

Public Assessment Report

Decentralised Procedure

**NORADRENALINE (NOREPINEPHRINE) 1 MG / ML
Concentrate for solution for infusion**

PL 31980/0001

UK/H/1425/01/DC

International Drug Licensing

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted International Drug Licensing a Marketing Authorisation (licence) for the medicinal product NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion (product licence number: 31980/0001). This medicine is available on prescription only.

NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion belongs to a group of medicines called the adrenergic and dopaminergic agents. NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion is used to restore normal blood pressure in emergencies when a patient's blood pressure is very low.

The data submitted in support of this application for NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10a Level 4 Chemical substance Level 5 Prescription only
Name of the active substance (INN)	Noradrenaline tartrate
Pharmacotherapeutic classification (ATC code)	Adrenergic and dopaminergic agents (C01CA03)
Pharmaceutical form	Concentrate for solution for infusion
Reference numbers for the decentralised Procedure	UK/H/1425/01/DC
Reference Member State	United Kingdom
Member States concerned	BE ES
Date of start of the procedure	23 June 2008
End date of decentralised procedure	12 January 2010
Marketing Authorisation Number	PL 31980/0001
Name and address of the authorisation holder	International Drug Licensing 36 avenue Hoche 75008 Paris FRANCE

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 2 mg Noradrenaline tartrate, equivalent to 1 mg Noradrenaline base

Each 4ml ampoule contains 8mg Noradrenaline tartrate equivalent to 4mg Noradrenaline base.

Each 8ml ampoule contains 16mg Noradrenaline tartrate equivalent to 8mg Noradrenaline base.

This medicinal product contains sodium.

Each ml of concentrate for solution for infusion contains 3.3 mg equivalent to 0.14 mmol of sodium

Each 4ml ampoule contains 13.0 mg equivalent to 0.57 mmol of sodium

Each 8ml ampoule contains 26.2 mg equivalent to 1.10 mmol of sodium

To be taken into consideration by patients on a controlled sodium diet.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless liquid

pH = 3.0 to 4.5

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 be administered through central venous devices to minimize the risk of extravasation and subsequent tissue necrosis.

Noradrenaline 1mg/ml concentrate should be diluted prior to intravenous infusion, either with dextrose 5%, or with isotonic dextrose saline. It should not be mixed with other medicines.

The final concentration of the infusion solution should be 80 mg/litre noradrenaline tartrate, which is equivalent to 40 mg/litre noradrenaline base. If other dilutions are used, check the calculation carefully before starting treatment.

Dilution instructions:

Either add 2 ml of Noradrenaline 1 MG/ML to 48 ml 5% dextrose (or isotonic dextrose saline) for administration by syringe pump, or add 20 ml of Noradrenaline 1 MG/ML to 480 ml 5% dextrose (or isotonic dextrose saline) for administration by drip counter.

In the both cases the final concentration of the infusion solution is 80 mg/litre noradrenaline tartrate, which is equivalent to 40 mg/litre noradrenaline base. If other dilutions are used check the calculation carefully before starting treatment.

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 should be at a control rate and the patient should be monitored carefully for the duration of noradrenaline (norepinephrine) therapy.

Adults:

Initial rate of infusion:

The initial rate of infusion should be between 10 ml/hour and 20 ml/hour (0.16 ml/min to 0.33 ml/min). This is equivalent to 0.8 mg/hr to 1.6 mg/hr noradrenaline tartrate (or 0.4 mg/hr to 0.8 mg/hr noradrenaline base).

Titration of dose:

Once an infusion of noradrenaline has been established the dose should be titrated 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 to 80 mm Hg – depending on the patient's condition).

Noradrenaline tartrate Infusion solution at 80 mg/L			
Patient's Weight	Posology (µg/kg/min) Tartrate	Posology (mg/h) Tartrate	Infusion rate (ml/h)
60 kg	0.2	0.72	9
	0.5	1.8	22.5
	1	3.6	45
	2	7.2	90

70 kg	0.2	0.84	10.75
	0.5	2.1	26.25
	1	4.2	52.5
	2	8.4	105
80 kg	0.2	0.96	12
	0.5	2.4	30
	1	4.8	60
	2	9.6	120

h: hour

If other dilutions are used check the calculation carefully before starting treatment.

