SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Norepinephrine Kalceks 1 mg/ml concentrate for solution for infusion

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.
Description after dilution:
Clear, colourless or yellowish solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Posology and method of administration

Restoration of blood pressure in acute hypotensive state: Blood volume depletion should always be corrected as fully as possible before any vasopressor is administered. When, as an emergency measure, intra-aortic pressures must be maintained to prevent cerebral or coronary artery ischemia, norepinephrine can be administered before and concurrently with blood volume replacement.

Diluent: Norepinephrine Kalceks should be diluted in glucose 50 mg/ml (5%) or sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) solution for injection. These glucose containing fluids are protection against significant loss of potency due to oxidation. Administration in saline solution alone is not recommended. Whole blood or plasma, if indicated to increase blood volume, should be administered separately (e.g. by use of a Y-tube and individual containers if given simultaneously).

Average dosage: Add the content of the ampoule (4 mg/4 ml) of Norepinephrine Kalceks to 1,000 ml of 50 mg/ml (5 %) glucose or sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) solution for injection. Each ml of this dilution contains 4 mcg of the norepinephrine base. 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 norepinephrine 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 pre-existing systolic pressure. The average maintenance dose ranges from 0.5 ml to 1 ml per minute (from 2 mcg to 4 mcg of norepinephrine base).

High dosage: Great individual variation occurs in the dose required to attain and maintain an adequate blood pressure. In all cases, dosage of norepinephrine should be titrated according to the response of the patient. Occasionally much larger or even enormous daily doses (as high as 68 mg norepinephrine 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 norepinephrine 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 norepinephrine 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. Norepinephrine 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, norepinephrine is used in the same manner as described under ‘Restoration of blood pressure in acute hypotensive states’ below.

Hepatic/renal impairment
There is no experience in treatment of hepatically or renally impaired patients.

Elderly
In general, dose selection for an elderly patient should be cautious, starting at the low end of the dosing range as to reflect the greater frequency of decreased hepatic, renal or cardiac function and concomitant disease or other drug therapy.

Paediatric population
The safety and efficacy of norepinephrine in children less than 18 years of age has not yet been established. No data are available.

Method of administration

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 colour or if it contains a precipitate. Avoid contact with iron salts, alkalis, or oxidizing agents.

Route of administration
Intravenous (IV) after dilution.

Norepinephrine Kalceks should be diluted and should be administered via a central venous catheter. The infusion should be at a controlled rate using drip counter.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Do not use undiluted.
Do not use with cyclopropane and halothane anaesthetics. For interactions see section 4.5.

4.4 Special warnings and precautions for use

Norepinephrine 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.

Norepinephrine should be used only in conjunction with appropriate blood volume replacement.

If norepinephrine 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 lactic acidosis. Blood volume replacement can be administered before and/or concurrently with this agent; however, if whole blood or blood plasma is indicated to increase blood volume, administer separately (e.g. if given simultaneously, use Y-tubing and individual containers).

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 norepinephrine is discontinued or the 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.

When infusing norepinephrine, the blood pressure and rate of flow should be checked frequently to avoid hypertension, which may be associated with bradycardia as well as headache and peripheral ischemia, including rarely gangrene of the extremities. Extravasation may cause local tissue necrosis (see section 'Extravasation' below).

Caution is advised in patients with major left ventricular dysfunction associated with acute hypotension. Supportive therapy should be initiated simultaneously with diagnostic evaluation. Norepinephrine should be reserved for patients with cardiogenic shock and refractory hypotension, in particular those without elevated systemic vascular resistance.

Occurrence of heart rhythm disorders during the treatment must lead to a reduction in the dosage.

Cardiac arrhythmias may arise when norepinephrine is used in conjunction with cardiac sensitizing agents, and may be more likely in patients with hypoxia or hypercarbia.

Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because norepinephrine may increase the ischemia and extend the area of infarction, unless in the opinion of the attending physician, the administration of norepinephrine is necessary as a life-saving procedure. Similar caution should be observed in patients with hypotension following myocardial infarction and in patients with angina, particularly Prinzmetal's variant angina, diabetes, hypertension or hyperthyroidism (see section 4.8).

