Public Assessment Report

Decentralised Procedure

Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

UK/H/1378/001/DC

UK licence no: PL 25975/0040

Cardinal Health UK 434 Limited
LAY SUMMARY

On the 2nd December 2010, the Medicine and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe. The licence was granted to the company Cardinal Health Ltd.

Noradrenaline is used to treat patients with low blood pressure. This medicine will be given to you in a hospital, under the direction of an experienced doctor.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

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<th>Product Name</th>
<th>Noradrenaline (Norepinephrine) 0.1 mg/ml Solution for Infusion in pre-filled syringe</th>
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<tbody>
<tr>
<td>Type of Application</td>
<td>Article 10.3</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Norepinephrine tartrate (rINN) (Noradrenaline tartrate)</td>
</tr>
<tr>
<td>Form</td>
<td>Powder for Solution for Infusion</td>
</tr>
<tr>
<td>Strength</td>
<td>0.1mg/ml</td>
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<tr>
<td>Marketing Authorisation Holder</td>
<td>Cardinal Health UK 434 Ltd</td>
</tr>
<tr>
<td></td>
<td>Bampton Road, Harold Hill, Essex, RM3 8UG, UK</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member State (CMS)</td>
<td>Denmark, Ireland, The Netherlands and Sweden</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/1378/001/DC</td>
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<td>10th November 2010</td>
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Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe (PL 25975/0040) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Noradrenaline (Norepinephrine) 0.1 mg/ml Solution for Infusion in pre-filled syringe.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution contains 0.2mg Noradrenaline Tartrate, equivalent to 0.1mg Noradrenaline. Each 50ml syringe contains 10mg Noradrenaline Tartrate equivalent to 5mg Noradrenaline.

For a full list of excipients see section 6.1

This medicinal product contains approximately 7.4mMol (170mg) Sodium per 50ml syringe. To be taken into consideration by patients on a controlled sodium diet.

This medicinal product contains 12.5mg sodium metabisulphite per 50ml syringe. May rarely cause severe hypersensitivity reaction and bronchospasm.

3 PHARMACEUTICAL FORM
Solution for Infusion in pre-filled syringe.

A 50ml pre-filled syringe containing a clear, colourless solution

The pH of the solution is 3.0 – 4.6 and the osmolality is 270-330 mOsmol/kg.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Noradrenaline is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration
Route of Administration:

For intravenous use only.

Noradrenaline should only be administered as an infusion at a controlled rate by a syringe pump.
Noradrenaline should not be diluted before use; it is supplied ready for use.

Site of injection:

Noradrenaline is used by intravenous infusion only. Infusions of noradrenaline should be given into a large vein via a central venous catheter.

Blood pressure control:

Measure blood pressure every two minutes at the beginning of the infusion until the desired blood pressure is obtained. Then every five minutes when desired the blood pressure is obtained, if the administration has to be continued. The infusion flow rate must be controlled constantly, and the patient should never be left unattended during infusion.

Initial Rate of Infusion

The initial rate of infusion, at a body weight of 70 kg should be between 4ml/hour and 8ml/hour however some clinicians may wish to start at lower initial infusion rates of 2ml/hour. These initial rates are approximately equal to a dosage of 0.05microgram/kg/min to 0.15microgram/kg/ml. This is equivalent to the following dosage:
Initial dosing instruction: Noradrenaline 0.1 mg/ml

<table>
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<tr>
<th>Body weight</th>
<th>Infusion rate ml/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 kg</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
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<tr>
<td>0.05 µg/kg/min</td>
<td>1.2</td>
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<tr>
<td>0.10 µg/kg/min</td>
<td>2.4</td>
</tr>
<tr>
<td>0.15 µg/kg/min</td>
<td>3.6</td>
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</table>

**Titration of Dose**
Once an infusion of Noradrenaline has been established the dose should be titrated in steps of 0.05 – 0.1 microgram/kg/min 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 mmHg) or to achieve an adequate mean arterial blood pressure (greater than 65 to 80 mm Hg- depending on the patient’s condition).