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

4.3 Contraindications

Use of Noradrenaline 1 mg/ml concentrate for solution for infusion is contraindicated in patients with known hypersensitivity to noradrenaline or to any of the excipients.

Hypotension due to blood volume deficit (Hypovolaemia)

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, norepinephrine 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

Warning:

- Noradrenaline should be used only in conjunction with appropriate blood volume replacement
- When infusing noradrenaline, the blood pressure and rate of flow should be checked frequently to avoid hypertension.
- The products administered by injection must always be visually inspected and cannot be used if the presence of particles or a change of colouring is noted.

- Extravasation risk:

The infusion site should be checked frequently for free flow. Care should be taken to avoid extravasation that would 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 might 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 an injection besides 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 salt 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.

Precautions for use:

Caution and respect of the strict indication must be retained in case of:

- major left ventricular dysfunction associated with acute hypotension, a careful evaluation of patient's is needed. 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. It should be started at a dosage of 2 to 4 µg/min and titrated upwards and titrated as necessary. If systemic perfusion or systolic pressure cannot be maintained at >90mmHg with a dosage of 15µg/min, it is unlikely that a further increase will be beneficial.

- 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.

- Caution is advised in patients with hyperthyroidism or diabetes mellitus.

- The elderly may be especially sensitive to the effects of noradrenaline. This medicinal product contains sodium.

To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Inadvisable combinations

+ **Volatile halogen 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 fibers).

+ **Serotonergic-adrenergic antidepressants:** paroxysmal hypertension with the possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibers).

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:** by extrapolation from non-selective MAO inhibitors, risk of 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.

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, Anti-arrhythmics.

Ergot alkaloids or oxytocin may enhance the vasopressor 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 therefore be weighed against the potential benefit to the mother.

Lactation

No information is available on the use of noradrenaline in lactation.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

- Vascular system: arterial hypertension and tissue hypoxia; ischemic injury due to potent vasoconstrictor action may result in coldness and paleness of 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 and chronotrope), acute cardiac insufficiency.
- Central nervous system: anxiety, insomnia, confusion, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nausea and vomiting.
- Urinary system: retention of urine.
- Respiratory system: respiratory insufficiency or difficulty, dyspnoea.
- Locally: possibility of irritation and necrosis at the injection site.
- Eyes: acute glaucoma; very frequent in patients anatomically predisposed with the closing of the iridocorn angle.

The continuous administration of vasopressor to maintain blood pressure in 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 α -blocking agent (phentolamine mesilate) whereas the administration of a β -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 β_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.

4.9 Overdose

In the event of overdose, the following may be observed: cutaneous vasoconstriction, bed sores, circulatory collapse, hypertension.

In the event of adverse reactions linked to an excessive dosage, it is recommended to reduce the dosage if possible.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Adrenergic and Dopaminergic Agent
ATC Code: C01CA03
(C: Cardiovascular system)

Noradrenaline has a very potent action on alpha receptors and a more moderate effect on beta-1 receptors. NORADRENALINE (NOREPINEPHRINE) 1 MG / ML causes generalised vasoconstriction, except for the coronary vessels which it dilates indirectly by increasing the oxygen consumption. 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

Two stereoisomers of Noradrenaline exist, the biologically active L-isomer is the one present in Noradrenaline (Norepinephrine) 1mg/ml Concentrate for solution for infusion

Absorption:

- Subcutaneous: Poor
- Oral: Noradrenaline is rapidly inactivated in the gastrointestinal tract following oral administration.
- After intravenous administration Noradrenaline has a plasmatic half-life of about 1 to 2 minutes

Distribution:

- Noradrenaline is rapidly cleared from plasma by a combination of cellular reuptake and metabolism. It does not readily cross the blood-brain barrier

Biotransformation:

- Methylation by catechol-o-methyltransferase
- Deamination by monoamine oxydase (MAO)
- Ultimate metabolites from both is 4- hydroxy-3-methoxymandelic acid
- Intermediate metabolites include normetanephrine and 3,4-dihydroxymandelic acid

Excretion:

- Noradrenaline is mainly eliminated as glucuronide or sulphate conjugates of the metabolites 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 pregnant uterus and lead to fetal asphyxia in late pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, hydrochloric acid or sodium hydroxide (qs pH 3.0 to 4.5) and water for injections.

