Public Assessment Report

Decentralised Procedure

EPHEDRINE HYDROCHLORIDE 3 MG/ML SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE

Procedure No: UK/H/2194/001/DC

UK Licence No: PL 19364/0048

UKR REGULATORY AFFAIRS LTD.
LAY SUMMARY

On 22 September 2010, Belgium and the UK agreed to grant a Marketing Authorisation to UKR Regulatory Affairs Ltd for the medicinal product Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe (PL 19364/0048; UK/H/2194/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 01 November 2010.

Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe is a prescription-only medicine (POM) used to treat low blood pressure that can occur during spinal or epidural anaesthesia.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe outweigh the risks, hence a Marketing Authorisation has been granted.
<table>
<thead>
<tr>
<th>Module</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Module 6: Steps taken after initial procedure</td>
<td>28</td>
</tr>
<tr>
<td>1</td>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Module 3: Product Information Leaflets</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Module 4: Labelling</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>Module 5: Scientific Discussion</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>Module 6: Steps taken after initial procedure</td>
<td>28</td>
</tr>
</tbody>
</table>
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Well-established use application, Article 10.(a)</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Ephedrine Hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>3 mg/ml Solution for Injection in Pre-filled Syringe</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>3 mg/ml.</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>UKR Regulatory Affairs Ltd, The Bull Pen, Home Farm, Banbury Road, Caversfield Oxfordshire, OX27 8TG, UK.</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Belgium</td>
</tr>
<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/2194/001/DC</td>
</tr>
<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 22 September 2010</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Solution for Injection contains 3 mg ephedrine hydrochloride.
Each 10 ml pre-filled syringe contains 30 mg ephedrine hydrochloride.

Excipients:
This medicinal product contains sodium.
Each ml of Solution for Injection contains 3.32 mg equivalent to 0.144 mmol of sodium.
Each 10 ml pre-filled syringe contains 33.2 mg equivalent to 1.44 mmol of sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection.
Clear, colourless liquid
pH = 4.5 to 5.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of hypotension from spinal or epidural anaesthesia.

4.2 Posology and method of administration
Ephedrine must be used solely by or under the supervision of the anaesthetist.
For intravenous use.

Adult and children over 12 years
Slow intravenous injection of 3 to 6 mg (maximum 9 mg), repeated as needed every 3-4 min to a
maximum of 30 mg. A lack of efficacy after 30 mg should lead to reconsideration of the choice of the
therapeutic agent.
The dose administered for 24 hours must not exceed 150 mg.

Children under 12 years
The paediatric dose is 0.5 to 0.75 mg/kg or 17-25 mg/m² every 3-4 minutes according to response.

Elderly
As for adults.

4.3 Contraindications
- Hypersensitivity to ephedrine
- Ischaemic heart disease
- Hypertension
- Thyrotoxicosis
- Prostatic hypertrophy

4.4 Special warnings and precautions for use
Special warnings
Ephedrine should be used with caution in patients who may be particularly susceptible to their effects,
particularly those with hyperthyroidism. Great care is also needed in patients with cardiovascular
disease such as ischaemic heart disease, arrhythmia or tachycardia, occlusive vascular disorders
including arteriosclerosis, hypertension, or aneurysms. Anginal pain may be precipitated in patients
with angina pectoris.

Care is also required when Ephedrine is given to patients with diabetes mellitus or closed-angle
glaucoma.
Ephedrine should be avoided or used with caution in patients undergoing anaesthesia with cyclopropane, halothane, or other halogenated anaesthetics, as they may induce ventricular fibrillation. An increased risk of arrhythmias may also occur if Ephedrine is given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants.

Many sympathomimetics interact with monoamine oxidase inhibitors, and should not be given to patients receiving such treatment or within 14 days of its termination. It is advisable to avoid sympathomimetics when taking reversible MAOIs.

Ephedrine increases blood pressure and therefore special care is advisable in patients receiving antihypertensive therapy. Interactions of Ephedrine with alpha- and beta-blocking drugs may be complex. Propranolol and other beta-adrenoceptor blocking agents antagonise the effects of beta2 adrenoceptor stimulants (beta2 agonists) such as salbutamol.

