LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Noradrenalin Pfizer
(noradrenaline tartrate)

SE/H/2612/001/MR

This module reflects the scientific discussion for the approval of Noradrenalin Pfizer. The Public Assessment Report was written in August 2011 by the previous RMS UK after initial procedure UK/H/3953/001/DC and is attached at the end of this document. RMS transfer from FI to SE was completed 19 June 2024. For information on changes after this date please refer to the module 'Update'.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

Safeguarding public health

Public Assessment Report

Decentralised Procedure

Noradrenaline (Norepinephrine) Img/ml Concentrate for Solution for Infusion

UK/H/3953/001/DC

UK licence no: PL 04515/0240

Hospira UK Limited

5 LAY SUMMARY

On 5 August July 2011, the Medicine and Healthcare products Regulatory Agency (MHRA) granted Hospira UK Limited a Marketing Authorisation (licence) for the medicinal product Noradrenaline (Norepinephfine) I mg/mL Concentrate of Solution for Infusion (PL 04515/0240). This licence was granted via the decentralised procedure (UVUW3953/001/DC).

Noradrenaline (Norepinephrine) 1 mg/mL Concentrate of Solution for Infusion belongs to a group of medicines called the adrenergic and dopammergic agents and IS used to restore and maintain normal blood pressure in emergencies when a patient's blood pressure is low.

No new or unexpected safety concems arose from this application and it was therefore judged that the benefits of taking Noradrenaline (Norepinephrine) I mg/mL Concentrate of Solution for Infusion outweighs the risks and a Marketing Authorisation was granted.

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Module 1

Product Name	Noradrenaline (Norephinephrine) Img/mL Concentrate for Solution for Infusion
Type of Application	Bibliographic Application, Article I Oa
Active Substance	Noradrenaline Tartrate
Form	Concentrate for solution for infusion
Strength	Img/mL
Marketing Authorisation Holder	Hospira UK Limited Queensway, Royal Leamington Spa Warwickshire, CV31 3RW, UK
Reference Member State (RMS)	
Concerned Member State (CMS)	Austria, Finland, France, the Netherlands, Sweden and Spam
Procedure Number	UkW3953/001/DC
End of Procedure	13 July 2011

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summmy of Product Characteristics (SmPC) for Noradrenaline (Norepmephrine) I mg/mL Concentrate for Solution for Infusion (PL 04515/0240 is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Noradrenaline (Norepinephrine) I mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 2 mg noradrenaline tartrate equivalent to 1 mg noradrenaline base.

1 ampoule of 2 ml contains 4 mg noradrenaline tartrate equivalent to 2 mg noradrenaline base.

1 ampoule of 4 ml contains 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base.

When diluted as recommended, each ml contains 80 micrograms noradrenaline tartrate equivalent to 40 micrograms noradrenaline base.

Excipients:
1 ampoule of 2 ml contains 0.29 mmol (or 6.7 mg) sodium.
1 ampoule of 4 ml contains 0.58 mmol (or 13.3 mg) sodium. For
a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion A clear colourless or yellowish solution
pH: 3.0-4.0
Osmolarity: approximately 280 mOsm/l

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for use as an emergency measure in the restoration of blood pressure in cases of acute hypotension.

4.2 Posology and method of administration

Route ofAdministration: For intravenous use.

Method ofadministration:
Administer as a diluted solution via a central venous catheter.
The infusion should be at a controlled rate using either a symmge pump or an infusion pump or a drip counter.

For dilution instructions see section 6.6.

Dosage:
Adults
Initial rate ofinfusion:
Xvymen diluted as recommended in section 6.6 (the concentration of the prepared infusion is 40 mg/litre noradrenaline base (80 mg/litre noradrenaline tartrate)) the initial rate of infusion, at a body weight of 70 kg, should be between 10 ml/hour and 20 ml/hour (0.16 to 0.33 ml./min). This is equivalent to 0.4 mg/hour to 0.8 mg/hour noradrenaline base (0.8 mg/hour to 1.6 mg/hour noradrenaline tartrate). Some clinicians may wish to start at a lower initial infusion rate of 5 nü/hour (0.08 ml/min), equivalent to 0.2 mg/hour noradrenaline base (0.4 mg/hour noradrenaline tartrate).

Titration ofdose:
Once an infusion of noradrenaline has been established the dose should be titrated in steps of 0.05-0.1 ug/kg/min of noradrenaline base according to the pressor effect observed. There is great individual variation in the dose required to attain and maintain nonnotension. The aim should be to establish a low normal systolic blood pressure (100 - 120 mm Hg) or to achieve an adequate mean arterial blood

ressure eater than 65 - 80 mm H —d	din on the atient's condition .

Noradrenaline Infusion Solution 40 m •tre 40 ml noradrenaline base			
Patient's Weight	Posology (gg/kg/min) noradrenaline base	Posology (mg/hour) noradrenaline base	Infusion Rate (ml/hour)
50 kg	0.05	0.15	3.75
		0.3	7.5
	0.25	0.75	18.75
			37.5
			75
60 kg	0.05	0.18	4.5
	0.1	0.36	9
	0.25	0.9	22.5
		1.8	45

			90
70 kg	0.05	0.21	5.25
	0.1	0.42	10.5
	0.25	1.05	26.25
			52.5
		4.2	105
80 kg	0.05	0.24	6
		0.48	12
	0.25	1.2	30
			60
		4.8	120
90 kg	0.05	0.27	6.75
	0.1	0.54	13.5
	0.25	1.35	33.75
			67.5
			135

Some clinicians may prefer to dilute to other concentrations. Ifdilutions other than 40 mg/l are used, check the infusion rate calculation carefully before starting treatment.

Renal or hepatic impainnent:
There is no experience in treatment of renally or hepatically impaired patients

Elderly:
As for adults but see section 4.4.

Children:
Not recommended.