6.2 Incompatibilities

This medicine must not be mixed with other medicinal products except those mentioned in the section 6.6.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

After dilution:

The physicochemical stability of diluted product (in 5% dextrose or isotonic dextrose saline) has been demonstrated for 48 hours at 25°C.

However, from a microbiological point of view, the diluted product should be used immediately. If the product is not used immediately, the duration and conditions of use are the sole responsibility of the user.

6.5 Nature and contents of container

4 ml and 8 ml clear glass ampoules packed in boxes of 10, 50 or 100 ampoules.

6.6 Special precautions for disposal

- Dilute in 5% dextrose or isotonic dextrose saline. Please refer to section 4.2 "Posology and method of administration".
- Do not use an opened ampoule.
- Do not use if you notice any type of coloration
- Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

International Drug Licensing
36 avenue Hoche
75008 Paris
FRANCE

8 MARKETING AUTHORISATION NUMBER(S)

PL 31980/0001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

02/03/2010

10 DATE OF REVISION OF THE TEXT

02/03/2010

Module 3

Product Information Leaflet

NORADRENALINE (NOREPINEPHRINE) 1 mg/ml CONCENTRATE FOR SOLUTION FOR INFUSION

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The name of this medicinal product is NORADRENALINE (NOREPINEPHRINE) 1 mg/ml Concentrate for solution for infusion, but will be referred as Noradrenaline (Norepinephrine) Concentrate throughout the whole leaflet.

In this leaflet:

1. What Noradrenaline (Norepinephrine) Concentrate is and what it is used for
2. Before you are given Noradrenaline (Norepinephrine) Concentrate
3. How you are given Noradrenaline (Norepinephrine) Concentrate
4. Possible side effects
5. How to store Noradrenaline (Norepinephrine) Concentrate
6. Further information

1. WHAT NORADRENALINE (NOREPINEPHRINE) CONCENTRATE IS AND WHAT IT IS USED FOR?

Noradrenaline (Norepinephrine) Concentrate is a drug that belongs to the group of adrenergic and dopaminergic agent.

Noradrenaline (Norepinephrine) Concentrate is indicated for the emergency restoration of blood pressure in cases of acute hypotension.

2. BEFORE YOU ARE GIVEN NORADRENALINE (NOREPINEPHRINE) CONCENTRATE

Do not use Noradrenaline (Norepinephrine) Concentrate:

- if you are hypersensitive to noradrenaline or to any of the excipients ;
- if you are hypotensive (have low blood pressure) that has been caused by hypovolaemia (low blood volume) ;
- if you are taking some anaesthetics such as halothane or cyclopropane (this may increase the risk of irregular heart beat).

Take special care with Noradrenaline (Norepinephrine) Concentrate (and inform your doctor):

- if you have extravasation risk ;
- if you have major left ventricular dysfunction (a heart condition) ;
- if you have coronary, mesenteric or peripheral vascular thrombosis ;
- if you have hypotension following myocardial infarction ;
- if you have Prinzmetal's variant angina ;
- if you have heart rhythm disorders during your treatment - you will need a reduced dose ;
- if you have hyperthyroidism or diabetes mellitus ;
- if you are elderly.

Your blood pressure and heart rate will be checked frequently during your treatment to avoid hypertension.