Adverse metabolic effects of high doses of beta2 agonists may be exacerbated by concomitant administration of high doses of corticosteroids; patients should therefore be monitored carefully when the 2 forms of therapy are used together although this precaution is not so applicable to inhalation therapy. Hypokalaemia associated with high doses of beta2 agonists may result in increased susceptibility to digitalis-induced cardiac arrhythmias. Hypokalaemia may be enhanced by concomitant administration of aminophylline or other xanthines, corticosteroids, or by diuretic therapy.

Precautions for use
Athletes: warning, this medicinal product contains an active substance that may cause a positive reaction in anti-doping tests.
This medicinal product contains sodium.
To be taken in consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction
Contraindicated combinations:
Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate)
Risk of vasoconstriction and/or of acute episodes of hypertension.

Combinations not recommended:
Volatile halogen anaesthetics
Serious ventricular arrhythmias (increase in cardiac excitability).

Tricyclic antidepressants (e.g. imipramine)
Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibers).

Noradrenergic-serotonergic antidepressants (minalciapran, venlafaxine)
Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibers).

Guanethidine and related products
Substantial increase in blood pressure (hyperreactivity linked to the reduction in sympathetic tone and/or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibers). If the combination cannot be avoided, use with caution lower doses of sympathomimetic agents.

Sibutramine
Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibers).

Combinations requiring precautions for use:
Nonselective MAO inhibitors
Increase in the pressor action of adrenaline and noradrenaline which is usually moderate. Should be used only under strict medical supervision.

Selective MAO-A inhibitors (moclobemide, toloxatone)
By extrapolation from nonselective MAO inhibitors. Risk of increase in the pressor action. Should be used only under strict medical supervision.
**Linezolide**
By extrapolation from nonselective MAO inhibitors.  
Risk of increase in the pressor action. Should be used only under strict medical supervision.

**Theophylline**
Concomittant administration of ephedrine and theophylline may result in insomnia, nervousness and gastrointestinal complaints.

**Corticosteroids**
Ephedrine has been shown to increase the clearance of dexamethasone.

**Antiepileptics:** increased plasma concentration of phenytoin and possibly of phenobarbitone and primidone.

**Antihypertensives:** sympathomimetics in anorectics and cold and cough remedies antagonise hypotensive effects of adrenergic neurone blockers; possible risk of hypertension with apraclonidine and adrenaline or noradrenaline; hypotensive effect of some other antihypertensives may be enhanced by dexfenfluramine and fenfluramine.

**Doxapram:** risk of hypertension.

**Oxytocin:** hypertension with vasoconstrictor sympathomimetics.

### 4.6 Pregnancy and lactation

**Pregnancy**
There are no or limited amount of data from the use of Ephedrine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. The use of ephedrine in pregnancy should be avoided as ephedrine crossed the placenta and this has been associated with an increase in fetal heart rate and beat-to-beat variability.

**Lactation**
Ephedrine is excreted in breast milk and therefore its use during lactation should be avoided. Irritability and disturbed sleep patterns have been reported in breast-fed infants.

### 4.7 Effects on ability to drive and use machines
Not relevant.

### 4.8 Undesirable effects

**Very common:** ≥1/10; **Common:** ≥1/100, <1/10; **Uncommon:** ≥1/1,000, <1/100; **Rare:** ≥1/10,000, <1/1,000; **Very rare:** <1/10,000; **Not known:** cannot be estimated from the available data

**Blood and lymphatic system disorders:**
Not known: primary hemostasis modifications

**Immune system disorders:**
Not known: hypersensitivity

**Psychiatric disorders:**
Common: confusion, anxiety, depression  
Not known: psychotic states, fear

**Nervous system disorders:**
Common: nervousness, irritability, restlessness, weakness, insomnia, headache, sweating  
Not known: tremor, hypersalivation

**Eye disorders:**
Not known: episodes of angle-closure glaucoma

**Cardiac disorders:**
Common: palpitations, hypertension, tachycardia  
Rare: cardiac arrhythmias  
Not known: anginal pain, reflex bradycardia, cardiac arrest, hypotension
Vascular disorders:
Not known: cerebral haemorrhage

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea
Not known: pulmonary oedema

Gastrointestinal disorders:
Common: nausea, vomiting
Not known: reduced appetite

Renal and urinary disorders:
Rare: acute urinary retention

Investigations:
Not known: hypokalaemia, changes in blood glucose levels

4.9 Overdose
In the event of overdose, the occurrence of nausea, vomiting, fever, paranoid psychosis, ventricular and supraventricular arrhythmias, hypertension, respiratory depression, convulsions and coma is observed. The lethal dose in humans is approximately 2 g corresponding to blood concentrations of approximately 3.5 to 20 mg/l.

