Public Assessment Report

Mutual Recognition Procedure

ANAPEN 500 MICROGRAMS IN 0.3ML SOLUTION FOR INJECTION (PRE-FILLED SYRINGE)

Procedure No: UK/H/0516/003/MR

UK Licence No: PL 18813/0003

LINCOLN MEDICAL LIMITED
ANAPEN 500 MICROGRAMS IN 0.3ML SOLUTION FOR INJECTION
PL 18813/0003

LAY SUMMARY

On 9 May 2011, Austria, Germany, Greece, France, Ireland, the Netherlands and Sweden agreed to grant Lincoln Medical Limited a Marketing Authorisation (licence) for Anapen 500 micrograms in 0.3ml Solution for Injection (PL 18813/0003; UK/H/0516/003/MR). A licence had previously been granted in the UK on 1 June 2009.

Anapen is an automatic injection device (Auto-Injector) containing adrenaline solution. The device injects a single dose of adrenaline into muscle. Anapen is used for the emergency treatment of serious allergic reactions or anaphylaxis caused by peanuts or other foods, drugs, insect bites or stings and other allergens, as well as exercise or an unknown cause.

Adrenaline is a natural hormone released in response to stress. In allergic reactions it stabilises blood pressure, heart function and breathing, and reduces swelling.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits outweigh the risks; hence a Marketing Authorisation has been granted.
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Module 1

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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Anapen 500 micrograms in 0.3ml solution for injection in a pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each millilitre contains 1.7 mg of adrenaline (epinephrine)
One dose of 0.3ml contains 500 micrograms of adrenaline (epinephrine)
Excipients: sodium metabisulphite (E223), sodium chloride
For full list of excipients see 6.1

3 PHARMACEUTICAL FORM
Solution for injection.
Clear colourless solution practically free from particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Emergency treatment for acute allergic reactions (anaphylaxis) caused by peanuts or other foods, drugs, insect bites or stings, and other allergens as well as exercise-induced or idiopathic anaphylaxis.

4.2 Posology and method of administration
Use only by the intramuscular route.

Anapen consists of a pre-filled syringe of adrenaline (epinephrine) contained in an auto-injection device. The whole is referred to as an auto-injector.

One Anapen injection should be administered intramuscularly immediately on the appearance of the signs and symptoms of anaphylactic shock. These may occur within minutes of exposure to the allergen and are most commonly manifested by urticaria, flushing or angioedema; more severe reactions involve the circulatory and respiratory systems. Inject Anapen only into the anterolateral aspect of the thigh, not the buttock. The injected area may be lightly massaged for 10 seconds following injection.

The effective dose is typically in the range 0.005-0.01 mg/kg but higher doses may be necessary in some cases.

Use in adults: The usual dose is 300 micrograms. Larger adults may require Anapen 500 micrograms to reverse the effect of an allergic reaction. In some circumstances a single dose of adrenaline (epinephrine) may not completely reverse the effects of an acute allergic reaction and for such patients a repeat injection may be given after 10-15 minutes.

Use in children: Anapen 500 micrograms is not recommended for use in children.

Anapen auto-injector is intended for immediate self-administration by a person with a history of anaphylaxis and is designed to deliver a single dose of 500 micrograms (0.3ml) adrenaline (epinephrine). For stability reasons 0.75ml is left in the syringe after use but the unit cannot be used again and should be safely discarded.

4.3 Contraindications
Hypersensitivity to adrenaline (epinephrine) or to any of the excipients (see section 4.4 for further information on sulphites)

4.4 Special warnings and precautions for use
Anapen contains sodium metabisulphite which can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma. Patients with these conditions must be carefully instructed in regard to the circumstances under which Anapen should be used.
All patients who are prescribed Anapen should be thoroughly instructed to understand the indications for use and the correct method of administration. Anapen is indicated as emergency supportive therapy only and patients should be advised to seek immediate medical attention following administration.