Taking other medicines

Tell your doctor or pharmacist if you are taking, or have recently taken, any other medicines, including medicines obtained without a prescription as they may interact with Noradrenaline (Norepinephrine) Concentrate. This is especially important of the following medicines:

- Halothane, cyclopropane: these medicines are anaesthetics, they cause insensibility to pain and are used before some operations. If you are taking these medicines as well as Noradrenaline this may increase the risk of irregular heart beat.
- Amitriptyline, Imipramine, Trimipramine, Moclobemide, Iproniazide, Phenelzine, Fluoxetine, Sertraline: these medicines are used for treatment of depression. Taking any of these medicines together with Noradrenaline can dangerously increase its concentration in the blood and therefore its pressor action.
- Linezolid, an antibiotic (drug used to treat infections caused by bacteria and other microorganisms), can dangerously increase Noradrenaline concentration in the blood and therefore its pressor action, when taken together.
- Alpha and beta-blockers: if you are taking these medicines as well as Noradrenaline this may increase the risk of severe hypertension.
- Thyroid hormones, Cardiac glycosides, Anti-arrhythmics: if you are taking these medicines as well as Noradrenaline this may cause increased cardiac effects.
- Ergot alkaloids or oxytocin may enhance the vasopressor and vasoconstrictive effects.

Pregnancy and breast-feeding

Please tell your doctor if you are pregnant, think you may be pregnant or are breast-feeding and your doctor will decide if Noradrenaline is appropriate for you. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Since Noradrenaline will be given to you in a hospital, your doctor will inform you when you will be able to drive or use machines.

Important information about some of the ingredients of Noradrenaline (Norepinephrine) Concentrate:

This product contains 13 mg of sodium per one 4 ml ampoule.

This product contains 26 mg of sodium per one 8 ml ampoule.

Please tell your doctor if you are on a low sodium diet.

3. HOW YOU ARE GIVEN NORADRENALINE (NOREPINEPHRINE) CONCENTRATE

Noradrenaline (Norepinephrine) concentrate will be given to you in a hospital by a doctor or nurse.

Dosage

The dose of Noradrenaline depends on the condition of the patient. Your doctor will know the best dose to use. Noradrenaline is first diluted and then usually infused into a vein. The dose can then be adjusted using a pump according to the response to treatment, with the aim to establish a normal blood pressure. The initial dose is 0.4 to 0.8 milligrams per hour of Noradrenaline (Norepinephrine) base.

If you have any questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

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

The following side effects have been reported:

- skin necrosis (death) if the infusion is not given directly into the vein,
- anxiety, insomnia, confusion, headaches, psychotic state, weakness, tremor, lower vigilance, anorexia, nausea, vomiting,
- difficulty in breathing, fast or slow heart rate, pain in the chest or throat,
- retention of urine,
- pallor (loss of skin colour), sweating, sensitivity to light.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NORADRENALINE (NOREPINEPHRINE) CONCENTRATE

Do not store above 30°C.

After dilution:

The physicochemical stability of diluted product (in 5% dextrose or in an isotonic dextrose saline) has been demonstrated for 48 hours at 25°C.

However, from a microbiological point of view, the diluted product should be used immediately. If the product is not used immediately, the duration and conditions of use are the sole responsibility of the user.

Do not use if you notice any type of coloration.

6. FURTHER INFORMATION

What Noradrenaline (Norepinephrine) Concentrate contains:

The active substance is Noradrenaline tartrate 2 mg, equivalent to Noradrenaline base 1 mg.

The other ingredients are: sodium chloride, sodium hydroxide or hydrochloric acid and water for injections.

What Noradrenaline (Norepinephrine) Concentrate looks like and contents of the pack:

Clear and colourless liquid of pH 3 to 4.5 packaged in a clear glass ampoule of 4 ml or 8 ml.

Each ml of concentrate for solution for infusion contains 2 mg Noradrenaline tartrate equivalent to 1 mg Noradrenaline base.

Each 4 ml ampoule contains 8 mg Noradrenaline tartrate equivalent to 4 mg Noradrenaline base.

Each 8 ml ampoule contains 16 mg Noradrenaline tartrate equivalent to 8 mg Noradrenaline base.

Boxes of 10, 50 or 100 ampoules.

