PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

NOREPINEPHRINE KALCEKS CONCENTRATE FOR SOLUTION FOR INFUSION 1 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of concentrate for solution for infusion contains norepinephrine tartrate equivalent to 1 mg norepinephrine.
Each ampoule containing 4 ml of concentrate for solution for infusion contains norepinephrine tartrate equivalent to 4 mg norepinephrine.

When diluted as recommended, each ml contains norepinephrine tartrate equivalent to 4 micrograms norepinephrine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOREPINEPHRINE KALCEKS is indicated to raise blood pressure in adult patients with severe, acute hypotension.

4.2 Posology and method of administration

Address hypovolemia before initiation of norepinephrine therapy. If the patient does not respond to therapy, suspect occult hypovolemia (see section 4.4).

Posology

Adults
After an initial dosage of 8 to 12 micrograms per minute via intravenous infusion, assess patient response and adjust dosage to maintain desired hemodynamic effect. Monitor blood pressure every two minutes until the desired hemodynamic effect is achieved, and then monitor blood pressure every five minutes for the duration of the infusion.
Typical maintenance intravenous dosage is 2 to 4 micrograms per minute.

Discontinuation of therapy
When discontinuing the infusion, reduce the flow rate gradually. Avoid abrupt withdrawal.

Method of administration

Intravenous use after dilution.

Dilute prior to use.
For instructions on dilution of the medicinal product before administration, see section 6.7.

Infuse norepinephrine into a large vein. Avoid infusions in the veins of the leg in the elderly or in patients with occlusive vascular disease of the legs (see section 4.4).
A drip counter or other suitable metering device is essential to permit an accurate estimation of the rate of flow in drops per minute. Avoid using a catheter-tie-in technique.

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).

4.4 Special warnings and precautions for use

Tissue ischemia
Administration of norepinephrine 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 norepinephrine (see section 4.2). Avoid norepinephrine 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 norepinephrine 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 (see section 4.2).

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 sodium chloride 9 mg/ml (0.9%) solution for injection in adults.
Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperaemic changes if the area is infiltrated within 12 hours.

Hypotension after abrupt discontinuation
Sudden cessation of the infusion rate may result in marked hypotension. When discontinuing the infusion, gradually reduce the norepinephrine infusion rate while expanding blood volume with intravenous fluids.

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

Paediatric population
Safety and effectiveness in paediatric patients have not been established.

Geriatric use
Clinical studies of norepinephrine 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 norepinephrine into the veins in the leg in elderly patients (see section 4.2).

Excipients
Ampoules containing 4 ml of concentrate for solution for infusion contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

MAO-inhibiting drugs
Co-administration of norepinephrine with monoamine oxidase (MAO) inhibitors or other drugs with MAO-inhibiting properties (e.g. linezolid) can cause severe, prolonged hypertension. If administration of norepinephrine 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.

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

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

Halogenated anaesthetics
Concomitant use of norepinephrine with halogenated anaesthetics (e.g. cyclopropane, desflurane, enflurane, isoflurane, and sevoflurane) may lead to ventricular tachycardia or ventricular fibrillation. The use of norepinephrine with halogenated anaesthetics is not recommended. If the administration of norepinephrine cannot be avoided, monitor cardiac rhythm in patients receiving concomitant halogenated anaesthetics.

Norepinephrine infusion solutions should not be mixed with other medications (except those mentioned in section 6.7).

4.6 Fertility, pregnancy and lactation

Pregnancy
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 foetal outcomes. There are risks to the mother and foetus 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 foetus is unknown since the average maintenance dose is ten times lower (see section 5.3). Increased foetal 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 section 5.3).
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/foetal 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 foetal 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 foetus.

Breast-feeding
There are no data on the presence of norepinephrine in either human or animal milk, the effects on the breast-fed 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.

4.7 Effects on ability to drive and use machines

No information is available. Therefore, driving or operating machinery is not recommended.

4.8 Undesirable effects

The following adverse reactions are described in greater detail in other sections:
- Tissue ischemia (see section 4.4)
- Hypotension (see section 4.4)
- Cardiac arrhythmias (see section 4.4)

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 oedema

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.