Use with caution in patients with heart disease e.g. coronary heart and cardiac muscle diseases (angina may be induced), cor pulmonale, cardiac arrhythmias or tachycardia. There is a risk of adverse reactions following adrenaline (epinephrine) administration in patients with hyperthyroidism, cardiovascular disease (severe angina pectoris, obstructive cardiomyopathy and ventricular arrhythmia and hypertension), phaeochromocytoma, high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia, hypokalemia, diabetes, or in elderly or pregnant patients. Repeated local injection can result in necrosis at sites of injection from vascular constriction. Accidental intravascular injection may result in cerebral haemorrhage due to a sudden rise in blood pressure. Accidental injection into hands or feet may cause loss of blood flow to adjacent areas due to vasoconstriction.

This medicinal product contains less than 1mmol sodium (23mg) per dose. i.e. essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction
The effects of adrenaline (epinephrine) may be potentiated by tricyclic antidepressants mixed noradrenergic-serotonergic antidepressants like venlafaxine, sibutramine or milnacipran and monoamine oxidase inhibitors (sudden blood pressure increase and possible cardiac arrhythmia), COMT blocking agent, thyroid hormones, theophylline, oxytocin, parasympatholytics, certain antihistamines (diphenhydramine, chlorpheniramine), levodopa and alcohol.

Severe hypertension and bradycardia may occur when adrenaline (epinephrine) is administered with non-selective beta-blocking medicinal products.

Concurrent therapy with sympathomimetics may potentiate the effects of adrenaline (epinephrine). Use Anapen with caution in patients receiving medicinal products which may sensitise the heart to arrhythmias, e.g. digitalis, quinidine, halogenated anaesthetics.

The pressor effects of adrenaline (epinephrine) may be counteracted by administration of rapidly acting vasodilators or alpha adrenergic blocking medicinal products. Anti-anaphylactic effects can be antagonised by beta-blocking agents, especially non-selective beta blockers.

Adrenaline (epinephrine) inhibits insulin secretion and diabetic patients may require upward adjustment of their insulin or other hypoglycaemic therapy.

4.6 Fertility, pregnancy and lactation
There are no adequate or well controlled studies of adrenaline (epinephrine) in pregnant women. Adrenaline (epinephrine) should only be used in pregnancy if the potential benefit justifies the potential risk to the foetus. Adrenaline (epinephrine) may dramatically reduce placental blood flow, although anaphylactic shock will do this too. Adrenaline (epinephrine) is not orally bioavailable; any adrenaline (epinephrine) excreted in breast milk would not be expected to have any effect on the nursing infant

4.7 Effects on ability to drive and use machines
It is not recommended that patients should drive or use machines following administration of adrenaline (epinephrine), since patients will be affected by symptoms of the anaphylactic shock.

4.8 Undesirable effects
The occurrence of undesirable effects depends on the sensitivity of the individual patient and the dose applied.

Common adverse reactions even at low doses due to adrenaline (epinephrine) include palpitations, tachycardia, sweating, nausea, vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness, anxiety, coldness of extremities.
Less frequently reported effects include hallucinations, syncope, hyperglycaemia, hypokalaemia, metabolic acidosis, mydriasis, difficulty in micturition with urinary retention, muscle tremor.

Adverse reactions which occur at higher doses or in susceptible individuals are cardiac arrhythmias (ventricular fibrillation/cardiac arrest), sudden rise of blood pressure (sometimes leading to cerebral haemorrhage), as well as vasoconstriction (e.g., in the skin, mucous tissues and kidneys).

Anapen contains a sulphite that may cause allergic-type reactions including anaphylactic reactions or life-threatening or less severe asthmatic episodes in certain susceptible patients.

4.9 Overdose

Overdose or accidental intravascular injection of adrenaline (epinephrine) may cause cerebral haemorrhage from a sudden rise of blood pressure. Death may result from acute pulmonary oedema arising from peripheral vascular constriction and cardiac stimulation.

The pressor effects of adrenaline (epinephrine) may be counteracted by rapidly acting vasodilators or alpha adrenergic blocking medicinal products. Should prolonged hypotension follow such measures, it may be necessary to administer another pressor medicinal product, such as noradrenaline.

Acute pulmonary oedema with respiratory embarrassment following adrenaline (epinephrine) overdose should be managed by administration of a rapidly acting alpha adrenergic blocking medicinal product such as phenolamine and/or with intermittent positive pressure respiration.