Special caution should be used for patients with liver failure, severe renal dysfunction, ischemic heart diseases and elevated intracranial pressure. Overdoses or conventional doses in hypersensitive persons

(e.g. hyperthyroid patients) may cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating and vomiting. Hypertension may eventually lead to acute pulmonary oedema, arrhythmia or cardiac arrest.

Care should be taken in diabetics as it increases the level of blood glucose (due to the glycogenolytic action in the liver and the inhibition of insulin release from the pancreas).

The elderly may be especially sensitive to the effects of norepinephrine due to the greater frequency of hepatic, renal or cardiac dysfunction and concomitant disease or other drug therapy.

The use of norepinephrine in children is not recommended (see sections 4.2 and 5.2).

Norepinephrine should only be used by doctors familiar with the selective indications for its use.

Where indicated, appropriate replacement therapy of blood or fluid together with adoption of the supine position with elevation of the legs, must be instituted and maintained prior to and/or during therapy with this product. When infusing norepinephrine, the blood pressure and rate of flow should be checked frequently to avoid hypertension. Therefore, it is desirable to record the blood pressure every two minutes from the time the administration started until the desired blood pressure is obtained and then every five minutes thereafter, if the administration is to be continued. The rate of flow must be watched constantly and the patient should never be left unattended while receiving norepinephrine. Hypertension may eventually lead to acute pulmonary oedema, arrhythmia or cardiac arrest.

The infusion of norepinephrine should be stopped gradually as sudden cessation may produce a catastrophic fall in blood pressure.

Extravasation
The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of norepinephrine 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. On rare occasions this may progress to superficial slough, particularly during infusion into leg veins in elderly patients or in those suffering from obliterative vascular disease. If blanching occurs, consideration should be given to changing the infusion site at intervals to allow the effects of local vasoconstriction to subside.

IMPORTANT – Antidote for extravasation ischaemia
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 hyperaemic changes if the area is infiltrated within 12 hours. Phentolamine should be given as soon as possible after the extravasation is noted and infusion should be stopped.

Excipients
This medicinal product 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

Norepinephrine should be used with extreme caution in patients receiving monoamine oxidase inhibitors or within 14 days of cessation of such therapy and in patients receiving tricyclic antidepressants, adrenergic-serotoninergic drugs or linezolid because severe, prolonged hypertension may result.

The use of pressor amines with cyclopropane, halothane, chloroform, enflurane or other halogenated anaesthetics may cause serious cardiac arrhythmias, because of the possibility of increasing the risk of ventricular fibrillation, norepinephrine should be used with caution in patients receiving these or any other cardiac sensitising agent or who exhibit profound hypoxia or hypercarbia.

The effects of norepinephrine may be enhanced by guanethidine, reserpine, methyldopa or tricyclic antidepressants. Concomitant administration of propofol and noradrenaline may lead to propofol infusion syndrome (PRIS).

Norepinephrine infusion solutions should not be mixed with other medications (except those mentioned in section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
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. These possible risks to the foetus should therefore be weighed against the potential benefit to the mother.

Breast-feeding
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 norepinephrine is administered to a nursing woman.

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

Table 2 lists adverse reactions that have been experienced following treatment with norepinephrine. This data has largely been collected from spontaneous reporting, and due to the problems in calculating reporting frequencies from spontaneous reporting, the frequency of the listed adverse reactions is ‘not known’ (cannot be estimated from the available data). The adverse reactions are reported in decreasing order of frequency within each system order class (SOC).