Treatment
The treatment of ephedrine overdose with this product may require intensive supportive treatment. Slow intravenous injection of labetalol 50-200mg may be given with electrocardiograph monitoring for the treatment of supraventricular tachycardia. Marked hypokalaemia (<2.8mmol.l-1) due to compartmental shift of potassium predisposes to cardiac arrhythmias and may be corrected by infusing potassium chloride in addition to propranolol and correcting respiratory alkalosis, when present.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Adrenergic and Dopaminergic Agent.
ATC Code: C01CA26

Ephedrine is a sympathomimetic amine acting directly on the alpha and beta receptors and indirectly by increasing the release of noradrenaline by the sympathetic nerve endings. As with any sympathomimetic agent, ephedrine stimulates the central nervous system, the cardiovascular system, the respiratory system, and the sphincters of the digestive and urinary systems. Ephedrine is also a monoamine oxidase (MAO) inhibitor.

5.2 Pharmacokinetic properties
After intravenous administration, ephedrine is completely biologically available, and after oral administration, the bioavailability of ephedrine has been reported to be above 90%.
Excretion depends on urine pH:
From 73 to 99% (mean: 88%) in acidic urine,
From 22 to 35% (mean: 27%) in alkaline urine.
After oral or parenteral administration, 77% of ephedrine is excreted in unchanged form in the urine. The half life depends on urine pH. When the urine is acidified at pH = 5, the half life is 3 hours; when the urine is rendered alkaline at pH = 6.3, the half life is approximately 6 hours.

5.3 Preclinical safety data
There is no pre-clinical data of relevance to the prescriber which is additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Citric acid monohydrate
Sodium citrate
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
2 years.
After opening: the product must be used immediately.

6.4 Special precautions for storage
Store the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container
10 ml polypropylene pre-filled syringe with a polypropylene tip cap and tamper proof seal, and is individually packaged in a transparent blister pack. The prefilled syringes are available in box of 1, 5, 10, 12 and 20.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Instructions for use:

Please prepare the syringe carefully as follows

The pre-filled syringe is for single patient only.
Discard syringe after use. DO NOT REUSE.

The content of un-opened and un-damaged blister is sterile, and must not be opened until use.
The product should be inspected visually for particles and discoloration prior to administration. Only clear colourless solution free from particles or precipitates should be used.
The product should not be used if the tamper evident seal on syringe is broken.

The external surface of syringe is sterile until blister is opened.

1) Withdraw the pre-filled syringe from the sterile blister.

2) Push on the plunger to free the bung.

3) Twist off the end cap to break the seals

4) Check the syringe seal has been completely removed. If not, replace the cap and twist again.
5) Expel the air by gently pushing the plunger.

6) Connect the syringe to the IV access. Push the plunger slowly to inject the required volume.

Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe

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 any further questions, 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.

In this leaflet:
1. What Ephedrine Injection is and what it is used for
2. Before you are given Ephedrine Injection
3. How Ephedrine Injection is given
4. Possible side effects
5. How to store Ephedrine Injection
6. Further information

1. WHAT EPHEDRINE INJECTION IS AND WHAT IT IS USED FOR
This product is used to treat low blood pressure that can occur during spinal or epidural anaesthesia.

2. BEFORE YOU ARE GIVEN EPHEDRINE INJECTION
Do not use Ephedrine Injection if:
• You know you are allergic (hypersensitive) to the active substance or to any of the ingredients of Ephedrine Injection
• You suffer from heart disease or any other heart conditions,
• You have high blood pressure and are currently receiving medication,
• You have an overactive thyroid gland or an enlarged prostate.

Take special care with Ephedrine Injection. Tell your doctor if:
• You are a diabetic,
• You know or suspect that you suffer from glaucoma,
• You are about to have an operation which requires that you be given an anaesthetic,
• You are currently taking or have taken within the last 14 days any monoamine oxidase inhibitor drug used to treat depression.