Duration of Treatment and Monitoring:
Noradrenaline should be continued for as long as vasoactive dmg 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 Theravv:
The noradrenaline infusion should be gradually decreased since abrupt withdrawal can result in acute hypotension.

4.3 Contraindications

Hypersensitivity to noradrenaline tartrate or to any of the excipients.

4.4 Special warnings and precautions for use

Noradrenaline should only be administered by healthcare professionals who are familiar with its 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, hypeltension or hyperthyroidism. Noradrenaline should be used with caution in patients who exhibit profound hypoxia or hypercarbia. 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 hypeflension.

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 infiltrated with phentolamine without delay.

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 flow and tissue perfusion with subsequent tissue hypoxia and lactic acidosis and possible ischaemic injury.

Contains sodium. To be taken into consideration by patients on a controlled sodium diet, see section 2.

4.5 Interaction with other medicinal products and other forms of interaction

The use of noradrenaline with volatile halogenated anaesthetic agents, monoamine oxidase inhibitors, linezolid, tricyclic antidepressants, adrenergic-serotoninergic dmgs or any other cardiac sensitising agents is not recommended because severe, prolonged hypefiension and possible arrhythmias may result.

4.6 Pregnancy and lactation

Pregnancy

Noradrenaline may impair placental perftsion 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

None stated.

4.8 Undesirable effects

System Organ Class	ndesirable effect
Psychiatric disorders	ety
ervous system disorders	eadache
ardiac disorders	hythmias (when used in conjunction with cardiac sensitising gents , brad cardia
ascular disorders	ypertension, peripheral ischaemia including gangrene of the xtremities, plasma volume depletion with prolonged use
Respirat01Y, thoracic and astinal disorders	spnoea
General disorders and administration site conditions	xtravasation necrosis at injection site

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, retrostemal pain, pallor, intense sweating and vomiting. In the event of overdosage, treatment should be withdrawn and appropriate corrective treatment initiated.

6 mnRMACOLOGICAL PROPERTIES

6.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC code: COI CA03

The vascular effects in the doses nonnally used clinically result from the simultaneous stimulation of alpha and beta adrenergic receptors in the heart and vascular system. Except in the heart, its action is

predominantly on the alpha receptors. This results in an increase in the force (and in the absence of vagal inhibition, in the rate) of myocardial contraction. Peripheral resistance increases and diastolic and systolic pressures are raised.
The increase in blood pressure may cause a reflex decrease in heart rate. Vasoconstriction may result in decreased blood flow in kidneys, liver, skin and smooth muscles. Local vasoconstriction may cause haemostasis and/or necrosis.
The effect on blood pressure disappears 1-2 minutes after stopping the inftsion.

6.2 Pharmacokinetic properties

Up to 16% of an intravenous dose is excreted unchanged in the urine with methylated and deaminated metabolites in free and conjugated fonns.

6.3 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 perftsion and induce fetal bradycardia. It may also exert a contractile effect on the utents and lead to fetal asphyxia in late pregnancy.

7 PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment) Water
for Injections

7.2 Incompatibilities

Noradrenaline must not be mixed with other medicinal products except those mentioned in section 6.6. Infrsion solutions containing noradrenaline tartrate have been reported to be incompatible with the following substances: alkalis and oxidising agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin. For compatibility with infusion bags see section 6.6.

7.3 Shelf life 18 months. aner dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25^{0}C when diluted to 4 mg/litre and 40 mg/litre noradrenaline base in sodium chloride 9 mg/ml (0.9%) solution or glucose 5% 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 nonnally not be longer than 24 hours at 2 to 8^{0}C.

7.4 Special precautions for storage Do not store above 25 ^{0}C.

7.5 Nature and contents of container

Ampoules containing 2 ml and 4 ml of concentrate. Pack
size of 5 ampoules.

7.6 Special precautions for disposal

Dilution instructions:
Dilute before use with glucose 5% solution or sodium chloride 9 mg/ml (0.9%) with glucose 5 % solution.
Either add 2 ml concentrate to 48 ml glucose 5% solution (or sodium chloride 9 mg/ml (0.9%) with glucose 5% solution) for administration by syringe pump, or add 20 ml of concentrate to 480 ml glucose 5 % solution (or sodium chloride 9 mg/ml (0 9%) with glucose 5% solution) for administration by drip counter. In both cases the final concentration of the infusion solution is 40 mg/litre noradrenaline base (which is equivalent to 80 mg/litre noradrenaline tanrate). Dilutions other than 40 mg/litre noradrenaline base may also be used (see section 4.2). If dilutions other than 40 mg/litre noradrenaline base are used, check the infusion rate calculation carefully before stalting treatment. The product is compatible with PVC infusion bags.

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

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW

8 ALARKETING AUTHORISATION NUMBER(S)

PL 04515/0240

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/08/2011

10 DATE OF REVISION OF THE TEXT

05/08/2011

Module 3
Product Information Leaflet

pACKAGE LEAFLET:

8 INFORMATION FOR THE USER

Hospwa

Noradrenaline (Norepinephrine) mg/ml Concentrate for Solution for Infusion

Noradrenaline (os noradrenaline lartrate)

Read all of this leaflet carefully before you start using this medicine
Keep this leaflet. You may need to read it agaim
If you have any further questions, please ask your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. may harm them, even f 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) I mg/ml Concentrate for Solution for Infusion but it Will be referred to as Noradrenaline (Norepinephrine) Concentrate throughout this 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 Noradrenaiine (Norepinephrine) Concentrate
4. possible side effects
5. HOW to store Noradrenaline (Norepinephrine) Concentrate
S. Further information

WHAT bmADRENALINE (NOREPINEPHRINE) CONCENTRATE IS AND WHAT IT IS USED FOR

Noradrenaline (Norepinephrine) Concentrate for Solution for Infusion is used in an emergency to increase blood pressure to normal levels.

