SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vipranop 5 micrograms/ml Solution for Injection and Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection/infusion contains 10 micrograms of noradrenaline (norepinephrine) tartrate monohydrate, equivalent to 5 micrograms noradrenaline (norepinephrine) anhydrous.

Each 20 ml vial contains 200 micrograms of noradrenaline (norepinephrine) tartrate monohydrate, equivalent to 100 micrograms of noradrenaline (norepinephrine) anhydrous.

Each 50 ml vial contains 500 micrograms of noradrenaline (norepinephrine) tartrate monohydrate, equivalent to 250 micrograms of noradrenaline (norepinephrine) anhydrous.

Excipient with known effect

This medicinal product contains sodium.

Each ml of solution for injection/infusion contains 3.54 mg equivalent to 0.15 mmol of sodium.

Each 20 ml vial contains approximately 71 mg equivalent to 3 mmol of sodium.

Each 50 ml vial contains approximately 177 mg equivalent to 7.5 mmol of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear and colourless solution, practically free from visible particles.

pH: 3.7 to 4.1

Osmolality: 260-320 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Restoration and maintenance of peri-operative blood pressure following hypotension induced by spinal or general anesthesia in adults.

4.2 Posology and method of administration

This presentation is suitable for perioperative setting, the concentration is not adapted to critical care setting.

Posology

This medicinal product should not be diluted before use: it is supplied ready to use and must not be mixed with other medicines. It is suitable for injection or continuous infusion through a peripheral venous line.

The patient should be monitored carefully for the duration of noradrenaline therapy.

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

Initial rate

The initial dose of infusion is between 0.02 µg/kg/min and 0.05 µg/kg/min of noradrenaline (equivalent to 0.04 µg/kg/min and 0.1 µg/kg/min of noradrenaline tartrate). An initial intravenous bolus of 5 µg to 10 µg of noradrenaline (10 µg to 20 µg noradrenaline tartrate) may be administered before the start of the infusion, following spinal anesthesia, or the induction of general anesthesia.

Titration of dose

Once an infusion of noradrenaline has been established the dose can be increased or decreased at the discretion of the attending physician to maintain an adequate target blood pressure during the peri-operative period. The dose should be adjusted according to age, weight and clinical condition of the patient.

Intravenous bolus of 5 µg to 10 µg noradrenaline (10 µg to 20 µg noradrenaline tartrate) can be administered if the blood pressure needs to be increased rapidly.

Noradrenaline (norepinephrine) infusion solution 5 micrograms/ml (noradrenaline base)			
Patient's weight	Posology (µg/kg/min) noradrenaline base	Posology (µg/kg/min) noradrenaline tartrate	Infusion rate (ml/h)
50 kg	0.01	0.02	6
	0.02	0.04	12
	0.03	0.06	18
	0.04	0.08	24
	0.05	0.1	31
	0.06	0.12	36
	0.07	0.14	42
	0.08	0.16	48
60 kg	0.01	0.02	7.2
	0.02	0.04	14.4
	0.03	0.06	21.6
	0.04	0.08	28.8
	0.05	0.1	36
	0.06	0.12	43.2
	0.07	0.14	50.4
	0.08	0.16	57.6
70 kg	0.01	0.02	8.4
	0.02	0.04	16.8
	0.03	0.06	25.2
	0.04	0.08	33.6
	0.05	0.1	42
	0.06	0.12	50.4
	0.07	0.14	58.8
	0.08	0.16	67.2
80 kg	0.01	0.02	9.6
	0.02	0.04	19.2
	0.03	0.06	28.8
	0.04	0.08	38.4
	0.05	0.1	48
	0.06	0.12	57.6
	0.07	0.14	67.2
	0.08	0.16	76.8
90 kg	0.01	0.02	10.8
	0.02	0.04	21.6
	0.03	0.06	32.4
	0.04	0.08	43.6
	0.05	0.1	54
	0.06	0.12	64.8
	0.07	0.14	75.6
	0.08	0.16	86.4

Duration of treatment and monitoring

Noradrenaline should be continued throughout the peri-operative period as long as considered necessary to maintain adequate blood pressure and tissue perfusion.

Withdrawal of therapy

Infusions 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 patients

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

This medicinal product is indicated for adults only.

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

Method of administration

For intravenous use.

This medicinal product is a ready to use solution for single use only, which should not be diluted before use.

It can be administered as a continuous infusion or bolus injection through a peripheral venous line.