Using other medicines
Tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without a prescription as they may interact with Ephedrine injection.
This is especially important of the following medicines:
• Cough and cold remedies
• Methyphenidate, used to treat “attention deficit hyperactivity disorder”
• Anaesthetics that are inhaled such as halothane
• Medicines used to treat depression
• Sympathomimetics, a medicine used as an appetite suppressant
• Insulin, used to treat diabetes
• Medicines used to treat asthma such as theophylline
• Corticosteroids, a type of medicine used to relieve swelling in a variety of different conditions
• Medicines for epilepsy
• Dexamethasone, a drug used to treat breathing problems
• Aspirin, a drug used during labour
• Medicines used to treat high blood pressure such as guanethidine

Pregnancy and breastfeeding
Please tell your doctor if you are pregnant or think you may be pregnant before you are given this medicine.
You should not be given this medicine if you are breastfeeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Laboratory Testing
This medicinal product contains an active ingredient that can induce positive results in anti-doping controls.

Important information about some of the ingredients of Ephedrine Injection
This medicinal product contains 3.32 mg (0.144 mmol) of sodium per ml of injection (a total of 33.2 mg or 1.44 mmol sodium in 10 ml syringe). This amount must be taken into consideration by patients on a salt-restricted diet.

The following information is intended for medical or healthcare professionals only. This is an extract from the Summary of Product Characteristics to assist in the administration of Ephedrine Injection. When determining appropriateness of use in a particular patient, the prescriber should be familiar with the Summary of Product Characteristics of the product.

Drug name: Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe

Safety information:
Ephedrine must be used solely by or under the supervision of the anaesthetist.
For intravenous injection.

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

Administration:
The pre-filled syringe contains a ready-to-use solution for injection containing 3 mg ephedrine hydrochloride in each ml of solution.
Adults and children over 12 years.
Slow intravenous injection of 3 to 6 mg (maximum 9 mg), repeated as needed every 3-4 min to a maximum of 30 mg. A lack of efficacy after 30 min should lead to reconsideration of the choice of the therapeutic agent.
The dose administered for 24 hours must not exceed 150 mg.
Children under 12 years.
The paediatric dose is 0.5 to 0.75 mg/kg or 17-25 mg/ml every 3-4 minutes according to response.

Elderly:
As for adults.

Overdose:
In the event of overdose, the occurrence of nausea, vomiting, fever, paranoid psychosis, ventricular and supraventricular arrhythmias, respiratory depression, convulsions and coma is observed.
The lethal dose in humans is approximately 2 g corresponding to blood concentrations of approximately 3.5 to 20 mg/l.

Treatment:
The treatment of ephedrine overdose with this product may require intensive supportive treatment. Slow intravenous injection of labetalol 50-200 mg may be given with electrocardiograph monitoring for the treatment of supraventricular tachycardia. Marked hypokalaemia (≤ 2.8 mmol/l) due to compartmental shift of potassium predisposes to cardiac arrhythmias and may be corrected by infusing potassium chloride in addition to propranolol and correcting respiratory alkalosis, when present.
3. HOW EPHEDRINE INJECTION IS GIVEN
Your doctor or nurse will administer Ephedrine Injection to you into a vein (intravenous). Your doctor will decide the correct dosage for you and when and how the injection should be administered.
Dosage
- Adults, elderly and children over 12 years: You will be given a slow injection into a vein of 3 to 6 mg (maximum 9 mg), repeated if necessary every 3-4 minutes to a maximum of 30 mg. The total dose must be lower than 150 mg/24 hours.
- Children under 12 years
Your child will be given a slow injection into a vein of 0.5-0.75 mg/kg or 17.25 mg/m² every 3-4 minutes according to response. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Ephedrine Injection can cause side effects, although not everybody gets them.
Common (affect less than 1 in 10 patients):
- Confusion, feeling worried, depression
- Nervousness, irritability, restlessness, weakness, sleeping problems, headache, sweating
- Palpitations, high blood pressure, fast heartbeat
- Shortness of breath
- Nausea, vomiting
Rare (affect less than 1 in 1000 patients):
- Irregular heartbeat
- Difficulty in passing urine
Other side effects (it is not known how often these occur):
- Affects blood clotting
- Allergy
- Change in your personality or the way you feel/think, fear
- Tremor, excessive salivary production
- Increased pressure in the eye (glaucoma)
- Pain over the heart, slow heartbeat, heart failure (cardiac arrest), low blood pressure
- Bleeding in the brain
- Breathing problems
- Reduced appetite
- A fall in blood potassium levels, changes in blood glucose levels
- Build up of a fluid within the lungs (pulmonary oedema)
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 EPHEDRINE INJECTION
Keep out of the reach and sight of children. You should not be given this medicine if it has passed the expiry date shown on the carton and syringe label. Your doctor or nurse will check this. Store the blister in the outer carton in order to protect from light. Any unused product or waste material should be disposed of in accordance with local requirements.