**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 noradrenaline therapy. The infusion must not be stopped suddenly but should be gradually withdrawn to avoid disastrous falls in blood pressure.

**Elderly**
As for Adults but see precautions.

**Children**
Not recommended due to insufficient data on safety and efficacy.

### 4.3 Contraindications
- Hypersensitivity to noradrenaline, or any of the excipients (see section 6.1 for details)
- Hypotension due to volume deficit
- 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.

### 4.4 Special warnings and precautions for use
**Extravasation risk:**
The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation that should cause a necrosis of the tissues surrounding the vein used for the injection. Because of the vasoconstriction of the vein wall with increased permeability, there can be some leakage of noradrenaline in the tissues surrounding the infused vein causing a blanching of the tissues which is not due to an obvious extravasation. Hence if blanching occurs, consideration should be given to changing the infusion site to allow the effects of local vasoconstriction to subside.

**Treatment of the ischemia due to extravasation:**
During an extravascular leak of the product or of an injection beside the vein, a tissue destruction can appear resulting from the vasoconstrictive action of the drug on the blood vessels. The injection zone must be then irrigated as quickly as possible with 10 to 15ml of physiological saline solution containing 5 to 10 mg of phentolamine mesilate. For this purpose, it is necessary to use a syringe provided with a fine needle and to inject locally.
The products administrated by injection must always be visually inspected and cannot be used if the presence of particles or a change of colouring is noted.

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. Similar caution should be observed in patients with hypotension following myocardial infarction and in patients with Prinzmetal’s variant angina.

Occurrence of heart rhythm disorders during the treatment must lead to a reduction in the dosage. Noradrenaline should be used only in conjunction with the appropriate blood volume replacement. When infusing noradrenaline, the blood pressure and rate of flow should be checked frequently to avoid hypertension.

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 (see section 4.8).

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 (see section 4.5)

Noradrenaline 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 because severe, prolonged hypertension may result.

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 the blood pressure and rate of flow should be checked frequently to avoid hypertension.

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

Caution is advised in patients with hyperthyroidism or diabetes mellitus.

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

Each ml of solution contains approximately 0.148 mmol (3.4 mg) of Sodium, 7.4 mmol sodium per 50ml. This may need to be taken into consideration if the patient is on a sodium controlled diet.

The elderly may be especially sensitive to the effects of noradrenaline.

The product contains Sodium Metabisulphite which may rarely cause severe hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see section 4.4).

Noradrenaline 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 because severe, prolonged hypertension may result.

The effects of Noradrenaline may be enhanced by guanethidine, reserpine, methyldopa or tricyclic antidepressants.
PAR Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

Caution is required when using Noradrenaline with the following drugs as they may cause increased cardiac effects: Thyroid hormones, Cardiac glycosides, Anti-arrhythmics.

Caution is required when using Noradrenaline with alpha and beta blockers as severe hypertension may result. The administration of a ß-blocking agent (propranolol) can result in a reduction of the stimulating effect of the product on the heart (coming from a β1 adrenergic action, that is to say cardiac arrhythmias) and result in an increase of the hypertensive effect following the reduction of arteriolar dilatation to the intervention of the β receptor (see section 4.9).

Ergot alkaloids or oxytocin may enhance the vassopressor and vasoconstrictive effects.

4.6 Pregnancy and lactation

Pregnancy

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 fetus should be weighed against the potential benefit to the mother.

Lactation

No information is available on use of noradrenaline in lactation.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

- Vascular system: Arterial hypertension and tissue hypoxia: Ischemic injury due to potent vasoconstrictor action which can result in coldness and paleness on the members and the face.
- Cardiac system: tachycardia, bradycardia (probably as a reflex result of blood pressure rising), arrhythmias, palpitations, increase in the contractility of the cardiac muscle resulting from the β adrenergic effect on the heart (inotrope + chronotrope), acute cardiac insufficiency.
- Central nervous system: anxiety, insomnia, confusion, cephalgia, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nauseas and vomiting.
- Eyes: acute glaucoma: very frequent with the persons anatomically predisposed with the closing of the iridocorneal angle.
- Urinary system: retention of urine.
- Respiratory system: respiratory insufficiency or difficulty, dyspnoea.
- Locally: possibility of irritation and necrosis at the injection site.