2. BEFORE YOU ARE GIVEN tORADRENAUNE (NOREPINEPHRINE) CONCENTRATE

You will not be given Nora&enaline (Norephephrine) Concentrate if

you are allergic (hypersensitive) to noradrenaline preparations or to any Of the other ingredients of this medicine (see section 6)

Special ccre will be taken if you

have diabetes
suffer from high pressure
have an over-active thyroid
have low levels of oxygen in the blood
have high levels Of carbon dioxide in the blood
a vein.
have clots or obstructions in the blood vessels supplying the heart. intestines, or other parts Of the body
have low blood pressure following a heart attack
have a type of angina (chest pain) called Prinzmetal's angina.
are elderly

Takhg Other medicines

any other medicines, ir,cluding medicines obtained without a prescription.

A number of medicines are known to increase the toxic effects of noradrenaline, such as:

monoamine oxidase inhibitors (antidepressants) . tri-cyclic antidepressants
linezoEid (an antibiotic) . anaesthetics (especially anaesthetic gases)
adrenergic-serotoninergic medicines, E.g. used in the treatment Of asthma and heart conditions.

Pregnancy and breast-feedng

Tell your doctor if you are pregnant or breast-feeding. Noradrenaline may harm the unborn baby. Your doctor will decide if you should be given Noradrenaline (Norepinephrine) Concentrate.

Ask your doctor or pharmacist for advice before taking any medicine.

Important information about one of the ing-edients of Noradrendine (Norepinephrine) Concentrate

The 2 ml ampoule contains 6.7 mg sodium, and the 4 ml ampoule contains 13.3 mg sodium. Take into consideration if you are on a low-sodium diet.

3. HOW you ARE GWEN NORADRENAUNE NREPINEPHXNE) CONCENTRATE

Noradrenaline (Nov-epinephrine)

Please tell your doctor or pharmacist if you are taking, or have recently taken,

Noradrenaline (Norepinephrine) 1 mg/ml

Concentrate for Solution for Infusion

The following information is intended for medical or healthcare professionals only:

For intravenous use.

Dilute before use.

Concentrate Will be given to you in hospital by a doctor or nurse. It is first diluted and then infused into

Administer as diluted solution Via a central venous catheter.

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

Incompatibiities

Infusion solutions containing noradrenaline tartrate have been reported to be incompatible with the following substances alkalis and oxidising

agents, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiocin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin. Dilution instructions

Dilute before use with glucose 5% solution or sodium chloride 9 mg/ml (0.9%) with glucose 5% solution.

Either add 2 ml Of concentrate to 48 ml glucose

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[redacted]

5% solution (or sodium chloride 9 mg/ml (0.9%)

The initial dose of Noradrenaline (Norepinephrine) Concentrate will depend on your medical condition. The usual dose is between 0.4 and C.B mg per hour. Your doctor will determine the correct dose for you. After the inltial dose your doctor will assess your response and adjust the dose accordingly. If you are given more Noradrenalhe (Norepinephrine) Concentrate Than you should be:

It is unlikely that you will receive too much as this medicine will be given to you in hospital. However, talk to your doctor or nurse if you have any concems.

Symptoms of overdose are severe high blood pressure, slow heartbeat, violent headache, light sensitivity, pain in the chest, pale colour, intense sweating and vomiting.

4. POSSIBLE SIDE EFFECTS

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

Tell your doctor immediately if you expenence:

- sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), feeling that you are going to faint . pain and/or swelling at the injection site

Tell your doctor as soon as possible if you experience

- slow heart rate
- abnormal heart rhythm
- breathing diff culties .

anxiety

- headaches
- cold extremities • pain in the extremities

Your doctor will monitor your blood pressure and blood volume.

It 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 (NOREPINEPI-RIFÆ) CONCENTRATE

Keep out of the reach and sight of children

Do not store above 25'C

Do not use after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

From a microbiological point of view, the product should be used immediately after dilution.

This medicine should not be used f the solution is brown in colour.

6. FURTHER INFORMATION

[redacted]

What Noradrena"ne (Norepinephrine) contains

The active substance is noradrenaline (as noradreneline tartrate)_

1 ml concentrate for solution for infusion contains 2 mg noradrenaline tartrate equivalent to 1 mg noradrenaline base. 1 ampoule of 2 ml contains 4 mg noradrenaline tattrate equivalent to 2 mg noradreneline base.

1 ampoule of 4 ml contains 8 mg noradrenalina tartrate equivalent to 4 mg noradrenaline base.

The other ingredients are:

- sodium chloride
- sodium hydroxide (for pH adjustment)
- hydrochloric acid (for pH adjustment)
- Water for Injections.

What Noradrena"ne (Norepinephrine) Concentrate looks like and contents of the pack:

This medicinal product is presented as a concentrate for solution for infusion. The solution is a clear colourless or yellowish solution.

It may be supplied in packs of 5 x 2 ml ampoules or 5 x 4 ml ampoules.

Marketing Authorisation Holder

Hospira UK Limited

Queensway

Leamington Spa CV31 3RW

Mm ufacturers

Hospira S_p.A.

Via Fosse Ardeatine 2

20060 Liscate - Milan

Italy

Hospira UK Limited

Queensway, Leamington Spa

Warwickshire. 3RW United Kingdom

Hospira Enterprises B,V.

Ramstad 22-11

$316 Almere

The Netherlands

This medicinal product is authorlsed in the Member States of the EEA under the following names:

mm/yyyy

This leaflet was last approved in

Austria Finland and Sweden:	Noradrenalin Hospira	Spain:	Noradrenalina Hospira
France:	Noradréneline Hospira	United Kingdom,	Noradrenaline (Norepinephrine)
The Netherlands;	Noradrenaline Hospira		

with glucose 5% solution) for administration by syringe pump, cr add 20 ml of concentrate to 480 ml glucose 5% solution (or sodium chloride 9 mg}ml (0.9%) with glucose 5% solution) for administration by drip counter. In both cases the final concentration of the infusion solution is 40 mg/litre noradrenaline base (which is equivalent to 80 mgJlitre noradrenaline tartrate) ;Dilutions other than 40 mg/litre noradrenaline base may also be used. If dilutions other than 40 mgllitre noradrenaline base are used, check the infusion rate calculation carefully before starting treatment.