Marketing Authorisation holder:

International Drug Licensing
36 avenue Hoche
75008 PARIS
FRANCE

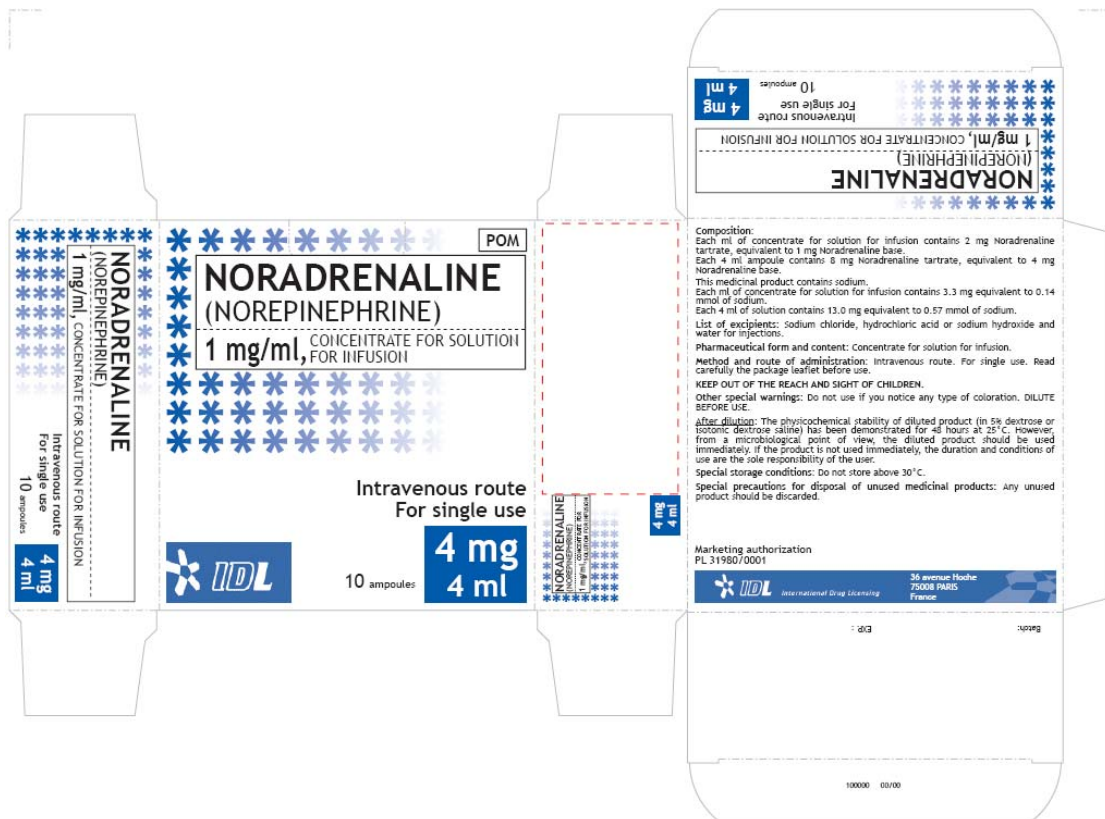
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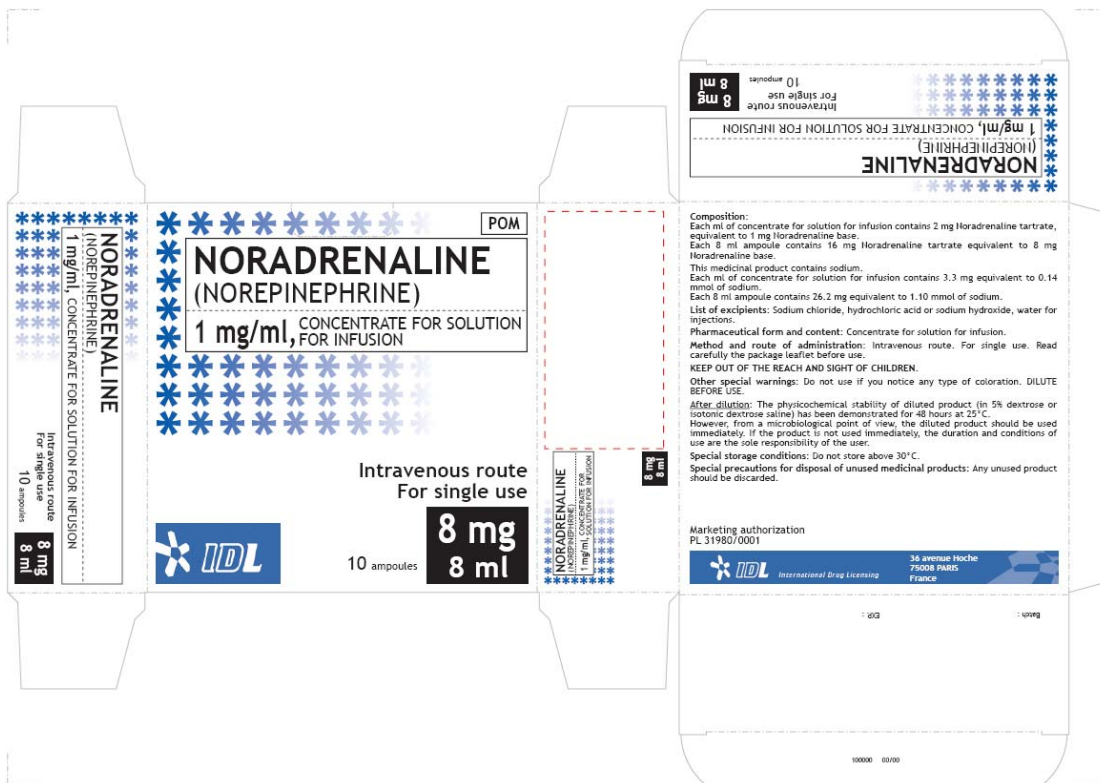
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Date of last leaflet update: January 2010.