The continuous administration of vasopressors to maintain blood pressure, in absence of blood volume replacement may cause the following symptoms:

- severe peripheral and visceral vasoconstriction (see section 4.4)
- decrease in renal blood output
- decrease in urine production
- insufficient level of oxygen in tissues
- increase of the lactic acid level in blood.

In case of hypersensitivity or overdosage, the following effects may appear more frequently: hypertension, photophobia, retrosternal pain, pharyngeal pain, pallor, intense sweating and vomiting (see section 4.9).
4.9 Overdose

Overdosage 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 overdosage, treatment should be withdrawn and appropriate corrective treatment initiated (see section 4.8).

The vasopressor effect (resulting from a adrenergic action on the vessels, that is to say hypertension) can be reduced by the concomitant administration of an \(\alpha\)-blocking agent (phentolamine mesilate). Whereas the administration of a \(\beta\)-blocking agent (propranolol) can result in a reduction of the stimulating effect of the product on the heart (coming from a \(\beta\) adrenergic action, that is to say cardiac arrythmias) and result in an increase of the hypertensive effect following the reduction of arteriolar dilatation to the intervention of the \(\beta\) receptor (see section 4.5).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic Group

Mechanism of Action:

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.

Pharmacodynamic Effects:

Noradrenaline (NA) is a catecholamine sympathomimetic. It is an endogenous compound with a short duration of action and is the neurotransmitter for most sympathetic post ganglionic fibres. It is stored in granules in the nerve axons and is released with adrenaline from the adrenal medulla. Exogenous administration of NA results in an increase in total peripheral resistance due to vasoconstriction of skin and mucosal blood vessels. This causes a resultant increase in systolic and diastolic blood pressure. There is little change in cardiac output, although cardiac blood flow is generally increased as a result of coronary dilation. These cardiovascular changes are generally accompanied by a bradycardia that is the result of a compensatory mechanisms mediated by the carotid aortic baroreceptor system. Blood flow to the kidneys is reduced, as is hepatic and splanchnic flow. The latter most likely as a result of constriction of the mesenteric vasculature.

5.2 Pharmacokinetic properties

The pharmacokinetic behaviour of Noradrenaline has been studied in critically ill head injured patients. Noradrenaline plasma clearance was found to be independent of infusion rate. Furthermore steady state plasma concentrations of Noradrenaline correlated with infusion rates. These observations suggest that Noradrenaline has linear pharmacokinetics over the dose range studied.

An observation in this study was the lack of a discernible relationship between Noradrenaline plasma concentrations and pharmacodynamic effects namely mean arterial pressure, cardiac index and systemic vascular resistance.

Following intravenous administration Noradrenaline is rapidly inactivated, particularly in the liver which is abundant in the enzymes responsible for its metabolism namely monamine oxidase (MAO) and catechol-O-methyl transferase (COMT)...

A small amount of Noradrenaline is excreted unchanged in the urine, in addition to the methylated and deaminated metabolites in free and conjugated forms.

In patients with phaeochromocytoma the excretion rate may be markedly increased.

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.
PAR Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

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 Metabisulphite (E223)
Disodium Edetate (E386)
Sodium Chloride
Water for Injections
Hydrochloric Acid (pH adjuster)
Sodium Hydroxide (pH adjuster)

6.2 Incompatibilities
Solutions containing Noradrenaline Tartrate have been reported to be incompatible with the following: Alkalis and oxidising agents, barbituates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium, iodide, streptomycin.

6.3 Shelf life
6 Months (unopened)
Once opened the product should be used immediately.

6.4 Special precautions for storage
Store between 2-8ºC Keep in the outer carton. Do not freeze.
Check the appearance before use. Do not use if the solution is discoloured or brown.

6.5 Nature and contents of container
Sterile 50ml COC plastic pre-filled syringe fitted with bromobutyl rubber tip cap and plunger. The syringe is supplied in a sealed pouch also containing a sachet of oxygen scavenger. The pouched syringes are supplied individually in cartons.