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

Site of infusion

This medicinal product should be infused through a peripheral or a central venous catheter.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

4.4 Special warnings and precautions for use

This medicinal product can be used as injection/infusion through a peripheral venous catheter.

The infusion should be at a controlled rate using either a syringe pump, an infusion pump or a drip counter. This presentation is suitable for perioperative setting, the concentration is not adapted to critical care setting.

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.

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. Special caution should be used for patients with liver failure, severe renal dysfunction, ischemic heart diseases and elevated intracranial pressure.

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).

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 section 4.2 and 5.2).

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

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

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 4.2 – Site of infusion).

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 hyperemic changes if the area is infiltrated within 12 hours. Phentolamine should be given as soon as possible after the extravasation is noted and noradrenaline infusion should be stopped.

This medicinal product contains 71 mg sodium per 20 ml vial, equivalent to 3.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 177 mg sodium per 50 ml vial, equivalent to 8.9 % 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

Combinations to be avoided

- *Volatile halogen anaesthetics:* severe ventricular arrhythmia (increase in cardiac excitability).
- *Imipramine antidepressants, guanethidine, reserpine:* 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).

Combinations requiring precautions for use

- *Non-selective 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, Linezolid and Methylene Blue:* by extrapolation from non-selective MAO inhibitors, risk of increase in the pressor action. Should only be used under close medical supervision.

Caution is required when using noradrenaline with 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 or oxytocin may enhance the vasopressor and vasoconstrictive effects.

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

Noradrenaline infusion solutions should not be mixed with other medications.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of noradrenaline in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. 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. These possible risks to the foetus should therefore be considered against the potential benefit to the mother.

This medicinal product is not recommended during pregnancy unless the clinical condition of the woman requires treatment with noradrenaline.

Breastfeeding

It is not known whether noradrenaline is excreted in human milk. However, noradrenaline is not orally absorbed, and exposure in milk is therefore not expected to have adverse effects for the suckling child. This medicinal product can be used with caution during breast-feeding.

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. Conditions in which noradrenaline is used exclude the possibility of driving or operating machinery.

4.8 Undesirable effects

Table 1 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 1: Adverse reactions reported with noradrenaline through spontaneous reporting

System Organ Class (SOC)	Adverse Reactions
Psychiatric disorders	Anxiety, insomnia.
Nervous system disorders	Transient headache, tremor, dizziness.
Eye disorders	Acute glaucoma.
Cardiac disorders	Bradycardia[1], arrythmia, electrocardiogram change, tachycardia, cardiogenic shock, stress cardiomyopathy.
Vascular disorders	Hypertension, peripheral ischaemia[2] including gangrene of the extremities, plasma volume depletion with prolonged use.
Respiratory, thoracic and mediastinal disorders	Dyspnea.
Gastrointestinal disorders	Nausea and vomiting.
Renal and urinary disorders	Retention of urine.
General disorders and administration site conditions	Extravasation, injection site necrosis

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

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

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:

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 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.

Management

In case of accidental overdose, as evidenced by excessive blood pressure elevation, reduce the rate of infusion, or discontinue this medicinal product until the condition of the patient stabilizes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The vascular effects of noradrenaline 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

Absorption

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 oxidase (MAO).
- Ultimate metabolites from both is 4-hydroxy-3-methoxymandelic acid.
- Intermediate metabolites include normetanephrine and 3,4-dihydroxymandelic acid.

Elimination

Noradrenaline metabolites are excreted in urine primarily as the sulfate conjugates and, to a lesser extent, as the glucuronide conjugates. Only small quantities of noradrenaline are excreted unchanged.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Disodium edetate

Hydrochloric acid (pH adjustment)

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C in a polypropylene syringe. From a microbiological point of view, the product 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 manipulation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.

Store the vial in the outer carton to protect from light. Do not freeze.

6.5 Nature and contents of container

20 ml or 50 ml clear type II glass vial closed with a chlorobutyl stopper and an aluminium cap.

Box of 1 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused contents.

This medicinal product is already diluted and ready to use. It should be used without prior dilution. It can be administered using either a syringe pump, or an infusion pump, or a drip counter capable of accurately and consistently delivering the minimum specified volume at a strictly controlled rate of infusion in line with the dose instructions specified in Section 4.2. This medicinal product is a clear and colourless solution, practically free from visible particles. The solution should not be used if the solution appears slightly yellow or pink, or is brown in colour, or if it contains particles or a precipitate.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 14434/0045

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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