Module 4

Labelling





Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion in the emergency restoration of blood pressure in cases of acute hypotension is approvable.

EXECUTIVE SUMMARY

Problem statement

This decentralised application is submitted under Art 10a of Directive 2001/83/EC, as amended, on the basis of 'well established use'.

The Applicant's dossier summarises the grounds and evidence to demonstrate that the constituents of the medicinal product have well-established use with an acceptable level of safety and efficacy (based on extensive clinical experience over 50 years). This is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, International Drug Licensing is applying for a marketing authorisation for NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion in Belgium and Spain.

About the product

Noradrenaline is a direct-acting, catecholamine sympathomimetic with pronounced effects on alpha-adrenergic receptors; it also stimulates beta₁ receptors but has little effect on beta₂ 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.

In acute hypotensive states, noradrenaline is used as the acid tartrate, but doses are expressed in terms of the base; noradrenaline acid tartrate 2 micrograms is equivalent to about 1 microgram of noradrenaline. Dilution and infusion rates are specified in the British National Formulary to deliver 0.4 mg/hr to 0.8 mg/hr noradrenaline base in the emergency treatment of shock.

General comments on the submitted dossier

The dossier is considered adequate.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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 of 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.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion are of sufficient quality in view of the present European regulatory requirements. The drug substance specification for the drug substance is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed and the results support the proposed re-test period

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis results show that the finished product meets the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. The stability data support the proposed shelf-life of 2 years with the storage precaution "Do not store above 30°C."

Non clinical aspects

The pharmacological, pharmacokinetic and toxicological properties of noradrenaline tartrate are well known. As noradrenaline tartrate is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The non-clinical overview has been written by a pharmacologist. The overview, that was written in 2007, refers to 55 references from the published literature dated up to 2004. The overview is considered to be acceptable in view of the fact that the toxicological properties of noradrenaline tartrate are well known.

There are no objections to the approval of NORADRENALINE (NOREPINEPHRINE) 1 MG / ML Concentrate for solution for infusion from a non-clinical point of view.

Clinical aspects

No clinical studies were conducted in support of this application and all the relevant clinical information provided in the Clinical Overview is literature based. The Clinical Overview was written in 2007 by an expert qualified in medicine and is adequate. There are 55 references up to 2004.

No new safety data have been submitted and none are required for this application.

Pharmacovigilance system

The RMS considers that the pharmacovigilance system fulfils the requirements. The Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

Assessment of User Testing

All product literature (SPC, PIL and labelling) is satisfactory. The package leaflet was submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet 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 they contain.

BENEFIT RISK ASSESSMENT

The benefit-risk ratio is considered favourable. A Marketing Authorisation should be granted