6. FURTHER INFORMATION
What Ephedrine Injection contains:
- The active ingredient is Ephedrine Hydrochloride. Each ml of Solution for injection contains 3 mg ephedrine hydrochloride. Each 10 ml prefilled syringe contains 30 mg ephedrine hydrochloride.
- The other ingredients are Sodium Chloride, Citric acid monohydrate, sodium citrate and Water for Injections and may contain hydrochloric acid or sodium hydroxide (for pH adjustments).

What Ephedrine Injection looks like and contents of the pack:
Ephedrine Injection is a clear and colourless liquid. It is supplied in a 10 ml polypropylene prefilled syringe with a polypropylene tip cap and tamper proof seal, and is individually packaged in a transparent blister pack.
The prefilled syringes are available in boxes of 1, 5, 10, 12 and 20 syringes. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:
UKR+ Regulatory Affairs Ltd
The Bull Pen, Home Farm
Banbury Road, Caversfield
Oxfordshire OX27 8TG
UK

Manufacturer:
LABORATOIRE AGUETTANT
1, rue Alexander Fleming
69007 LYON CEDEX
France
This leaflet was last approved in 10/2010.

Instructions for use:
Please prepare the syringe carefully as follows:
The pre-filled syringe is for single patient only.
Discard syringe after use. DO NOT REUSE.
The content of un-opened and undamaged blister is sterile, and must not be opened until use.
The product should be inspected visually for particles and discoloration prior to administration. Only clear colourless solution free from particles or precipitates should be used.
Do not use the product if the tamper evident seal on syringe is broken.
The external surface of syringe is sterile until blister is opened.
1) Withdraw the pre-filled syringe from the sterile blister.
2) Push on the plunger to free the bung.
3) Twist off the end cap to break the seals.
4) Check that the syringe seal has been completely removed. If not, replace the cap and twist again.
5) Expel the air by gently pushing the plunger.
6) Connect the syringe to the IV access. Push the plunger slowly to inject the required volume. Any unused product or waste material should be disposed of in accordance with local requirements.

Storage and Shelf life:
Do not use this product after the expiry date which is stated on the carton and syringe label. The expiry date refers to the last day of that month.
After opening, the product must be used immediately. Store the blister in the outer carton in order to protect from light.
Module 4
Labelling

Carton:
Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe

Slow IV injection

Composition:
Each ml of Solution for Injection contains 3 mg ephedrine hydrochloride.
Each 10 ml pre-filled syringe contains 30 mg of ephedrine hydrochloride.

Excipients:
Sodium chloride; citric acid monohydrate; sodium citrate; hydrochloric acid or sodium hydroxide and water for injections.

See Package Leaflet for further information.

Pharmaceutical form and contents:
Solution for injection.
5 x 10 ml pre-filled syringes

Method and route of administration:
Read the package leaflet before use.
For single patient only. Discard syringe after use.
For slow intravenous injection.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Other special warnings:
Do not use if tamper evident seal on syringe is broken.
The external surface of syringe is sterile until blister is opened.
Use only if solution is clear and colourless and free from visible particles.

After opening, the product must be used immediately.

Special storage conditions:
Store the blister in the outer carton in order to protect from light.

Use as directed by a physician

Marketing authorisation holder:
UKR Regulatory Affairs Ltd
The Bull Pen, Home Farm
Bansbury Road, Caversfield
Oxfordshire OX27 8TG
UK
Ephedrine Hydrochloride
3 mg/ml Solution for Injection in Pre-filled Syringe

Slow IV injection

Composition:
Each ml of Solution for Injection contains 3 mg ephedrine hydrochloride.
Each 10 ml pre-filled syringe contains 30 mg of ephedrine hydrochloride.

Excipients:
Sodium chloride, citric acid monohydrate, sodium citrate, hydrochloric acid or sodium hydroxide and water for injections.

See Package Leaflet for further information.

Pharmaceutical form and contents:
Solution for injection, 10 x 10 ml pre-filled syringes

Method and route of administration:
Read the package leaflet before use.
For single patient only. Discard syringe after use.