6.6 Special precautions for disposal
Any unused product should be discarded appropriately.
For single use only. Discard any unused contents.
The solution should not be used if it is brown in colour.

7 MARKETING AUTHORITY NUMBER(S)
Cardinal Health UK 434 Limited
Bampton Road,
Romford,
Essex
RM3 8UG

8 MARKETING AUTHORITY NUMBER(S)
PL 25975/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/12/2010

10 DATE OF REVISION OF THE TEXT
02/12/2010
**Module 3**  
Product Information Leaflet

**NAME OF THE MEDICINAL PRODUCT**
Noradrenaline (Norepinephrine) 0.1 mg/ml Solution for Infusion in pre-filled syringe

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each ml contains 0.1 mg Noradrenaline Tartrate, equivalent to 0.1 mg Noradrenaline. Each 2 ml syringe contains 0.2 mg Noradrenaline Tartrate equivalent to 0.2 mg Noradrenaline.

**INDICATIONS**
For use in the treatment of hypovolaemic shock including in those with renal or cardiac insufficiency or cardiac arrest. The drug has additional applications in the treatment of neurogenic shock, septic shock, haemorrhagic shock, head injury, deep hypothermia, spinal or epidural anaesthesia, postoperative shock, major burns and hypotensive states.

**CLINICAL PARTICULARS**

**Therapeutic Indications**
Noradrenaline is indicated for the treatment of hypotension due to severe hypovolaemia or hypovolaemic shock, hypovolaemic shock due to haemorrhage, haemorrhagic shock, postoperative shock, shock due to cardiac arrest or failure, shock due to spinal or epidural anaesthesia, multiple trauma, haemorrhage due to trauma, severe burns, septic shock, anaphylaxis, prolonged hypotension in patients after cardiac surgery, and hypotension following general anaesthesia.

**Pharmacology and Method of Administration**
Noradrenaline should be administered only as an infusion at a controlled rate by a syringe pump. Noradrenaline solution for injection should not be diluted before use, as it is supplied ready for use.

**Site of Injection**
Noradrenaline should not be used intravenously. If injection of noradrenaline is given intramuscularly, it should be given into a large deep muscle mass, such as the gluteus maximus in the buttock.

**Route of Administration**
Noradrenaline should be administered intravenously by a slow infusion. It should not be administered by bolus injection. The rate and duration of infusion, and the dose administered, should be titrated against the patient's response. Noradrenaline has a short duration of action (up to 15 minutes) in serum-free plasma and is rapidly metabolised in vivo. The half-life is approximately 15-30 minutes in serum-free plasma.

**DOSAGE AND ADMINISTRATION**

The initial dose, given as a slow infusion over one to two minutes, is 0.5-1 mg and the maintenance dose is 0.5-2 mg per hour, depending on the patient's response. Dosage should be titrated according to the patient's response. It is recommended to use a constant infusion of noradrenaline to maintain blood pressure.

**Side Effects**
Systemic administration of noradrenaline may produce side effects, such as headache, palpitations, paresthesia, chest pain, and other symptoms associated with vasomotor instability. These side effects are usually transient and subside as the patient's blood pressure stabilizes. If symptoms are severe, the infusion should be discontinued.

**Special Precautions**

Noradrenaline should be used with caution in patients with cardiovascular disease, including hypertensive and coronary artery disease. The drug may increase the risk of ischaemic heart disease in these patients.

**Contraindications**
Noradrenaline should not be used in patients with known hypersensitivity to noradrenaline or to similar sympathomimetic agents. It should also be used with caution in patients with a history of cardiac, respiratory, or central nervous system disorders, as well as in children and pregnant women.

**Overdosage**
Overdosage of noradrenaline may cause serious cardiovascular effects, such as tachycardia, hypertension, angina pectoris, and arrhythmias. In cases of overdose, the infusion should be stopped immediately and the patient should be monitored closely for signs of ongoing cardiovascular instability. If symptoms persist, supportive care should be provided, and appropriate medical consultation should be sought.