The product is compatible with PVC infusion bags.

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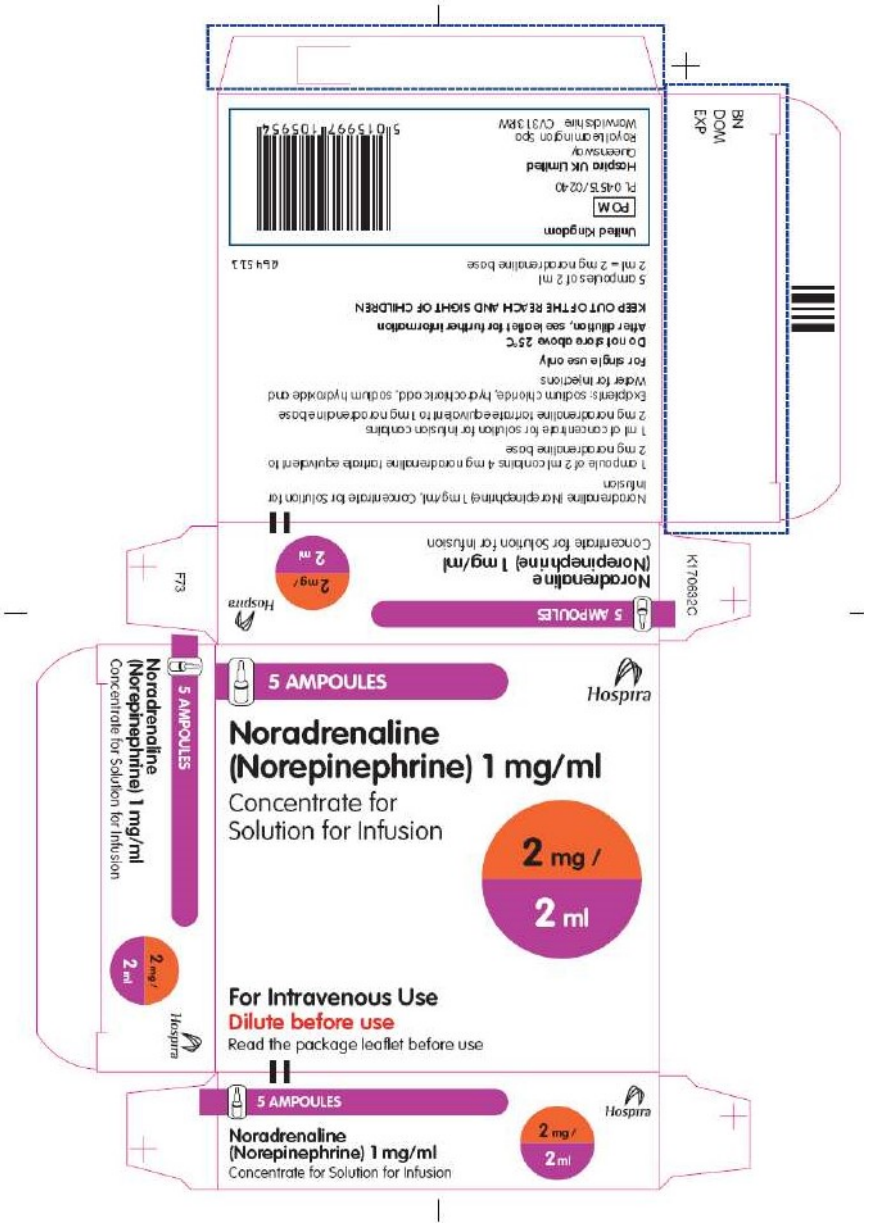
Any unused product or waste material should be disposed of in accordance with local requirements. Shelf life aftg dilution

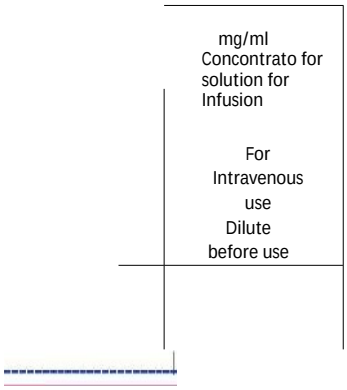
Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC when diluted to 4 mgflitre and 40 mg/litre noradrenaline bese in sodium chloride S mg/ml (0.9%) solution or glucose 5% solution. However, from a microbiological point of view, the product should be used immediately. If 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 to 8'C.

