Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Norden (Norepinephrine Bitartrate Injection USP 2 mg/ml) 4ml Injection

2. Qualitative and quantitative composition

Each ml contains:
Norepinephrine bitartrate USP 2 mg Eq. to Norepinephrine 1 mg
Water for injection BP Q.S.

Excipients with known effects
Sodium Chloride BP

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Concentrate for solution for infusion. A clear, colourless solution.
pH: Between 3.0 – 4.5

4. Clinical particulars

4.1 Therapeutic indications

Indicated 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
Initial rate of infusion:
When diluted as recommended (the concentration of the prepared infusion is 40 mg/litre noradrenaline base (80 mg/litre noradrenaline tartrate)) the initial rate of infusion, at a body weight of 70 kg, should be between 10 ml/hour and 20 ml/hour (0.16 to 0.33 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).

Noradrenaline Infusion Solution **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

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.

Renal or hepatic impairment:
There is no experience in treatment of renal or hepatical impaired patients.

Elderly:
As for adults but see section 4.4.

Paediatric population:
Not recommended.

Duration of Treatment and Monitoring:
Noradrenaline should be continued for as long as vasoactive drug support is indicated. The patient should be monitored carefully for the duration

of therapy. Blood pressure should be carefully monitored for the duration of therapy.

Withdrawal of Therapy:
The noradrenaline infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

Route of administration
Intravenous use after dilution.

Noradrenaline (Norepinephrine) 1 mg/ml concentrate for solution for infusion should be diluted and administered via a central venous catheter. The infusion should be at a controlled rate using either a syringe pump or an infusion pump, or a drip counter.

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

4.3 Contraindications

Hypersensitivity to noradrenaline tartrate or any of the excipients listed in section 6.1.

Hypotension due to blood volume deficit (hypovolaemia).

Do not use with cyclopropane and halothane anaesthetics. For interactions, see section 4.5.

The use of pressor amines during cyclopropane or halothane anaesthesia may cause serious cardiac arrhythmias. Because of the possibility of increasing the 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.

The administration in the veins of the lower limbs of the elderly and patients with occlusive diseases due to possible vasoconstriction should be avoided (see section 4.4)

4.4 Special warnings and precautions for use

Do not use undiluted.

Noradrenaline 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.

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

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 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 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).

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.

Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline may increase the ischemia 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 (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 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 sections 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 before 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.

Extravasation

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation of noradrenaline 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
Ampoules containing 1 ml, 2 ml, 4 ml, or 5 ml of concentrate for solution for infusion contain less than 1 mmol sodium (23 mg) per ampoule, that is to say, essentially 'sodium-free'.

Each ampoule containing 8 ml of concentrate for solution for infusion contains 26.4 mg (1.12 mmol) sodium, equivalent to 1.32 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Each ampoule containing 10 ml of concentrate for solution for infusion contains 33 mg (1.40 mmol) sodium, equivalent to 1.65 % 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).
- Imipramine antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).
- Serotoninergic-adrenergic antidepressants: paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).
- 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.

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. Noradrenaline should be used with caution in patients receiving these or any other cardiac sensitising agent or who exhibit profound hypoxia or hypercarbia.

Combinations requiring precautions for use
- Non-selective monoamine oxidase (MAO) inhibitors: increase in the pressor action of the sympathomimetic, which is usually moderate. Should only be used under close medical supervision.
- Selective MAO-A inhibitors: by extrapolation from non-selective MAO inhibitors, risk of an increase in the pressor action. Should only be used under close medical supervision.
- Linezolid: by extrapolation from non-selective MAO inhibitors: risk of increase in the pressor action. Should only be used under close medical supervision.

Noradrenaline should be used with extreme caution in patients receiving MAO inhibitors or within 14 days of cessation of such therapy.

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.

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 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. Because many drugs are excreted in human milk, caution should be exercised when noradrenaline is administered to a nursing woman.

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

4.7 Effects on the ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions are reported in decreasing order of frequency within each system order class (SOC).

Adverse reactions reported with noradrenaline 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 site conditions	Extravasation, injection site necrosis

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

The continuous administration of a vasopressor to maintain blood pressure in the 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 noradrenaline 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 Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Overdose may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance, and decreased cardiac output. These may be accompanied by violent headache, photophobia, retrosternal pain, pallor, intense sweating, and vomiting. In the event of overdose, treatment should be withdrawn and appropriate corrective treatment initiated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Pharmacodynamics properties
The vascular effects in the doses normally 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.
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) 1 mg/ml concentrate for solution for infusion.

Absorption
- Subcutaneous: Poor
- Oral: Noradrenaline is rapidly inactivated in the gastro-intestinal 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 metabolite 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 pregnant uterus and lead to fetal asphyxia in late pregnancy.

6. Pharmaceutical Particulars

6.1 List of Excipients

Sodium Chloride BP
Tartaric Acid BP
Sodium Metabisulphite BP
Sodium hydroxide BP
Water for Injection BP

6.2 Incompatibilities

Noradrenaline 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: alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin.

6.3 Shelf-Life

24 months
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 25 ° C and 2-8 ° C when diluted to 4 mg/litre and 40 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 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. Protect from light. Do not allow to freeze.

6.5 Nature and Content of container

5 x 4 mL amber glass ampoules packed in a transparent plastic tray in a printed carton along with package insert.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused contents.

The solution should be visually inspected prior to use. 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%) solution or
– sodium chloride 9 mg/ml (0.9%) with glucose 50 mg/ml (5%) solution.

Either add 2 ml concentrate to 48 ml glucose 50 mg/ml (5%) solution (or any of the other above mentioned solutions for dilution) for administration by syringe pump, or add 20 ml of concentrate to 480 ml glucose 50 mg/ml (5%) solution (or any of the other above mentioned solutions for dilution) for administration by drip counter. In both cases the final concentration of the infusion solution is 40 mg/litre noradrenaline (which is equivalent to 80 mg/litre noradrenaline (norepinephrine) tartrate). Dilutions other than 40 mg/litre noradrenaline may also be used (see section 4.2). If dilutions other than 40 mg/litre noradrenaline are used, check the infusion rate calculation carefully before starting treatment.

The product is compatible with polyvinyl chloride (PVC) infusion bags.

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

7. Marketing Authorization Holder

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8. Marketing Authorization Number
CTD10095

9. Date of first authorization/renewal of the authorization
25/05/2023

10. Date of revision of the text
10/05/2025