**Notes**

Noradrenaline is a potent vasoconstrictor and should be used with caution in patients with pre-existing cardiovascular disease. It should be administered only by personnel trained in the management of cardiovascular emergencies.

**References**

PAR Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

PAR Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

UK/H/1378/001/DC

1. WHAT IS NORADEL NARELLE FOR INFUSION AND WHAT IS IT USED FOR?

Noradrenaline is a medicine used to treat patients with seriously low blood pressure.

2. BEFORE NORADEL NARELLE SOLUTION FOR INFUSION IS USED

You should not be given Noradrenaline Solution for Infusion in the following cases:

- You are allergic to any of the ingredients present in this product.

3. HOW TO USE NORADEL NARELLE SOLUTION FOR INFUSION

A fluid drip will usually be given alongside this medicine.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Noradrenaline Solution for Infusion can cause side effects although not everybody gets them.

5. STORAGE OF NORADEL NARELLE SOLUTION FOR INFUSION

Keep out of the reach of and sight of children.

6. FURTHER INFORMATION

What Noradrenaline Solution for Infusion contains:

What Noradrenaline Solution for Infusion looks like and contents of the pack:

This leaflet is supplied as a 5ml syringe which contains a clear sterile solution, free from visible particles. Each 5ml syringe contains 1.5mg noradrenaline tartrate equivalent to 1.5mg noradrenaline. The solution is supplied in a sealed pouch which also contains a sachet of a syringe cover. The punctured syringe is supplied with a plunger to be inserted into a syringe.
PAR Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

UK/H/1378/001/DC

Pregnancy and lactation
Pregnancy
Noradrenaline may impair placental perfusion and reduce fetal oxygen. It may also exert a contractile effect on the uterine smooth muscle and lead to fetal asphyxia in late pregnancy. These possible risks to the fetus should be weighed against the potential benefit to the mother.

Lactation
Information on the effects of this medicinal product in breast-feeding is available, but it is insufficient to define a risk to the suckling child.

Effects on ability to drive and use machines
None stated.

Undesirable effects
• Vascular system: Hypertension and tachycardia; Isolated cases of arterial vasospasm have been reported;
• Cardiac system: Tachycardia, bradypnoea; Generally, a reflex fall in blood pressure occurs;
• Renal system: Hypertension; Polyuria;
• Ocular system: Paroxysmal glucose• Regulatory system: Restlessness, anxiety, dysarthria;
• Respiratory system: Hypertension, bronchospasm, laryngospasm, asthma;
• Skin and subcutaneous tissues: Rash, sweating, flushing;
• Digestive system: Nausea, vomiting;
• Musculoskeletal system: Arthralgia, myalgia;
• Other: Overdosage may cause respiratory depression, fasciculations, muscle weakness and convulsions.

In case of overdose, the following effects may appear more frequently:
• Hypertension:
• Hypokalemia:
• Tachycardia:
• Cardiac arrhythmia:
• Renal failure:
• Ocular hypertension:
• Respiratory distress:
• Skin rash:
• Digestive upset:
• Muscle weakness:
• Convulsions:

In case of overdose, the following effects may appear more frequently:
• Hypotension:
• Hypokalemia:
• Tachycardia:
• Cardiac arrhythmia:
• Renal failure:
• Ocular hypertension:
• Respiratory distress:
• Skin rash:
• Digestive upset:
• Muscle weakness:
• Convulsions:

Overdosage
Overdosage may result in severe hypertension, reflex bradycardia, muscle weakness and convulsions.)

Dosage and administration
Noradrenaline solution is intended for use in emergency situations only. The solution is supplied in a pre-filled syringe for intravenous infusion. The syringes are supplied in a sealed pouch containing a vial of syringe cannula. The syringe is supplied in a sealed pouch containing a vial of syringe cannula. The syringes are supplied individually in cartons.

Special precautions for disposal
Any unused product should be discarded appropriately.

