SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Noradrenaline (Norepinephrine) Kabi 1 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The composition per ampoule is given in the following table:

Amount of concentrate	Amount of noradrenaline base	Amount of noradrenaline tartrate
1 ml	1 mg	2 mg
4 ml	4 mg	8 mg
5 ml	5 mg	10 mg
8 ml	8 mg	16 mg
10 ml	10 mg	20 mg

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

Excipient with known effects:

This medicinal product contains 3.4 mg sodium per ml.

8 ml of concentrate for solution for infusion contains 27.2 mg sodium. 10 ml of concentrate for solution for infusion contains 34 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless to pale yellow solution, practically free from visible particles.

pH: 3.0 – 4.0

Osmolarity: approximately 300 mOsm/l

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Noradrenaline (Norepinephrine) Kabi 1 mg/ml concentrate for solution for infusion is 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

Posology

Adults

When diluted as recommended in section 6.6, the final concentration of the infusion solution is 40 mg/litre noradrenaline base, which is equivalent to 80 mg/litre noradrenaline tartrate.

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.

Initial rate of infusion:

The initial rate of infusion should be between 10 ml/hour and 20 ml/hour (0.16 to 0.32 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).

Table 1 Dose titration of noradrenaline solution for infusion

Noradrenaline solution for infusion 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

Duration of treatment and monitoring

The noradrenaline infusion should be continued until adequate blood pressure and tissue perfusion are maintained without therapy. The patient should be monitored carefully for the duration of noradrenaline therapy.

Noradrenaline should only be administered by healthcare professionals who are familiar with its use and have appropriate facilities to adequately monitor the patient.

Withdrawal of therapy

The noradrenaline infusion should be reduced gradually, avoiding abrupt withdrawal which can result in acute hypotension.

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 (see section 4.4).

Paediatric population

The safety and efficacy of noradrenaline in children and adolescents aged less than 18 years old has not yet been established. No data are available.

Method of administration

Route of administration

For intravenous use only after dilution.

For instructions on dilution of the medicinal product before administration, see section 6.6.

The infusion should be at a controlled rate using either a syringe pump or an infusion pump or a drip counter.

Noradrenaline (Norepinephrine) Kabi 1 mg/ml concentrate for solution for infusion should be administered as a diluted solution and it should be administered via a central venous catheter.

If not using a central venous catheter, whenever possible, noradrenaline infusion should be administered into a large vein, particularly an antecubital vein, to minimize the risk of ischemic necrosis (skin, extremities) (see section 4.4 “Extravasation”).

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.

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) (see section 4.4).

- Do not use with cyclopropane and halothane anaesthetics as this may cause serious cardiac arrhythmias including ventricular fibrillation. For interactions see section 4.5.

4.4 Special warnings and precautions for use

Do not use undiluted.

Noradrenaline is contraindicated in 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 (see section 4.3).

Noradrenaline should be used only in conjunction with appropriate blood volume replacement (see section 4.8).

If noradrenaline 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 noradrenaline 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; gangrene of extremities has been rarely reported.

When infusing noradrenaline, 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).

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, unless in the opinion of the attending physician, the administration of noradrenaline 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.

Caution is advised in patients with 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.

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

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

The use of pressor amines with chloroform, enflurane or other halogenated anaesthetics may cause serious cardiac arrhythmias. Because of the possibility of increasing risk of ventricular fibrillation, noradrenaline should be used with caution in patients receiving these or any other cardiac sensitising agent or who exhibit profound hypoxia or hypercarbia (see section 4.5).

The use with cyclopropane and halothane anesthetics is contraindicated (see section 4.3).

Noradrenaline should be used with extreme caution in patients receiving monoamine oxidase (MAO) 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 (see section 4.5).

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 edema, 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).

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

The use of noradrenaline in children is not recommended (see section 4.2 and 5.2).

Noradrenaline 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 noradrenaline, 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 noradrenaline. Hypertension may eventually lead to acute pulmonary oedema, arrhythmia or cardiac arrest.

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

The vasopressor effect (resulting from the adrenergic action on 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.

Extravasation

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of noradrenaline tartrate 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.

Occlusive vascular diseases (e.g. atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease) are more likely to occur in the lower extremity than in the upper extremity; therefore, avoid the veins of the leg in elderly patients or in those suffering from such disorders.

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.

Sodium

This medicinal product contains 3.4 mg sodium per ml, equivalent to 0.17 % 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 halogenated anaesthetics: severe ventricular arrhythmia (increase in cardiac excitability) (see sections 4.3 and 4.4).