Table 2 Adverse reactions reported with norepinephrine through spontaneous reporting

System Organ Class (SOC)	**Adverse Reactions**
Psychiatric disorders	Anxiety, insomnia, confusion, weakness, psychotic state
Nervous system disorders	Transient headache, tremor
Cardiac disorders	Bradycardia[1], arrhythmia, electrocardiogram change, tachycardia, cardiogenic shock, stress cardiomyopathy, palpitations, increase in the contractility of the cardiac muscle resulting from the beta-adrenergic effect on the heart (inotrope and chronotrope)
Vascular disorders	Hypertension, peripheral ischaemia[2] including gangrene of the extremities, plasma volume depletion with prolonged use, ischaemic injury due to potent vasoconstrictor action may result in coldness and paleness of the limbs
Gastrointestinal disorders	Nausea, vomiting
Skin and subcutaneous tissue disorders	Paleness, scarification of the skin, bluish skin colour, hot flushes or skin redness, skin rash, hives or itching
Renal and urinary disorders	Retention of urine
Respiratory, thoracic and mediastinal disorders	Dyspnoea
General disorders and administration	Extravasation, injection site necrosis

site conditions	

[1] Bradycardia, probably as a reflex result of a rise in blood pressure
[2] Ischaemia, due to potent vasoconstrictor action and tissue hypoxia

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.

The vasopressor effect (resulting from the adrenergic action on the vessels) can be reduced by the concomitant administration of an alpha blocking agent (phentolamine mesilate) whereas the administration of a beta blocking agent (propranolol) may result in a reduction of the stimulating effect of the product on the heart and in an increase of the hypertensor effect (through reduction of arteriolar dilatation), resulting from beta-1 adrenergic stimulation.

Prolonged administration of any potent vasopressor may result in plasma volume depletion which should be continuously corrected by appropriate water and electrolyte replacement therapy. If plasma volumes are not corrected, hypotension may recur when the norepinephrine infusion is discontinued, or blood pressure may be maintained with the risk of severe peripheral and visceral vasoconstriction with diminution in blood flow.

Hypertension may occur, which may be associated with bradycardia as well as headache and peripheral ischemia, including gangrene of the extremities.

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 Centre for Adverse Drug Reaction Monitoring by visiting the website portal.npra.gov.my

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.

Norepinephrine has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. Norepinephrine causes generalised vasoconstriction, except for the coronary vessels which it dilates indirectly by increasing the oxygen consumption. 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.
The vascular effects of norepinephrine in the doses usually 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. 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.

5.2 Pharmacokinetic properties

Up to 16% of an intravenous dose is excreted unchanged in the urine with methylated and deaminated metabolites in free and conjugated forms.

Paediatric population
No data on experience of pharmacokinetic studies in paediatric age groups is available.

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, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine, sulfafurazole.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

Unopened: 2 years

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.

6.4 Special precautions for storage

Do not store above 30 °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 6.3.

6.5 Nature and contents of container

Colourless glass ampoules with one point cut containing 4 ml solution.
Ampoules are packed in liner. Liners are placed into an outer carton.

Pack sizes: 10 ampoules.

6.6 Special precautions for disposal and other handling

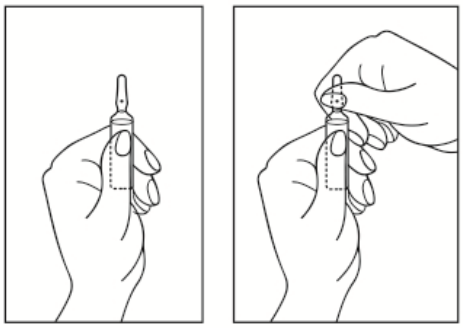
For single use only. Discard any unused contents.

Dilute before use (see section 4.2).

Description after dilution:
Clear, colourless or yellowish solution, practically free from visible particles.

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 REGISTRATION HOLDER AND MANUFACTURER

Product Registration Holder:
Eucogen Sdn Bhd
6A, Jalan Sungai Burung U
32/U, Bukit Rimau, 40460 Shah
Alam, Selangor, Malaysia

Manufacturer:
HBM PHARMA S.R.O.
Sklabinska 30, Martin, 036 80, SLOVAKIA

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8. DATE OF REVISION OF THE TEXT

09/2022

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