Marketing Authorisation Holder
Cardinal Health UK Ltd
Rampart Road
Hendon Hill
Kemble, Evesham
WR11 4BG
United Kingdom

Marketing Authorisation Number(s)
PL 152075/004
Date of first authorisation/renewal of the authorisation
11/10/2019

Cardinal Health
Rampart Road
Hendon Hill
Kemble, Evesham
WR11 4BG
United Kingdom
Module 4
Labelling

Label

Noradrenaline (Norepinephrine) 0.1mg/ml solution for infusion in pre-filled syringe

Each 50ml pre-filled syringe contains Noradrenaline 0.5mg/50ml (0.1mg/ml) of noradrenaline base.

This is equivalent to noradrenaline tartrate 1mg/50ml. Healthcare professionals must initially check the dose as specified in the base or should verify the dosage with the prescriber or check with a pharmacist. Each ml of solution contains 0.03mg Noradrenaline tartrate, equivalent to 0.05mg Noradrenaline.

For single use only. Discard any remaining solution. This product is ready to use solution and must not be further diluted before use.

Barcodes can be read by scanner-equipped Ampic infusion systems.

Store between 2-8°C. Keep in the carton. Do not freeze. For single patient use only. Do not re-use. Discard any remaining solution. For IV use only. Keep out of reach and sight of children. P00007/S/00000

Cardinal Health

Patient name:
Infusion commenced by:
Signed:
Date:

Bally
Eps:
MA Holder: Cardinal Health
Bampton Road, Warfield Hill, Remford Essex, WD3 2OG, UK
PAR Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe

UK/H/1378/001/DC
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
On 10th November 2010, Denmark, Ireland, The Netherlands, Sweden and the UK agreed to grant a Marketing Authorisation (MA) to Cardinal Health UK 434 Ltd for the medicinal product Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/1378/001/DC). After the national phase, an MA was granted in the UK on 2nd December 2010 (PL 25975/0040).

This application was made under Article 10.3 of Directive 2001/83/EC for Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe, containing the known active substance noradrenaline tartrate. The reference medicinal product for this application is Levophed Solution (PL 00071/5056R) authorised to Smithkline Beecham (SWG) on 25th September 1989. The licence underwent a change of ownership on the 1st June 2005; currently authorised to Hospira Enterprises B.V( PL 23061/0006) with product name as Levophed Injection 1:1000. The reference product is a solution that needs to be diluted before administration by infusion. The product proposed in this application is presented as a solution for infusion and is in a form that does not require further dilution prior to administration.

Noradrenaline is indicated for the emergency restoration of blood pressure in cases of acute hypotension. Noradrenaline is a direct-acting catecholamine sympathomimetic with pronounced effects on alpha-adrenergic receptors; it also stimulates beta_1 receptors but has little effect on beta_2 receptors. The major effects of Noradrenaline relate to its alpha-agonist properties. It causes peripheral vasoconstriction, leading to an increase in systolic and diastolic blood pressure, which is accompanied by reflex slowing of the heart rate. Blood flow is reduced in the kidneys, liver, skin, and usually skeletal muscle. Noradrenaline causes the pregnant uterus to contract; high doses liberate glucose from the liver and have other hormonal effects similar to those of adrenaline. Beta-stimulant effects of Noradrenaline have a positive inotropic action on the heart, but there is little bronchodilator effect. It produces little stimulation of the CNS.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfills the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of
any adverse reaction suspected of occurring either in the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). The reference product has been in use for many years and the safety profile of the active is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Noradrenaline Tartrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Adrenergic and Dopaminergic Agents C01CA03</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Powder for Solution for Infusion 0.1mg/ml</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1378/01/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Denmark, Ireland, The Netherlands and Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 25975/0040</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Cardinal Health UK 434 Ltd</td>
</tr>
<tr>
<td></td>
<td>Bampton Road, Harold Hill, Essex, RM3 8UG, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Norepinephrine Tartrate

BAN: Noradrenaline Tartrate

Chemical Name: (1R)-2-Amino-1-(3,4-dihydroxyphenyl)ethanol hydrogen (2R,3R)-2,3-dihydroxybutanedioate monohydrate

Structure:

![Chemical Structure Image]

Molecular formula: \( \text{C}_{12}\text{H}_{17}\text{NO}_9\cdot\text{H}_2\text{O} \)

Molecular weight: 337.3

The active substance, noradrenaline tartrate, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

Manufacture

All aspects of the manufacture and control of the active substance noradrenaline tartrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with Directive 2002/72/EC (as amended).