For slow intravenous injection.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Other special warnings:
Do not use if tamper evident seal on syringe is broken.
The external surface of syringe is sterile until blister is opened.
Use only if solution is clear and colourless and free from visible particles.
After opening, the product must be used immediately.

Special storage conditions:
Store the blister in the outer carton in order to protect from light.
Use as directed by a physician

Marketing authorisation holder:
UKR Regulatory Affairs Ltd
The Buit Pet, Home Farm
Burley Road, Saffron Walden
Oxon 07 01
UK
Sterile Blister:
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe (PL 19364/0048; UK/H/2194/001/DC) could be approved. This application was submitted by the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Belgium as Concerned Member State (CMS).

This application was made under Article 10(a) of 2001/83/EC, as amended, a so-called ‘well-established medicinal use’ application. This product is a prescription-only medicine (POM) indicated for the treatment of hypotension from spinal or epidural anaesthesia.

Ephedrine belongs to a group of medicines called adrenergic and dopaminergic agents. It is a sympathomimetic amine acting directly on the alpha and beta receptors and indirectly by increasing the release of noradrenaline by the sympathetic nerve endings. As with any sympathomimetic agent, ephedrine stimulates the central nervous system, the cardiovascular system, the respiratory system, and the sphincters of the digestive and urinary systems. Ephedrine is also a monoamine oxidase (MAO) inhibitor.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 22 September 2010. After a subsequent national phase, the licence was granted in the UK on 01 November 2010.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Ephedrine Hydrochloride 3 mg/ml Solution for Injection in Pre-filled Syringe |
| Name(s) of the active substance(s) (INN)          | Ephedrine hydrochloride                                                     |
| Pharmacotherapeutic classification (ATC code)    | Adrenergic and dopaminergic agent (C01CA)                                  |
| Pharmaceutical form and strength(s)              | 3 mg/ml Solution for Injection                                              |
| Reference numbers for the Mutual Recognition Procedure | UK/H/2194/001/DC                                                          |
| Reference Member State (RMS)                     | United Kingdom                                                             |
| Concerned Member State (CMS)                     | Belgium                                                                    |
| Marketing Authorisation Number(s)                | PL 19364/0048                                                              |
| Name and address of the authorisation holder      | UKR Regulatory Affairs Ltd, The Bull Pen, Home Farm, Banbury Road, Caversfield Oxfordshire, OX27 8TG, UK. |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Ephedrine hydrochloride
Chemical name: (1R,2S)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride

Structure:

```
\begin{tikzpicture}
  \node at (0,0) {H};
  \node at (0.5,0) {O};
  \node at (-0.5,0) {N};
  \node at (0,0.5) {CH$_3$};
  \node at (0,-0.5) {CH$_3$};
  \node at (1.5,0) {HCl};
  \draw (0,0) -- (0.5,0);
  \draw (-0.5,0) -- (0,0);
\end{tikzpicture}
```

Molecular formula: C$_{10}$H$_{16}$ClNO
Molecular weight: 201.7
Appearance: Ephedrine hydrochloride is a white or almost white crystalline powder or colourless crystals. It is very soluble in water and freely soluble in alcohol

Ephedrine hydrochloride is the subject of a European Pharmacopoeia monograph.

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

P. Medicinal Product

Other Ingredients
Other ingredients consist of the pharmaceutical excipients sodium chloride, citric acid monohydrate, sodium citrate, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient. None of the excipients used are sourced from materials of animal or human origin.

Pharmaceutical Development
The objective of the development programme was to develop a clear, colourless, isotonic, pyrogen free solution for injection in a sterile ready to use 10 ml polypropylene pre-filled syringe intended for parenteral use to treat hypotension from spinal or epidural anaesthesia.

Details of the pharmaceutical development of the product have been supplied and are satisfactory.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.
**Container-Closure System**
The finished product is supplied in 10 ml polypropylene pre-filled syringes with a polypropylene tip cap and tamper-proof seal, and is individually packaged in a transparent blister pack. The pre-filled syringes are available in pack sizes of 1, 5, 10, 12 and 20.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened sterile pre-filled syringe, with the special storage conditions 'Store the blister in the outer carton in order to protect from light'. After opening the product must be used immediately.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been 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, as amended. 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 it contains.

The Marketing Authorisation Holder has stated that they do not intend to market all pack sizes of the product at this present time. However, they have committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

**MAA form**
The MAA form is pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
There are no objections to the approval of this product from a pharmaceutical viewpoint.