Adrenaline (epinephrine) overdose may also result in transient bradycardia followed by tachycardia; these can be followed by potentially fatal cardiac arrhythmias which may be treated by beta adrenergic blocking medicinal products. These must be preceded or accompanied by an alpha-adrenergic blocker to control the alpha-mediated effects on the peripheral circulation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C01 CA 24

Adrenaline (epinephrine) is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha and beta adrenergic receptors and its effects on target organs are, therefore, complex. It is the medicinal product of choice to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise induced anaphylaxis.

Adrenaline (epinephrine) has a strong vasoconstrictor action through alpha adrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacotoxicological features in anaphylactic shock. Through its stimulation of bronchial beta adrenergic receptors, adrenaline (epinephrine) has a powerful bronchodilator action which alleviates wheezing and dyspnoea. Adrenaline (epinephrine) also alleviates pruritus, urticaria and angioedema associated with anaphylaxis.

5.2 Pharmacokinetic properties

Adrenaline (epinephrine) is rapidly inactivated in the body, mostly in the liver by the enzymes COMT and MAO. Much of a dose of adrenaline (epinephrine) is excreted as metabolites in urine. The plasma half life is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption so that the effects may last longer than the half life suggests.

5.3 Preclinical safety data

Adrenaline (epinephrine) has been widely used in the clinical management of allergic emergencies for many years. There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.
PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride,
sodium metabisulphite (E223),
hydrochloric acid
water for injections.

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

6.3 Shelf life
2 years

6.4 Special precautions for storage
Do not store above 25°C. To protect from light store in the original package.

6.5 Nature and contents of container
Anapen consists of a pre-filled syringe contained in a single use auto-injection device.

The syringe contains adrenaline (epinephrine) solution. The auto-injection device delivers 0.3ml of this solution.

The immediate container is a glass syringe sealed by a rubber plunger at one end, and at the other end by a rubber needle shield.

Syringe
BD (Becton Dickinson) borosilicate glass type 1, 27G 1/2”

Plunger
BD (Becton Dickinson) black chlorobutyl rubber PH 701/50

In a pack size of 1.

6.6 Special precautions for disposal
Instructions for use
A Parts of the Anapen Autoinjector:
Before using the Anapen Auto-Injector, the patient needs to know about the parts of the Auto-Injector. These are shown in the picture.

- Rotating cover over solution window:
The patient rotates the cover over the solution windows to line up the lenses with the solution windows on the autoinjector body.

- Solution window: The patient looks through the lens into this window before the injection to check that the solution is clear and ready to use.

- Injection indicator: Before the injection, the patient can see a white plastic plunger through the window. This means that the Anapen Auto-Injector has not been fired by mistake or tampered with. After the injection, the injection indicator turns red. This indicates that the Anapen Auto-Injector has been fired correctly.

- Black needle shield (reversible): This protects the needle when the patient is not using the Anapen Auto-Injector. The patient pulls the needle shield off before the injection. After the
injection, the patient turns the black needle shield around and puts it back onto the same end of Anapen Auto-Injector, to cover the needle.

- **Grey safety cap:** This covers the red firing button. It stops the button from being pushed by mistake.

The patient must not remove the black needle shield or the grey safety cap until they need to use the Anapen Auto-Injector.

B. Checking the Anapen Auto-Injector

Before using the Anapen Auto-Injector, the patient must check it as follows:

1. Rotate the cover over the solution windows fully anti-clockwise as shown by the arrow to line up the lenses with the solution windows on the autoinjector body.

2. Look through the lens into the **solution window**. Check that the solution is clear and colourless.
   
   If it is cloudy, coloured or contains particles, discard the Anapen Auto-Injector.

3. Make sure that the **injection indicator** is not red. If it is red, this means that the Anapen Auto-Injector has already been fired and you must discard it.

4. Rotate the cover over the solution windows fully back clockwise as shown by the arrow, to ensure both solution windows are covered. Put the Anapen Auto-Injector back in the carton until you need to use it.

C. Using the Anapen Auto-Injector

If the black needle shield has been removed, the patient must not put their thumb, fingers or hand over the open end (needle end) of the Anapen Auto-Injector.

To use the Anapen Auto-Injector, the patient must follow the steps below:

1. Remove the black needle shield by pulling hard in the direction of the arrow.
   
   This also removes a grey protective needle sheath.