Module 4
Labelling

Carton



Noradrenalne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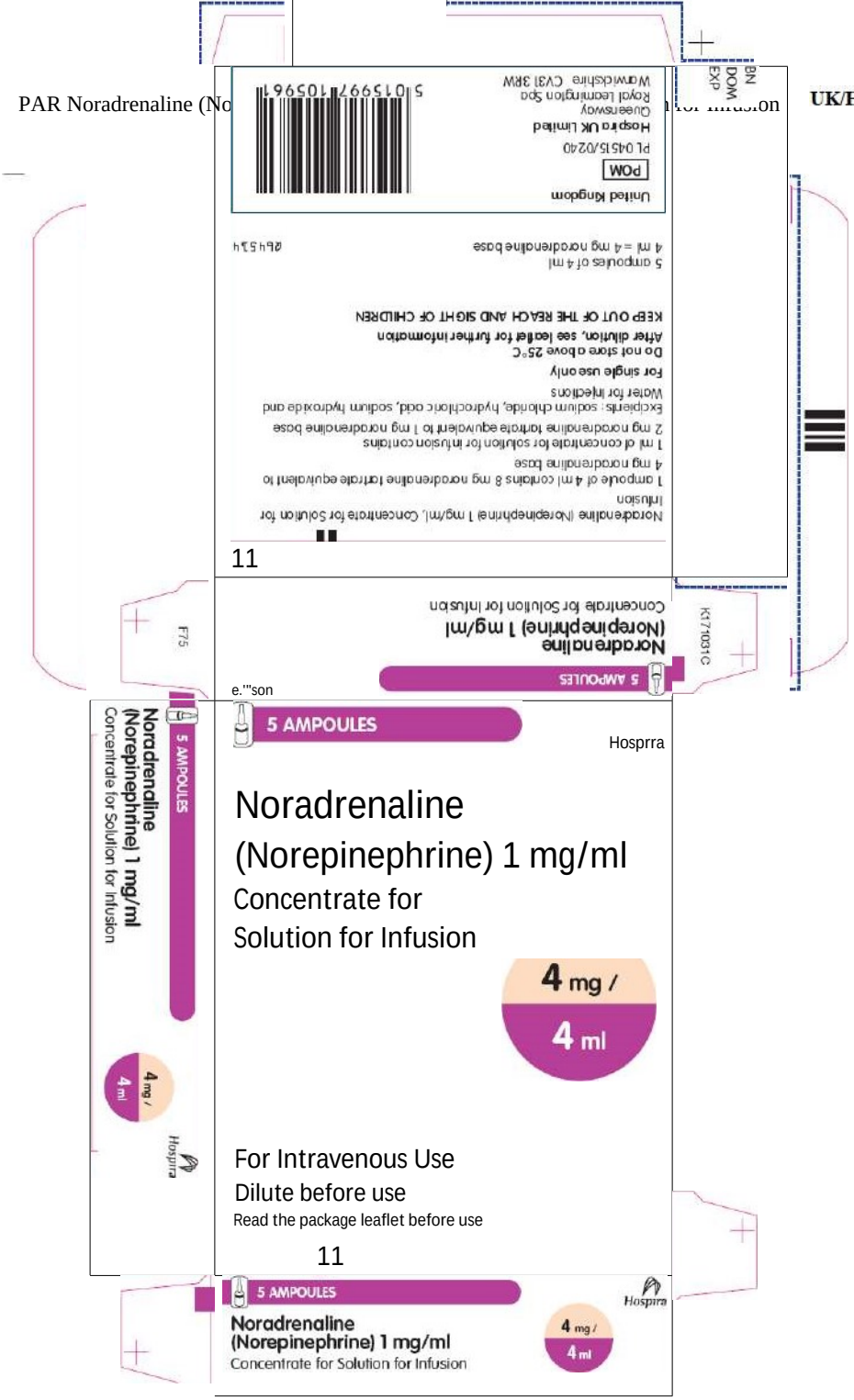
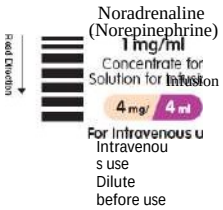
before use


United Kingdom
POM
PL 04515/0240
Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
EXP
BN
DOM
Noradrenaline (Norepinephrine) 1 mg/ml, Concentrate for Solution for Infusion
1 ampoule of 4 ml contains 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base
1 ml of concentrate for solution for infusion contains 2 mg noradrenaline tartrate equivalent to 1 mg noradrenaline base
Excipients: sodium chloride, hydrochloric acid, sodium hydroxide and Water for Injections
For single use only
After dilution, see leaflet for further information
Do not store above 25°C
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
5 ampoules of 4 ml
4 ml = 4 mg noradrenaline base
11
Noradrenaline (Norepinephrine) 1 mg/ml
Concentrate for Solution for Infusion
5 AMPOULES
Hospira
Noradrenaline
(Norepinephrine) 1 mg/ml
Concentrate for Solution for Infusion
4 mg / 4 ml
For Intravenous Use
Dilute before use
Read the package leaflet before use
11


Noradrenaline
(Norepinephrine)
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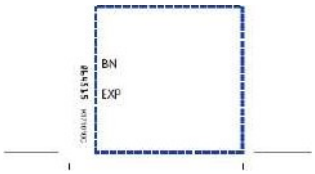


Module 5
Scientific discussion during initial procedure

9 1 INTRODUCTION

On 13 July 2011, Austria, Finland, France, the Netherlands, Spain, Sweden and the UK agreed to grant a Marketing Authorisation (MA) to Hospira UK Limited for the medicmal product Noradrenaline I mg/mL Concentrate for Solution for Infusion. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (UK/H/3953/001/DC). After the national phase, a licence was granted in the UK on 5 August 2011 (PL 04515/0240).

This is an abridged, bibliographic application for Noradrenaline I mg/mL Concentrate for Solution for Infusion, submitted under Article IOa (well-established use) of Directive 2001/83/EC, as amended.

Noradrenaline I mg/mL Concentrate for Solution for Infusion is indicated for use as an emergency measure m the restoration of blood pressure in cases of acute hypotension.

Noradrenaline taltrate belongs to the phannacotherapeutic group, adrenergic and dopaminergic agents (ATC code: COI CA03). The vascular effects in the doses nonnally 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 predommantly on the alpha receptors; this results in an Increase in the force (and in the absence of vagal inhibition, in the rate) of myocardial contraction. Peripheral resistance increases and diastolic and systolic pressures are raised.
The Increase m blood pressure may cause a reflex decrease in heart rate.
Vasoconstriction may result in decreased blood flow in kidneys, liver, skin and smooth muscles. Local vasoconstriction may cause haemostasis and/or necrosis.

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application was for a bibliographic application for aproduct containing an active substance of well-established use. A bioequivalence study is not necessary to suppolt this application for an aqueous solution that is parenteral product that is administered parenterally (intravenously), see 'Clinical Aspects ' .

