**Summary of Product Characteristics**

## 1. Name of the Medicinal Product

1.1 Product Name: Norvita IV

1.2 Strength: Each ml contains: Norepinephrine bitartrate eq. to Norepinephrine 1 mg

1.3 Pharmaceutical Dosage Form: Concentrate for solution for infusion.

## 2. Quality and Quantitative Composition

2.1 Qualitative Declaration: Norepinephrine bitartrate

2.2 Quantitative Declaration: Each ml contains: Norepinephrine bitartrate equivalent to Norepinephrine 1 mg.

## 3. Pharmaceutical Form: A clear, colorless sterile solution for injection.

## 4. Clinical Particulars

4.1 Therapeutic indication:

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

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

4.2 Posology and method of administration:

Posology

**Acute hypotensive states**:

Adult

- The usual initial dosage is 8-12 mcg/minute IV and observe response; adjust rate of flow to establish a low normal BP (systolic, 80-100 mmHg).
- The maintenance dosage is 2-4 mcg/minute IV; doses up to 68 mg/day may be needed

**Adjunctive Treatment in Cardiac Arrest**:

Adult

- The initial dosage is 8-12 mcg/minute IV and observe response; adjust rate of flow to establish a low normal BP (systolic, 80 to 100 mmHg)
- The maintenance dosage is 2-4 mcg/minute IV; doses up to 68 mg/day may be needed

Pediatric

- The infusion rate administration is 0.1 to 2 mcg/kg/minute, adjusted based on patient response.

**Renal or hepatic impairment**:

- There is no experience in treatment of renally or hepatically impaired patients.

**Elderly**:

- As for adults but the elderly patients may be especially sensitive to the effects of noradrenaline.

**Duration of Treatment and Monitoring**:

- It 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.

Method of administration:

Norepinephrine Bitartrate Injection is a concentrated, potent drug which must be diluted in dextrose containing solutions prior to infusion. Administer as a continuous infusion via an infusion pump or other apparatus to control the rate of flow. An infusion should be given into a large vein, Central line administration is preferred.

**Dilution instructions**:

Dilute before use with a dextrose-containing solution (5% dextrose injection with or without 0.9% sodium chloride injection). These dextrose containing fluids are protection against significant loss of potency due to oxidation. **Administration in saline solution alone is not recommended** because of possible loss of potency due to oxidation.

**Preparation for administration**:

Continuous IV infusion: Norepinephrine bitartrate is stated to be compatible with various infusion solution. However, dilute with Dextrose 5% in water, Dextrose 5% in normal saline (0.9%) are recommended diluents for infusion. Concentrations ranging from 4 to 16 mcg/mL are typically used in clinical practice.

Solutions of norepinephrine should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate. Avoid contact with iron salts, alkalis, or oxidizing agents

4.3 Contraindications

- Hypersensitivity to noradrenaline tartrate or to any of the excipients listed in section 6.1.
- During anesthesia with cyclopropane or halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation.

4.4 Special warnings and precautions for use

- Elderly patients may be especially sensitive to the effects of noradrenaline.
- 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. Similar caution should be observed in patients with hypotension following myocardial infarction, in patients with Prinzmetal's variant angina and in patients with diabetes, hypertension or hyperthyroidism.
- Site of Infusion: Administer infusions into a large vein, particularly an antecubital vein. Avoid catheter tie-in technique, if possible. Avoid leg veins in elderly patients or in those suffering from occlusive disorders (eq, atherosclerosis, arteriosclerosis, diabetic endarteritis, Buerger's disease). Gangrene has been reported in a lower extremity when infusions were given in an ankle vein.
- Noradrenaline should be used with caution in patients who exhibit profound hypoxia or hypercarbia.
- Norepinephrine should be used only in conjunction with appropriate blood volume replacement. When infusion noradrenaline, the blood pressure and rate of flow should be checked frequently to avoid hypertension.
- Extravasation of the solution may cause local tissue necrosis. The infusion site should be checked frequently. If extravasation occurs, the infusion should be stopped and the area should be infiltrate with diluted phentolamine (5-10 mg in 10-15 mL of saline) with a fine hypodermic needle. Phentolamine should be administered as soon as possible after extravasation is noted to prevent sloughing/ necrosis.
- Sulfite sensitivity: Norepinephrine Bitartrate Injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.
- 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 the infusion 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 and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischemic injury.