2. Remove the grey safety cap from the red firing button by pulling as indicated by the arrow.

3. Hold the open end (needle end) of Anapen against the outer part of the thigh. If necessary, can use Anapen through light clothing, such as denim, cotton or polyester.

4. Press the red firing button so that it clicks. Keep holding the Anapen Auto-Injector against the outer thigh for 10 seconds. Slowly remove Anapen from the thigh. Then gently massage the injection area.

5. The **injection indicator will have turned red.** This shows that the injection is complete. If the injection indicator is not red, injection must be repeated with a new Anapen.
6. After the injection, the needle sticks out. To cover it, click the wide end of the black needle shield back on the open end (needle end) of Anapen Auto-Injector (as indicated by the arrow).

Seek medical advice. Give used Anapen to the hospital or pharmacist for proper disposal.

7
MARKETING AUTHORISATION HOLDER
Lincoln Medical Ltd
Unit 8 Wilton Business Centre
Wilton
Salisbury SP2 0AH
United Kingdom

8
MARKETING AUTHORISATION NUMBER(S)
PL 18813/0003

9
DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/06/2009

10
DATE OF REVISION OF THE TEXT
26/04/2012
Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Anapen® 500 micrograms
in 0.3 ml solution for injection
in a pre-filled syringe
Adrenaline (Epinephrine) Auto-Injector

Read all of this leaflet carefully before you start using this medicine.
• Keep this leaflet. You may need to read it again.
• If you have further questions, please ask your doctor or your pharmacist.
• This medicine has been prescribed for you personally and you should 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1 - What Anapen is and what it is used for?
2 - Before you use Anapen
3 - How to use Anapen
4 - Possible side effects
5 - How to store Anapen
6 - Further information

1 What Anapen is and what it is used for?
• Anapen consists of a pre-filled syringe of adrenaline contained in an automatic injection device (Auto-Injector).
• This injects a single dose of adrenaline into muscle.
• This medicine is for emergency only and you should seek immediate medical attention after using your Auto-Injector.
• Adrenaline is a natural hormone released in response to stress. In acute allergic reactions it improves blood pressure, heart function and breathing, and reduces swelling. Adrenaline is also known as epinephrine.
• Anapen is used for the emergency treatment of serious allergic reactions or anaphylaxis caused by peanuts or other foods, drugs, insect bites or stings and other allergens as well as exercise or an unknown cause.

2. Before you use Anapen
Do not use Anapen
• If you are allergic (hypersensitive) to adrenaline or any of its other ingredients (see section below for information on sulphites).

Take special care with Anapen
• Your doctor should have carefully instructed you when to use and the correct way to use your Anapen Auto-Injector.
• You should tell your doctor if you are suffering from heart disease, including angina, hyperthyroidism, high blood pressure, lowered potassium levels and increased calcium in the blood, disorders of the blood circulation, phaeochromocytoma (a type of tumour in the adrenal gland), raised pressure inside the eye (glaucoma), kidney or prostate disease diabetes or any other medical condition.
DOSAGE AND ADMINISTRATION

Children: The usual dose is 300 micrograms.

In adults over 60 years of age: A repeat injection may be given after 10 to 15 minutes.

INFORMATION FOR USERS

WARNING
Accidental injection into a blood vessel may result in skin damage at sites of injection. Accidental injection into the hand or foot may result in loss of blood flow to the affected part. You should immediately seek medical advice at the nearest hospital.

Using other medicines
You should also tell your doctor if you are presently receiving medicines particularly:

- Medicines for heart disease, such as digitals (digoxin), beta-blockers, quinidine.
- Medicines for depression, such as tricylic antidepressants, monoamine oxidase inhibitors (MAOIs), serotonin and noradrenaline reuptake inhibitors (SNRIs).
- Medicines for diabetes; your doctor may change the dosage of your medication after using Anapen.
- Medicines for Parkinson's disease.
- Medicines for thyroid disease.
- Other medicines: antihistamines such as diphenhydramine or chlorpheniramine, theophylline, ipratropium and oxtropium (used to treat asthma, including chesty cough), oxytocin (used in labour in pregnancy), inhaled anaesthetics, alpha adrenergic blockers (used to treat high blood pressure), sympathomimetics (used to treat asthma, other airways disease and nasal congestion).

