

Noradrenaline Kalceks should also not be given to patients with mesenteric or peripheral vascular thrombosis (because of the risk of increasing ischemia and extending the area of infarction) unless, in the opinion of the attending physician, the administration of Noradrenaline Kalceks is necessary as a life-saving procedure.

Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or noradrenaline. Hence, the use of Noradrenaline Kalceks during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation.

The same type of cardiac arrhythmias may result from the use of Noradrenaline Kalceks in patients with profound hypoxia or hypercarbia.

7. WARNINGS

Noradrenaline Kalceks should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

PRECAUTIONS

General

Avoid Hypertension: Because of the potency of Noradrenaline Kalceks and because of varying response to pressor substances, the possibility always exists that dangerously high blood pressure may be produced with overdoses of this pressor agent. It is desirable, therefore, to record the blood pressure every two minutes from the time administration is started until the desired blood pressure is obtained, then every five minutes if administration is to be continued.

The rate of flow must be watched constantly, and the patient should never be left unattended while receiving Noradrenaline Kalceks. Headache may be a symptom of hypertension due to overdosage.

Site of Infusion: Whenever possible, infusions of Noradrenaline Kalceks should be given into a large vein, particularly an antecubital vein because, when administered into this vein, the risk of necrosis of the overlying skin from prolonged vasoconstriction is apparently very slight. Some authors have indicated that the femoral vein is also an acceptable route of administration. A catheter tie-in technique should be avoided, if possible, since the obstruction to blood flow around the tubing may cause stasis and increased local concentration of the drug. Occlusive vascular diseases (for example, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower than in the upper extremity. Therefore, one should avoid the veins of the leg in elderly patients or in those suffering from such disorders. Gangrene has been reported in a lower extremity when infusions of Noradrenaline Kalceks were given in an ankle vein.

Extravasation: The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of Noradrenaline Kalceks into the tissues, as local necrosis might ensue due to the vasoconstrictive action of the drug. Blanching along the course of the infused vein, sometimes without obvious extravasation, has been attributed to vasa vasorum constriction with increased permeability of the vein wall, permitting some leakage.

This also may progress on rare occasions to superficial slough, particularly during infusion into leg veins in elderly patients or in those suffering from obliterative vascular disease. Hence, if blanching occurs, consideration should be given to the advisability of changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

IMPORTANT — **Antidote for Extravasation Ischemia:** To prevent sloughing and necrosis in areas in which extravasation has taken place, the area should be infiltrated as soon as possible with 10 ml to 15 ml of saline solution containing from 5 mg to 10 mg of phentolamine, an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, with the solution being infiltrated liberally throughout the area, which is easily identified by its cold, hard, and pallid appearance. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

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

Drug Interactions

Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or noradrenaline. Hence, the use of Noradrenaline Kalceks during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of Noradrenaline Kalceks in patients with profound hypoxia or hypercarbia.

Noradrenaline Kalceks should be used with extreme caution in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed.

Pregnancy

Animal reproduction studies have not been conducted with Noradrenaline Kalceks. It is also not known whether Noradrenaline Kalceks can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Noradrenaline Kalceks should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Noradrenaline Kalceks is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of noradrenaline 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.

Noradrenaline Kalceks infusions should not be administered into the veins in the leg in elderly patients (see ***PRECAUTIONS***, **General**).

8. ADVERSE REACTIONS

The following reactions can occur:

Body As a Whole: Ischemic injury due to potent vasoconstrictor action and tissue hypoxia.
Cardiovascular System: Bradycardia, probably as a reflex result of a rise in blood pressure, arrhythmias and stress cardiomyopathy.
Nervous System: Anxiety, transient headache.
Respiratory System: Respiratory difficulty.
Skin and Appendages: Extravasation necrosis at injection site.

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 Noradrenaline Kalceks 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 ischemic injury. Gangrene of extremities has been rarely reported.

Overdoses or conventional doses in hypersensitive persons (e.g., hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal 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.

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)

OVERDOSAGE

Overdosage with Noradrenaline Kalceks may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output. In case of accidental overdosage, as evidenced by excessive blood pressure elevation, discontinue Noradrenaline Kalceks until the condition of the patient stabilizes.

9. DOSAGE AND ADMINISTRATION

Noradrenaline tartrate Injection is a concentrated, potent drug which must be diluted prior to infusion. An infusion of Noradrenaline Kalceks should be given into a large vein (see *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 Kalceks can be administered before and concurrently with blood volume replacement.

Diluent: Noradrenaline Kalceks should be diluted in sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution, or sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) 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 Kalceks to 1,000 ml of a sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution, or sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) solution. Each ml of this dilution contains 4 mcg of the base of noradrenaline. 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 noradrenaline 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 noradrenaline 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 Kalceks should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg noradrenaline 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 (glucose) 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 Kalceks 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 Kalceks 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 Kalceks'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 Kalceks 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.

Do not use the solution if it has a brown color or if it contains a precipitate. Avoid contact with iron salts,

alkalis, or oxidizing agents.

This medicinal product must not be mixed with other medicinal products except those mentioned in

section 10.

The product is compatible with polyvinyl chloride (PVC), ethyl vinyl acetate (EVA) or polyethylene (PE) infusion bags.

10. SHELF-LIFE

The expiry date is indicated on the packaging materials.

Shelf life after opening the ampoule

Once opened, the diluted solution should be prepared immediately.

For single use only, discard any residual solution.

Shelf life after dilution

Chemical and physical in-use stability has been demonstrated for 48 hours at 25 °C and 2-8 °C when diluted to 4 mg/litre noradrenaline in sodium chloride 9 mg/ml (0.9%) solution or glucose 50 mg/ml (5%) solution, or sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) solution.

From a microbiological point of view, the diluted solution 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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

11. HOW SUPPLIED

Noradrenaline Kalceks contains the equivalent of 4 mg base of noradrenaline per each 4 ml ampoule (1 mg/ml). Supplied as:
Colourless glass ampoules containing 4 ml solution in boxes of 10.

Do not store above 25 °C.

Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 10.

Manufacturer:

HBM Pharma s.r.o., Sklabinska 30, 036 80 Martin, Slovakia

Marketing Authorization Holder:

A.L.Medi-Market Ltd., 3 Hakatif Street, Emek Hefer Industrial Park, 3877701, Israel

Marketing authorization number: 171-54-36591-99

Revised in February 2023 according to MOH's guidelines.