4.5 Interaction with other medicinal products and other forms of interactions

- Cyclopropane and halothane anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of intravenously administered epinephrine or norepinephrine. Hence, the use of Norepinephrine during cyclopropane and halothane anesthesia is generally considered contraindicated because of the risk of producing ventricular tachycardia or fibrillation. The same type of cardiac arrhythmias may result from the use of Norepinephrine in patients with profound hypoxia or hypercarbia.
- The use of noradrenaline with volatile halogenated anaesthetic agents, monoamine oxidase inhibitors, linezolid, tricyclic antidepressants, adrenergic-serotoninergic drugs or any other cardiac sensitising agents is not recommended because severe, prolonged hypertension and possible arrhythmias may result.

4.6 Pregnancy and lactation

**Pregnancy**: Category C. Animal reproduction studies have not been conducted. Norepinephrine is an endogenous catecholamine and crosses the placenta.

**Lactation**: It is not known if norepinephrine is excreted in breast milk. The recommends that caution be exercised when administering norepinephrine to breast-feeding women.

4.7 Effects on ability to drive and use machine

None stated.

4.8 Undesirable effects

| System Organ | Undesirable effect |
|---|---|
| Cardiovascular | Bradycardia, probably as a reflex result of a rise in blood pressure, arrhythmias. |
| Nervous | Anxiety, transient headache. |
| Dermatologic | Extravasation necrosis at injection site. |
| Respiratory | Respiratory difficulty. |
| Miscellaneous | Ischemic injury due to potent vasoconstrictor action and tissue hypoxia. |

4.9 Overdose

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

## 5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Stimulates beta-1 adrenergic receptors and alpha-adrenergic receptors causing increased contractility and heart rate as well as vasoconstriction, thereby increasing systemic blood pressure and coronary blood flow; clinically, alpha effects (vasoconstriction) are greater than beta effects (inotropic and chronotropic and effects).

5.2 Pharmacokinetic properties

Absorption: After IV administration, a pressor response occurs rapidly. The effect on blood pressure disappears 1-2 minutes after the infusion is discontinued.

Distribution: Norepinephrine localizes mainly in sympathetic nervous tissue. The drug crosses the placenta but not the blood-brain barrier.

Elimination: The drug is metabolized in the liver and other tissues by a combination of reactions involving the enzymes catechol-O-methyltransferase (COMT) and monoamine oxide (MAO). The major metabolites are normetanephrine and 3-methoxy-4-hydroxy mandelic acid (vanillylmandelic acid, VMA), both of which are inactive. Up to 16% of Norepinephrine intravenous dose is excreted unchanged in the urine.

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 metabisulfite
- Sodium chloride
- Sodium hydroxide (for pH adjustment)
- Hydrochloric acid (for pH adjustment)
- Water for injection

6.2 Incompatibilities

Infusion solutions containing Norepinephrine bitartrate have been reported to be incompatible with the following substances: alkalis and oxidizing agent, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, aminophylline, Pantoprazole Sodium and Insulin.

6.3 Shelf life

24 months.

After dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 30±2 $^{o}$C when dilute to 4 mg/litre and 16 mg/litre norepinephrine base in Dextrose 5% in water and Dextrose 5% in normal saline (0.9%) solution. However, 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 2-8 $^{o}$C.

6.4 Special precautions for storage

Store below 30°C

For storage conditions after dilution of the medicinal product, see section 6.3.

Do not use the solution if its color is pinkish or darker than slightly yellow or if it contains a precipitate.

6.5 Nature and contents of container

4, 8 mL amber glass vial (Type I) with aluminium flip-off/Chlorobutyl rubber and 4, 8 mL amber glass ampoule (Type I) packed or unpacked in a box of 1, 10 and 12 vials/ampoules.

**7. Marketing Authorization Holder**

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nong Son, Chiang Yuen,

Mahasarakham 44160, Thailand

**8. Marketing Authorization Numbers**

1A 15053/63

**9. Date of authorization**

19/03/2020

**10. Date of revision of the text**

19/03/2020