Inform your doctor, health professional or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Using Anapen with food and drink
Alcohol may adversely affect this medicine by increasing the effects of this medicine.

Pregnancy and breast-feeding
- It is not clear whether taking adrenaline during pregnancy is of risk to the unborn child. This should not deter you if you are pregnant from using Anapen in an emergency, as your life might be in danger. You should discuss this with your doctor before such an emergency occurs.
- Adrenaline would not be expected to have any effect on the breast-feeding infant. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
You should not drive or use machinery after injecting this medicine, since you may still be experiencing the effects of an anaphylactic shock.

IMPORTANT INFORMATION ABOUT SOME OF THE INGREDIENTS OF ANAPEN:
Anapen contains sodium metabisulphite (E223) which can cause allergic type reactions and difficulty in breathing, especially in those with a history of asthma.

You should tell your doctor if you know you are allergic to sodium metabisulphite. This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium free.

3. How to use Anapen
- Always use the medicine exactly as your doctor has instructed you.
- Check with your doctor or pharmacist if you are unsure.
- Only inject into the thigh muscle.
- For single use only, please ensure you discard safely immediately after use.
- The reaction usually starts within minutes of contact with the allergen and the person may experience:
  - Itching of the skin, a raised urticarial rash (nettle rash), flushing and swelling of eyes, lips or tongue.
  - Difficulty in breathing due to swelling of the throat. Wheezing, shortness of breath and coughing may result from tightening of the muscles in the lungs.
  - Other symptoms of anaphylaxis including headache, vomiting and diarrhoea.
- Collapse and loss of consciousness due to a sudden lowering of blood pressure.

When you experience these signs and symptoms use the Anapen Auto-Injector immediately. You must only inject this medicine into the muscle on the outer part of your thigh, not the buttock.

For use in adults
- The usual dose is 300 micrograms.
- For larger adults the 300 micrograms dose may not be sufficient and these patients may need Anapen 500 micrograms in the autoinjector.
- In circumstances where a single dose of adrenaline does not completely reverse the effect of an allergic reaction, a repeat injection may be given after 10 to 15 minutes.

Use in children
Anapen 500 micrograms is not recommended for use in children.

You should notify your doctor or attend the nearest hospital as soon as possible after use of Anapen. Make sure you explain that you have received an injection into your thigh muscle of adrenaline. Show the doctor the box and these instructions.
Instructions for use

A. Parts of the Anapen Auto-Injector

Before you use your Anapen Auto-Injector, you need to know about the parts of the Auto-Injector. These are shown in the picture:

- Rotating cover over solution window: You rotate the cover over the solution windows to line up the lenses with the solution windows on the Auto-Injector body.
- Solution window: You look through the lens into this window before the injection to check that the solution is clear and ready to use.
- Injection indicator: Before the injection, you can see a white plastic plunger through the window. This means that the Anapen Auto-Injector has not been fired by mistake or tampered with. After the injection, the injection indicator turns red. This indicates that the Anapen Auto-Injector has been fired correctly.
- Black needle shield (reversible): This protects the needle when you are not using the Anapen Auto-Injector. You pull the needle shield off before the injection. After the injection, turn the black needle shield around and put it back onto the same end of Anapen Auto-Injector, to cover the needle.
- Grey safety cap: This covers the red firing button. It stops the button from being pushed by mistake.

Do not remove the black needle shield or the grey safety cap until you need to use your Anapen Auto-Injector.

B. Checking your Anapen Auto-Injector

Before you use your Anapen Auto-Injector, you must check it as follows:

1. Rotate the cover over the solution window fully anticlockwise as shown by the arrows to line up the lenses with the solution windows on the Auto-Injector body.
2. Look through the lens into the solution window. Check that the solution is clear and colourless. If it is cloudy, coloured or contains particles, discard the Anapen Auto-Injector.
3. Make sure that the injection indicator is not red.
   If it is red, this means that the Anapen Auto-Injector has already been fired and you must discard it.
4. Rotate the cover over the solution window fully back clockwise as shown by the arrows to ensure both solution windows are covered.
   Put the Anapen Auto-Injector back in the carton until you need to use it.