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 cun•ent 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 satisfact01Y 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 tenitories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the phannacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for phannacovigilance and has the necessary means for the notification of any adverse reaction suspected of occun•ing either m the Community or in a third country. The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concems requiring additional risk mmilmsation have not been identified, a risk mimmisation system is not considered necessary. The reference product has been m use for many years and the safety profile of the active substance is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). This was an application for a generic product and there is no reason to conclude that the marketing of this product will change the overall use pattem of the existing market.

10 11. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Noradrenaline (Norephinephrine) Imp/mL Concentrate for Solution for Infusion
Name s of the active substance s	Noradrenaline Tartrate
Pharmacotherapeutic classification (ATC code)	Adrenergic and dopaminergic agents ATC code: cm CA03
Pharmaceutical fonn and strength(s)	Concentrate for solution for infusion. 1m ml
Reference numbers for the Decentralised Procedure	UK/W3953/001/DC
Reference Member State	United Kin dom
Member States concemed	Austria, Finland, France, the Netherlands, Spain and Sweden.
Malketin Authorisation Number s	PL 04515/0240
Name and address of the authorisation holder	Hospira UL Limited Queensway Royal Leamington Spa Wanvickshire CX31 3RW United Kin dom

11 111 SCIENTIFIC OVERVIEW AND DISCUSSION

12 111.1 QUALITY ASPECTS

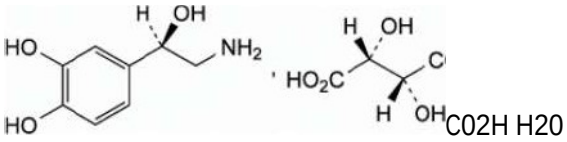
DRUG SUBSTANCE

Noradrenaline tartrate

Chemical name: (IR)-2-ammo-l-(3, 4-dihydroxyphenyl)ethanol hydrogen (2R, 3R)2,3-dihydroxybutanedioate, monohydrate

CAS number: 69815-49-2

Stmcture:

13 

Molecular formula: C8H11N03.C4H606.H20

Molecular weight: 337.3

General Properties

Description:

Noradrenaline tafirate is a white to faintly grey odorless powder.

Solubility:

Noradrenaline taltrate is freely soluble in water, slightly soluble in ethanol (96%) and practically insoluble in chlorofonn and in ether.

Noradrenaline taltrate is the subject of a US Pharmacopoeia (USP) monograph.

14 Manufacture

Synthesis of the drug substance from the designated stalting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are m place for all staffing materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfact01Y for ensurmg compliance with the relevant specifications.

Appropriate data have been supplied to characterise the active substance. All potential known impurities have been identified and charactefised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primalY packaging has been shown to comply with current guidelines conceming contact with foodstuffs.

Appropriate stability data have been generated to suppolt a suitable re-test period when stored in the proposed packaging.

15 DRUG PRODUCT Description and Composition

The product is presented as a clear, colourless or yellowish concentrate for solution for infusion. Each Iml of concentrate for solution for infusion contains 2 mg norarenaline tartrate equivalent to I mg noradrenaline base. »vmen diluted as recommended, each mL contams 80 micrograms noradrenaline tartrate equivalent to 40 micrograms noradrenaline base.

Other ingredients consist of the pharmaceutical excipients, sodium chloride, sodium hydroxide (pH adjustment), hydrochloric acid (pH adjustment) and water for Injections. All the ingredients m the concentrate comply with their relevant Ph.Eur monographs. Appropriate justification for the inclusion of each of the excipients has been provided. Satisfactory Certificates of Analysis for each of the excipients have been presented. The applicant has provided a declaration confirming that there are no matenals of human or animal origin contamed in the product, or used in the manufacturing process. Furthermore, no genetically modified organisms are used m the manufacture of the excipients.

16 Pharmaceutical Development

Details of the phannaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a stable concentrate for infusion containing I mg noradrenaline base per mL.

17 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 6 commercial-scales batches were provided.

18 Finished Product Specification

Finished product specifications are provided for both release and shelf—life, and are satisfactory. These provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional phannaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Batch data are provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

19 Container Closure System

The finished product is licensed for marketing in clear glass ampoules (Type I glass (Ph.Eur)). Each ampoule of 2 mL contains 4 mg noradrenaline tartrate equivalent to 2 mg noradrenalme base; each 4 mL ampoule contains 8 mg noradrenaline tartrate equivalent to 4 mg noradrenaline base. Ampoules are packaged with the Patient Infonnation Leaflet (PIL) into cardboard outer cartons in pack sizes of 5 ampoules. Satisfactory specifications and Certificates of Analysis for all packaging components

used have been provided. The glass ampoules comply with Ph Eur requirements and are suitable for contact with solutions for infusion.

20 Stability

Finished product stability studies have been conducted in accordance with cunent guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 18 months has been set when unopened, which is satisfactory. Storage instluctions are 'Do not store above 25 ^{0}C'.

'In-use 'stability studies have been can-ied out on the finished product once the ampoule has been opened and diluted. For storage conditions after dilution see Section 6.3 of the Summary Product Characteristics (SmPC).

21 Compatability Studies

Compatibility studies of the product were performed with 5 % glucose solution and 0.9 % sodium chloride solution, as proposed for administration.

22 Quality Overall Summary

A satisfactory quality overview is provided and has been prepared by an appropriately qualified expelt. The curriculum vitae of the expert has been provided.

23 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and labelling are 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 the PIL contains.

MAA Form

The MAA fonn is satisfactory from a phannaceutical perspective.

24 Conclusion

There are no objections to approval of Noradrenaline I mg/l mL Concentrate for Solution for Infusion from a phannaceutical point of view.