- 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).

- Digitalis glycosides.

- Levodopa.

- Chlorpheniramine hydrochloride, tripelennamine hydrochloride and desipramine: significantly increase the toxicity of noradrenaline.

- Antihistamines, as some may block the intake of catecholamines by peripheral tissues and increase the toxicity of injected noradrenaline.

- Combinations requiring precautions for use and a close medical supervision (see section 4.4)

- Non-selective monoamine oxidase (MAO) inhibitors: increase in the vasopressor effect of the sympathomimetic which is usually moderate.

- Selective MAO-A inhibitors: by extrapolation from non-selective MAO inhibitors, risk of increase in the vasopressor effect.

- Linezolid: by extrapolation from non-selective MAO inhibitors, risk of increase in the vasopressor effect.

- The effects of noradrenaline may be enhanced by guanethidine, guanadrel, reserpine, methyldopa or tricyclic antidepressants, amphetamine, doxapram, mazindol, rauwolfia alkaloids.

- Caution is required when using noradrenaline with alpha and 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 (ergoloid mesylates, ergotamine, dihydroergotamine, ergometrine, methylergometrine, and methysergide) or oxytocin may enhance the vasopressor and vasoconstrictive effects.

- Concomitant administration of propofol and noradrenaline may lead to propofol infusion syndrome (PRIS).

- Desmopressin or vasopressin: its antidiuretic effect is diminished.

- Lithium decreases the effect of noradrenaline.

- Noradrenaline infusion solutions should not be mixed with other medications (except those mentioned in section 6.6).

4.6 Fertility, Pregnancy and lactation

Pregnancy

Noradrenaline 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. Nursing is generally not advised during use of noradrenaline as emergency treatment of acute hypotension.

Fertility

No studies have been performed to collect fertility data for noradrenaline.

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 noradrenaline. 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 noradrenaline through spontaneous reporting

System Organ Class	**Undesirable effect**
Psychiatric disorders	Anxiety, insomnia, confusion, weakness, psychotic state
Nervous system disorders	Transient headache, tremor
Eyes disorders	Acute glaucoma (very frequent in patients anatomically predisposed with a closing of the iridocorneal angle).
Cardiac disorders	Bradycardia[1], arrhythmia (see section 4.4),
	electrocardiogram change, tachycardia, cardiogenic shock, stress cardiomyopathy, palpitations, increase in the contractility of the cardiac muscle resulting from the betaadrenergic effect on the heart (inotrope and chronotrope), acute cardiac insufficiency
Vascular disorders	Hypertension (see section 4.4), peripheral ischaemia[2] including gangrene of the extremities, plasma volume depletion with prolonged use
Respiratory, thoracic and mediastinal disorders	Dyspnoea, respiratory insufficiency or difficulty
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 tract disorders	Retention of urine
General disorders and administration site conditions	Extravasation, necrosis at injection site

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

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

The continuous administration of vasopressor to maintain blood pressure in absence of blood volume replacement may cause the following symptoms (see section 4.4):

- severe peripheral and visceral vasoconstriction
- decrease in renal blood flow - decrease in urine production
- hypoxia
- increase in lactate serum levels.

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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Overdosage may result in 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.

Management

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

The vascular effects 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.

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 (Norepinephrine) Kabi 1 mg/ml concentrate for solution for infusion 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. 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.

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

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for Injections

6.2 Incompatibilities

Noradrenaline (Norepinephrine) Kabi 1 mg/ml concentrate for solution for infusion 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: iron salts, alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, sulfadiazine, sulfafurazole.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25 °C.

Keep the ampoule 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

Type I clear glass ampoules containing:

1 ml of concentrate (in pack sizes of 5, 10 or 50);

4 ml, 5 ml, 8 ml and 10 ml of concentrate (each in pack sizes of 5 or 10).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only.

The solution is to be visually inspected prior to use. The solution should not be used if it has brown colour or if it contains any visible particles.

Dilution instructions:

Either add 2 ml concentrate to 48 ml diluent for administration by syringe pump or add 20 ml of concentrate to 480 ml diluent 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 following diluents can be used: sodium chloride 9 mg/ml (0.9% w/v) with glucose 50 mg/ml (5% w/v) infusion glucose 50 mg/ml (5% w/v) infusion sodium chloride 9 mg/ml (0.9% w/v) infusion

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 18719/0028

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2021

10 DATE OF REVISION OF THE TEXT

02/12/2021