**III.2 NON-CLINICAL ASPECTS**

**Pharmacology**
Ephedrine was demonstrated to increase heart rate and blood pressure effectively in rats and cats under anaesthesia with ED$_{20}$ values for blood pressure of 0.27 mg/kg i.v. in rats and 0.018 mg/kg i.v. and 0.066 mg/kg intraduodenally in cats, and with heart rates of 0.48 mg/kg i.v. in rats and 0.044 mg/kg in cats. In horses, ephedrine at a dose of 0.06 mg/kg i.v. during light and deep halothane anaesthesia resulted in an increase of arterial blood pressure that was based on an increase in cardiac output and stroke volume. In pregnant ewes, anaesthesia caused a marked fall of blood pressure and heart rate followed by a decrease of oxygen concentration and an increase in carbon dioxide concentration and a fall in uterine blood
flow, fetal blood pressure and fetal blood oxygen. These changes were almost completely restored by the administration of ephedrine at dose levels between 0.1 and 2.0 mg/kg i.v. Ephedrine was shown to exert local anaesthesia at concentrations between 0.25% and 5% when injected beneath the sciatic nerve in rats, causing a complete blockade of motor function and nociception.

The non-clinical pharmacodynamics data discussed by the Expert support the proposed clinical use of the product, particularly the data from pregnant ewes.

Safety pharmacology
The effects seen were generally related to the central nervous system and manifested as increased locomotor activity, salivation, increased body temperature, and reduced food intake, mostly in rats. Ephedrine at doses between 3 and 200 mg/kg, generally intraperitoneally, and in a single investigation subcutaneously, exerted dose-dependent effects on the central nervous system at all doses and were attributed to interactions with dopamine or nicotinic receptors.

Pharmacokinetics
Ephedrine was rapidly absorbed from the gastro-intestinal tract in mice reaching maximum blood levels at 5 – 6 minutes after dosing. The absorption half-life was 1.15 minutes. Elimination from plasma was also rapid with a half-life of 30.6 minutes. Ephedrine was widely distributed with the highest concentrations in the kidneys, followed by the liver, spleen and lungs. In dogs but not in rats, a high concentration was found in the brain. In human volunteers, ephedrine crossed the placenta almost freely resulting in blood levels in the fetuses around 71% of those in the mothers.

Metabolism of ephedrine in humans, dogs and several species of rodents was shown to include primarily three reactions: aromatic hydroxylation, N-dealkylation, and oxidative deamination. However, the extent to which ephedrine is metabolised and the major metabolites produced vary with species.

The major route of elimination in humans is urinary, with 88% being excreted within 24 hours and 97% within 48 hours. In dogs after intraperitoneal administration, 65.5% of the dose was excreted in urine within 24 hours, and in rats, 86.4% within 40 hours. Excretion in faeces accounted for 4.5% within 40 hours in the rat after intraperitoneal dosing. In dairy cattle, ephedrine was excreted in the milk at concentrations of more than four-fold the plasma concentrations.

Toxicology
The acute toxicity of ephedrine has been reported in a variety of species by different routes. It was of moderate toxicity with LD₅₀ values ranging between 410 and 785 mg/kg, by the subcutaneous route of between 41 and 1150 mg/kg, by the intraperitoneal route of between 109 and 254 mg/kg and by the intravenous route of between 58 and 175 mg/kg. Toxicity was mainly to the central nervous system, and was manifested as hyperkinesias, convulsions, ataxia, lethargy and epistaxis.

The administration of ephedrine in drinking water caused a massive reduction of water consumption with possibly secondary effects. Subacute administration of high concentrations in the diet caused reduced body weights in rats at 1000 ppm and above with hyperexcitability and rough coat but without any changes in organ pathology. In mice, concentrations of 310 and 630 ppm caused reduced body weight and hyperexcitability, also
without any pathology. At higher concentrations, several males died from fighting. In obese mice, body weight loss was also the main effect and was attributed partially to reduced food consumption and also to thermogenesis. Apart from the reduction in body weights and food consumption, no clear treatment-related effects were seen in the long-term carcinogenicity studies in rats and mice at doses up to 9 and 11 mg/kg in male and female rats and up to 29 and 25 mg/kg in male and female mice respectively.

Although marginal genotoxic effects were seen in vitro, the two long-term carcinogenicity studies in mice and rats were negative. N-nitroso-ephedrine and the co-administration of sodium nitrate and ephedrine were carcinogenic in old studies in low numbers of animals not conducted to current standards.