111.2 NON-CLINICAL ASPECTS

PHARMACOLOGY

25 GLP aspects

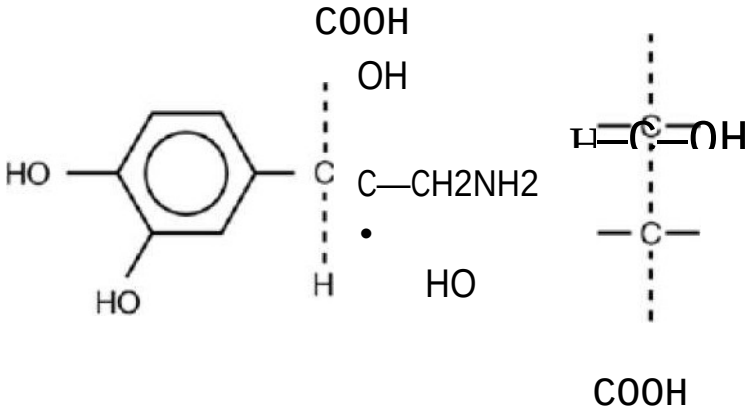
This application is based on well-established use and as such, no new non-clinical data are available. The GLP status of the published studies is not known.

26 Brief summary

Noradrenaline is a sympathomimetic neurotransmitter with 01, and 131 adrenergic agonist properties. Millen administered therapeutically, it produces direct effects on both vascular and cardiac muscle. It is a strong vasoconstrictor, increasmg peripheral vascular resistance and raising mean alterial blood pressure.

27 Physical chemistry

Stmcture of the active substance, noradrenaline taltrate:



28 Primary pharmacodynamics

Noradrenaline is a sympathormmetic neurotransmitter and a member of the catecholamine family, with 01, and adrenergic agonist properties.

Endogenous noradrenaline has dual roles as a neurotransmitter and honnone. It is the main neurotransmitter at most postganglionic adrenergic nelves. Endogenous noradrenaline is released m response to stressors, such as exercise or Imminent danger, resulting in the fight or flight response.

Therapeutic administration of noradrenaline has direct effects on both vascular and cardiac muscle, via the adrenergic receptors 01, and 131. Pressor doses of noradrenaline increase peripheral vascular resistance, thereby rmsing mean arterial blood pressure. Due to the negative feedback baroreceptor response in patients with an intact healt nerve reflex, heart rate is slowed and blood flow to the kidneys and liver is reduced.

29 Secondary pharmacodynamics

Secondary phannacodynanncs were not specifically discussed in the overview, being grouped with drug interactions. Agonist activity at adrenergic receptors (contracts most vascular smooth muscle and increases force of contraction of heart), (contracts some vascular smooth muscle, platelet aggregation), and 131 (increases force and rate of contraction of heart) will result in vasoconstriction, increased peripheral resistance and increased mean arterial blood pressure as mentioned above, with negative feedback reducing blood flow to some organs.

30 Safety pharmacology

Safety phannacology studies in line With current guidance have been conducted for noradrenaline. Potentially cardiotoxic effects of noradrenaline via the generation of free

radicals were discussed. In isolated rabbit hearts, noradrenaline at micromolar concentrations enhanced myocardial ischerma even in the absence of functional effects on the heart.

31 Pharmacodynamic drug interactions

Monoamme oxidase (MAO) inhibitors may lead to increased noradrenaline release, resulting in severe hypeffension. Tricyclic antidepressants can inhibit noradrenaline reuptake into the neuron and again may result in severe hypertension. Cyclopropane and halothane anaesthetics Increase autonomic üTitability and may sensitise the myocardium to administered noradrenalme, with a risk of ventricular tachycardia or fibrillation. This information is mcluded in the SmPC.

Overall conclusions

Noradrenaline is a catecholamine sympathomimetic agent With ul, 02 and 131 agonist activities. It is used as an emergency measure m the restoration of blood pressure in cases of acute hypotension. Higher doses can result in prolonged and severe hypertension, reflex bradycardia and ventricular anhythmias.

PHARMACOKINETICS

32 Methods of analysis

Noradrenaline in arterial blood was measured using HPLC in one repolted study in septic shock or trauma patients.

33 Absorption

Noradrenaline is poorly absorbed when administered by the subcutaneous route and is not bioavailable when admimstered orally. Noradrenaline must therefore be administered intravenously by infusion into a large vein, as there is a risk of necrosis of the overlymg skin from prolonged vasocontriction. In humans, intravenously administered noradrenaline has one-compartment linear phannacokinetics. Circulating noradrenaline has a half-life of about I to 2 minutes. For septic shock and trauma patients administered therapeutic doses of noradrenalme, the tenninal elimination half-life ranged from 2.0 to 6.8 min, and was significantly longer in more severely ill patients.

The basal arterial plasma level of noradrenaline is similar in humans and dogs, and is approximately 100 to 200 pg/mL. During stress, these levels can increase 50- to 100-fold.

34 Distribution

Circulating endogenous noradrenaline is removed from the system by reuptake into the nerve tenninals, by diffusion out of the action site, and by metabolic transformation. Exogenously administered noradrenaline is primarily cleared by hepatic metabolism and to a smaller extent by the kidneys (—16% found in urine).

It does not readily cross the blood:brain barrier. It is not known whether it is distributed into milk.

35 Metabolism

Noradrenaline is metabolised by monoamine oxidase (MAO) and catechol-Omethyltransferase (COMT), which are present throughout the body. These enzymes catalyse oxidative deamination and O-methylation, respectively, the ultimate product

from both being 4- hydroxy-3-methoxymandelic acid. Most of the noradrenaline entering the circulation is Omethylated in the liver. Sulphate and glucuronide conjugates are also formed.

36 Excretion

In the rat, about 90% of a noradrenaline dose was excreted via the kidneys, with the rest in the faeces. In humans, about 16^0 0 of an intravenous dose was excreted unchanged in the urine, with the remainder as metabolites.

37 Pharmacokinetic drug interactions

Pharmacokinetic drug interactions were not discussed m the non-clinical overview. Given the short plasma half-life of adrenaline and the enzymes involved m its metabolism, pharmacokinetic drug reactions are probably tmlikely to occur.

Other pharmacokinetic studies None repolted.