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT

Description and Composition

The finished product is presented as a clear colourless solution, each ml of solution containing 0.2mg noradrenaline tartrate, equivalent to 0.1mg noradrenaline. Each 50ml syringe contains 10mg noradrenaline tartrate equivalent to 5mg noradrenaline.

Other ingredients consist of pharmaceutical excipients, namely sodium metabisulphite (E223), disodium edetate (E386), sodium chloride, water for injections, hydrochloric acid (pH adjuster) and sodium hydroxide (pH adjuster). Appropriate justifications for the inclusion of each excipient have been provided.

All excipients used comply with their respective European Pharmacopeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. None of the excipients contain material of animal or human origin. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.
**Pharmaceutical Development**

The aim of the pharmaceutical development programme was to produce a ready-to-use preparation that was an alternative to Levophed 1:1000 (2mg/ml) concentrate for solution for infusion (Hospira Enterprises B.V). Suitable pharmaceutical development data have been provided for this application.

The physico-chemical properties of the drug product have been provided and are in-line with the BP monograph for noradrenaline injection.

**Impurity Profiles**

Comparative impurity data were provided for the test and reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. Satisfactory analytical results from batches representative of commercial scale were provided.

**Finished Product Specification**

Finished product specifications are provided for both release and shelf-life, and are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided for three production-scale batches of the product, which demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The finished product is licensed for marketing in sterile 50ml COC plastic pre-filled syringe fitted with bromobutyl rubber tip cap and plunger. The syringe is supplied in a sealed pouch also containing a sachet of oxygen scavenger. The pouched syringes are individually packaged in cartons also containing the technical prescribing information leaflet. Each syringe contains the equivalent to 5mg of noradrenaline. All primary product packaging complies with Directive 2002/72/EC (as amended), concerning materials in contact with parenteral products.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 6 months (unopened) has been set; once the product has been opened the product should be used immediately. Storage instructions are ‘Store between 2-8°C’. ‘Keep in the outer carton’ and ‘Do not freeze’.

**Bioequivalence Study**

The product is formulated for administration as a solution by the intravenous route. Hence there is no requirement for a bioequivalence study.
Quality Overall Summary
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Conclusion
The test product is presented as a ready to use solution for infusion of noradrenaline 0.1mg/ml, using Levophed Injection 1:1000 Injection (Hospira Enterprises) as the reference product. The scientific and technical data supporting the pharmaceutical quality of the application are satisfactory.

There are no objections to approval of Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe from a pharmaceutical point of view.

III.2 PRE-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of noradrenaline tartrate are well-known. Therefore, no further studies are required and the applicant has provided none.

The pre-clinical overview was written by a suitably qualified person and is satisfactory. The *curriculum vitae* of the expert has been provided.

The SmPC is satisfactory from a pre-clinical viewpoint and is consistent with that for the reference product.

There are no objections to approval of Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe from a pre-clinical point of view.

III.3 CLINICAL ASPECTS
Pharmacokinetics
No new data have been submitted and none are required for an application of this type.

The absence of studies has been justified according to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions). Whilst the test product contains the same active substance in an aqueous solution, as the reference product, the concentration of active substance is different. However, manipulation
of the infusion rates ultimately means that the test and reference products are infused at the same final dose per unit time. Thus the absence of a biostudy is accepted.

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
Noradrenaline is a well-known product with an acceptable adverse event profile, no additional safety studies are required.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA form is medically satisfactory.

Conclusion
There are no objections to approval of Noradrenaline (Norepinephrine) 0.1mg/ml Solution for Infusion in pre-filled syringe from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Noradrenaline (Norepinephrine) 0.1mg/ml for Infusion in pre-filled syringe are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for an application of this type.

CLINICAL
The applicant has made reference to clinical data and experience in the use of the reference product, Levophed 1:1000. The application is satisfactory from a clinical perspective.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with noradrenaline tartrate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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