No studies to current standards on fertility have been conducted. However, anti-estrogenic effects of ephedrine have been found in immature rats given ephedrine at a dose of 5 mg/kg orally, indicating the potential for effects on female fertility. The potential for teratogenicity of ephedrine is discussed extensively in the literature, but the only available data on teratogenicity were derived from a study in chick embryos. Dose-related teratogenicity was seen, but the relevance of this finding to humans is unknown.

Ephedrine has been shown to cause contact sensitisation; an appropriate contra-indication has been included in Section 4.3 of the SmPC.

Two of the excipients contain sodium; a warning has been included in Section 4.4 of the SmPC for patients on sodium-controlled diets.

The active substance, the excipients and the syringe comply with the Ph. Eur. and there are no non-clinical concerns in respect of the impurities.

**Environmental Risk Assessment**

The applicant has provided an adequate justification for the absence of a formal environmental risk assessment. Since this is an application for a well-established product, it is not expected to increase the amount of material reaching the environment, and there is no need for an environmental risk assessment to be conducted.

**Summary of product Characteristics (SmPC)**

The SmPC is satisfactory from a non-clinical viewpoint.

**Non-Clinical Expert Report**

The non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

**Overall Conclusion on the non-clinical part**

The applicant has provided an adequate review of the available non-clinical data. There are no new non-clinical data identified in the literature review that would change the benefit-risk analysis for ephedrine.

There are no objections to the approval of this product from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS

Pharmacokinetics
No new pharmacokinetic studies have been provided. The applicant has submitted an overview of the pharmacokinetic profile of ephedrine following administration via various routes.

Following intranasal application of 5 mg and 10 mg ephedrine, Cmax and AUC up to 8 h were proportional to the doses. Elimination half-life was approximately 6 h. Following an oral dose of 50 mg ephedrine, plasma levels were substantially higher than after a nasal dose, Tmax (2h) was constant and dose-proportionality of Cmax and AUC were independent of route of administration (Berlin et al.; 2001).

Plasma half-life of ephedrine has been reported to range from 3 to 6 hours, depending on urinary pH (Sweetman, 2007).

Ephedrine has been shown to cross the placenta barrier and increase the fetal heart rate as well as atrial natriuretic peptide (LaPorta et al., 1995).

Pharmacodynamics
No new pharmacodynamic studies are submitted. The applicant has presented an overview of the pharmacodynamic effects of ephedrine on various organs.

Ephedrine is a sympathomimetic amine acting directly on the alpha and beta receptors and indirectly by increasing the release of noradrenaline by the sympathetic nerve endings. As with any sympathomimetic agent, ephedrine stimulates the central nervous system, the cardiovascular system, the respiratory system, and the sphincters of the digestive and urinary systems. Ephedrine is also a monoamine oxidase (MAO) inhibitor.

Clinical efficacy
No new efficacy studies have been provided. The applicant has presented an overview of the efficacy in the proposed indications of ephedrine from published literature.

Spinal and epidural anaesthesia cause alterations in the cardiovascular system which contribute to the onset of hypotension (Morgan, 1994). The main effects are mediated by blockade of presynaptic sympathetic nerve fibers by local anaesthetics. In addition to volume expansion and physical methods to increase venous return vasoconstrictors such as ephedrine, phenylephrine, epinephrine or dopamine are used to reverse hypotension associated with spinal or epidural anaesthesia.

Clinical Safety
No new safety studies have been provided and the safety profile of ephedrine is well recognised.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are medically satisfactory

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
MAA Form
The MAA form is medically satisfactory.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

A suitable justification has been provided for not submitting a Risk Management Plan (RMP) for this product.

Conclusion
There are no objections to the approval of this application from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ephedrine Hydrochloride 3 mg/ml Solution for Injection 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.

NON-CLINICAL
No new non-clinical studies have been conducted in support of this application, which is acceptable as the pharmacology, pharmacokinetics and toxicology of ephedrine is well-known. The non-clinical overview comprises a satisfactory review of the relevant literature.

EFFICACY
No new efficacy data were submitted and none were required for an application of this type.

No new safety data have been submitted or required for this well-established use application.

PRODUCT LITERATURE
The SmPC PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Ephedrine has been in clinical use in the treatment of hypotension associated with spinal and epidural anaesthesia for many years. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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