38 Overall conclusions on pharmacokinetics

Noradrenaline has a short plasma half-life and is administered by intravenous infusion. It is cleared from the circulation by cellular re-uptake and enzymatic Inactivation. It does not readily cross the blood:brain barmier.

Noradrenaline is metabolised by catechol-O-methyltransferase (COMT) and monoamme oxidase (MAO), and conjugates of the methylated and deaminated products are excreted via the urine.

TOXICOLOGY

39 Single dose toxicity

The acute intravenous toxicity ofnoradrenaline was reported in rats and mice. The toxic effects included depression, blanching of extremities, dyspnoea, loss of muscular coordination leading to clonic convulsions and death following respiratory anest. Rats were more sensitive than rmce. Symptoms of overdose in humans Include severe hypertension, reflex bradycardia, marked Increase in peripheral resistance and decreased cardiac output. These may be accompanied by violent headache, photophobia, retrostemal pain, pallor, intense sweating and vomiting. In addition, ventricular an-hythrmas and local gangrene resulting from peripheral vasoconstriction may occur.

40 Repeated-dose toxicity

There are reportedly no repeated-dose studies in the literature. Again given the wellestablished use of noradrenaline clinically, and the proposed posology, this is not considered to be an issue.

41 Genotoxicity

A standard package of genotoxicity studies has not been conducted. An in vitro Comet assay in human lymphocytes was reported in the literature. In this study, all doses of noradrenaline (10, 50, 500, and 550 PM) induced highly significant ($P < 0.001$) increases of tail moments compared to untreated lymphocytes, whilst maintaining good

cell viability. At the highest concentration used, there was a 7.5-fold increase in tail moment. The concentrations used are higher than those found clinically and noradrenaline is not considered to be a genotoxlc risk.

Carcinogenicity

No studies have been conducted and are not required.

42 Reproductive and developmental toxicity

Studies reported in the literature are old and not comprehensive.

In hamsters, noradrenaline at 0.5mg/kg subcutaneously from Day 7 to 10 increased resorptions, decreased litter size and delayed the ossification of the metatarsals.

Intravenous infusion of noradrenaline Into pregnant ewes increased the matemal alterial pressure and decreased uterine and placental blood flow significantly. These changes were sufficient to transiently cause the changes of fetal blood gas status (increase Pcm, decrease P02 and lung liquid flow) and renal fimctions (decrease urine flow rate).

Administration of noradrenaline in late pregnancy has been reported to provoke uterine contractions and can lead to fetal asphyxia.

43 Local tolerance

Noradrenaline is üTitant and can cause extravasation with possible local tissue necrosis around the mjection site. The product should be diluted either with dextrose 5%, or with isotonic dextrose saline prior to use and the diluted solution administered via a central venous catheter.

44 Other toxicity studies

No other studies were reported. The non-clinical overview states that there are no impurities or degradants present at levels above the ICH qualification limits and as such, no studies are required to qualify the impurity profile.

45 Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) states that the chug product is essentially similar in chemical structure, fommlation and known phannacological properties to the reference product and that there is no reason to conclude that marketing of such an additional product will change the overall usage pattem of the existing market. Appropriate precautionmy and safety measures to be observed when the product is administered to patients and for the disposal of waste products have been included m the SmPC and product labelling. This justification for the absence of a formal ERA is acceptable.

46 Non-Clinical Overview

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

47 Summary of Product Characteristics (SmPC)

Section 4.6 and 5.3 are satisfactory from a non-clinical viewpoint.

There are no objections to approval of Noradrenal I mg/mL Concentrate for Solution for Infusion from a non-clinical point of view.

48 111.3 CLINICAL ASPECTS

No new study has been submitted as this is a stand alone application based on wellestablished use. Noradrenaline has been used for a long time to restore blood pressure in patients with acute hypotension due to clinical conditions such as shock including septic shock and cardiogenic shock. A number of publications have ben submitted to support the efficacy and safety of noradrenaline; this is satisfactory.

Biowaiver

Since noradrenaline tartrate is prepared as a solution for IV infusion, it can be considered bioequivalent to any other IV formulation of noradrenalme, in accordance with the EU guideline on bioequivalence.

Pharmacokinetics

No new data have been submitted for this, well-established use, application.

Pharmacodynamics

No new data have been submitted and none are required for an application of this type. Noradrenaline is a potent a-adrenergic receptor agonist. It causes peripheral vasoconstriction and Increases peripheral vascular resistance consequentially leading to higher diastolic and systolic blood pressure.

Clinical efficacy

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

49 Clinical safety

No new safety data have been submitted or are required for this well-established use application. As noradrenaline tartrate is a well-known product with an acceptable adverse event profile, this is satisfactory.

50 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.

51 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPCs and PILS are acceptable from a clinical perspective and are consistent with those for the reference product. The labelling is clinically acceptable and IS in-line with current requirements.

MAA form

The MAA form is satisfactory from a clinical perspective.

52 Conclusion

There are no objections to approval of Noradrenaline I mg/ mL Concentrate for Solution for Infusion from a clinical point of view.

53 IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT QUALITY

The important quality charactenstics ofNoradrenaline I mg/ mL Concentrate for Solution for Infusion 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.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this

54 EFFICACY

No new data are submitted and none are required for this type of application.

The published literature supports the efficacy of this product in the proposed indications. The safety and efficacy of noradrenaline tartrate is well-known. The presented evidence for wellestablished use of the active substance is sufficient.

The literature review identifies no new safety issues or concems. The safety profile of noradrenaline tartrate is well-known.

55 PRODUCT LITERATURE

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

A 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.

56 BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concems have been identified. Noradrenaline tartrate is an active substance of well-known safety and efficacy. It has been used for a number of decades in the EC. Extensive clinical experience with noradrenaline tartrate is considered to have demonstrated the therapeutic value of the active substance. The benefit/lisk ratio is therefore considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application e	Scope	Outcome