4.9 Overdose

Symptoms
Overdosage may result in headache, severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output. These may be accompanied by violent headache, cerebral haemorrhage, photophobia, retrosternal pain, pallor, fever, intense sweating, pulmonary oedema and vomiting.

Treatment
In case of accidental overdose, as evidenced by excessive blood pressure elevation, discontinue the drug until the condition of the patient stabilises.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cardiac therapy, adrenergic and dopaminergic agents, ATC code: C01CA03

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).

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.

5.2 Pharmacokinetic properties

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 litres. 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 litres/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
Norepinephrine 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.

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.

Norepinephrine 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.

A study in pregnant sheep receiving high doses of intravenous norepinephrine (40 micrograms/min, at approximately 10 times the average maintenance dose of 2-4 micrograms/min in human, on a mg/kg basis) exhibited a significant decrease in maternal placental blood flow. Decreases in foetal 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), foetal microscopic liver abnormalities and delayed skeletal ossification were observed at

approximately 2 times the maximum recommended intramuscular or subcutaneous dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5mg/kg/day from пestation Day 7-10).

Carcinogenesis, mutagenesis, and fertility studies have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

Infusion solutions containing norepinephrine tartrate have been reported to be incompatible with the following substances: iron salts, alkalis and oxidising agents. Whole blood or plasma, if indicated to increase blood volume, should be administered separately.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.7.

6.3 Shelf life

2 years.

6.4 Shelf life after opening the ampoule and dilution

Shelf life after opening the ampoule
Once opened, the diluted solution should be prepared immediately.

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated for 48 hours at 30 °C and 2-8 °C when diluted to 4 mg/litre in 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Special precautions for storage

Do not store above 30 °C.
Keep the ampoules in the outer carton in order to protect from light.

6.6 Nature and contents of container

4 ml of solution filled in colourless glass ampoules with one point cut. The ampoules are packed in liner and placed into carton box.

Pack size: 10 ampoules

6.7 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

The solution should be visually inspected prior to use for particulate matter and discoloration. The solution should not be used if it contains any visible particles/solids.

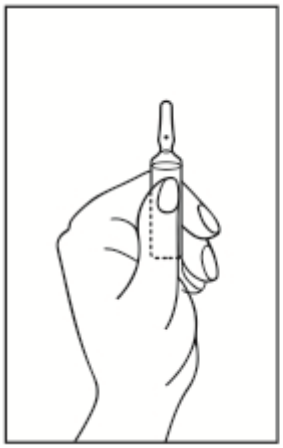
Do not use the solution for infusion if it has a brown colour.

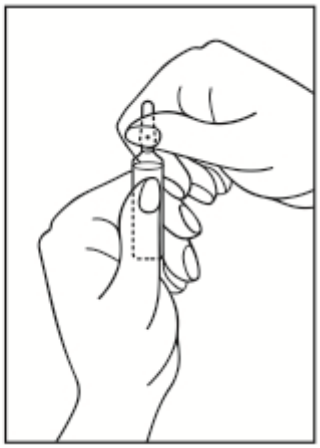
Dilute before use with:
– glucose 50 mg/ml (5%) solution or
– sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) solution.

Add the content of one ampoule (4 mg/4 ml) of NOREPINEPHRINE KALCEKS to 1,000 ml of 50 mg/ml (5 %) glucose (or another compatible diluent mentioned above). Each ml of this dilution contains 4 micrograms of the norepinephrine base. Glucose reduces loss of potency due to oxidation. Administration in saline solution alone is not recommended. Use higher concentration solutions in patients requiring fluid restriction.

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

Instruction of ampoule opening:
1) Turn the ampoule with coloured point up. If there is any solution in the upper part of the ampoule, gently tap with your finger to get all the solution to the lower part of the ampoule.
2) Use both hands to open; while holding the lower part of the ampoule in one hand, use the other hand to break off the upper part of the ampoule in the direction away from the coloured point (see the pictures below).





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

7. PRODUCT OWNER AND MANUFACTURER

Product Owner:
AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

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

8. MARKETING AUTHORISATION NUMBER

SINXXXXXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

11/2022