C. Using the Anapen Auto-Injector

If the black needle shield has been removed, do not put your thumb, fingers or hand over the open end (needle end) of the Anapen Auto-Injector.

To use the Anapen Auto-Injector, follow the steps below:

1. Remove the black needle shield by pulling hard in the direction of the arrow. This also removes a grey protective needle sheath.
2. Remove the grey safety cap from the red firing button by pulling as indicated by the arrow.
3. Hold the open end (needle end) of Anapen against the outer part of your thigh.
   If necessary, you can use Anapen through light clothing, such as denim, cotton or polyester.
4. Press the red firing button so that it clicks. Keep holding the Anapen Auto-Injector against your thigh for 10 seconds. Slowly remove Anapen from your thigh. Then gently massage the injection area.
5. The injection indicator will have turned red.
   This shows that the injection is complete.
   If the injection indicator is not red, you must repeat the injection with a new Anapen.
6. After the injection, the needle sticks out.
   To cover it, click the wide end of the black needle shield back on the open end (needle end) of Anapen Auto-Injector (as indicated by the arrow).
Seek medical advice. Take this leaflet and your Anapen with you.
Give your used Anapen to the hospital or pharmacist for proper disposal.

If you use more Anapen than you should
• If you inject too much adrenaline or inject the medicine accidentally into a blood vessel or finger, you should seek immediate medical attention at the nearest hospital.
• If you have further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side-effects
Like all medicines, Anapen can have side-effects, although not everybody gets them.
• Anapen contains sodium metabisulphite (E223) which can cause allergic type reactions and difficulty in breathing especially in those with a history of asthma. You should seek immediate medical attention if you experience these side-effects.
• Common side-effects of adrenaline include a sensation of heart pounding (palpitations), rapid or uneven heartbeat, sweating, nausea, vomiting, difficulty in breathing, dizziness, weakness, pale skin (pallor), trembling, headache, apprehension, nervousness, anxiety and coldness of extremities.
• Other less frequent side-effects include hallucinations, fainting, dilated pupils, difficulty in urinating, muscle shakes, raised blood pressure and changes to the blood such as high sugar levels, low potassium levels and high acid content.
• Occasionally, at high doses, or in susceptible patients, a sudden increase in blood pressure which may cause bleeding into the brain, irregular heartbeat and heart attack and reduced blood flow to the skin, mucous tissues and kidneys may occur.

If any side-effects get serious or you notice any side-effects not mentioned in this leaflet, please inform your doctor, healthcare professional or pharmacist.

5. How to store Anapen
Keep out of reach and sight of children
• Do not use the Anapen Auto-Injector after the expiry date (exp. date) shown on the carton.
• Do not store above 25°C.
• To protect from light store in the original package.
Medicines should not be disposed of via wastewater or household waste.
Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Never give your Anapen Auto-Injector to another person even if his or her symptoms are similar to yours. This medicine is for your personal use only.

6. Further information
What Anapen contains
• The active substance is adrenaline (epinephrine) 500 micrograms in 0.3ml.
• The medicine also contains: sodium metabisulphite (E223), sodium chloride, hydrochloric acid, water for injections.

What Anapen looks like and the contents of the pack
Anapen 500 micrograms in 0.3ml solution for injection consists of a pre-filled syringe of adrenaline solution for injection contained in an auto injection device (Auto-Injector). It is produced in a dosage strength of 500 micrograms in 0.3ml solution for injection.
Anapen is supplied in units of 1.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation Holder
Lincoln Medical Limited, Unit 8, Wilton Business Centre, Wilton Salisbury, SP2 0AH, UK
Manufacturer: Owen Mumford Limited – Brook Hill Woodstock Oxon OX20 1TU UK

This medicinal product is authorised in Member States of the EEA under the following names:
United Kingdom, Ireland, Greece, Austria: Anapen 500 micrograms in 0.3 ml Solution for Injection
France: Anapen 0,5mg/0,3ml Solution for injection
Germany: Anapen 500 mikrogramm solution for injection
Sweden: Anapen 0,5 mg/0,3 ml Solution for injection
The Netherlands: Anapen 0,5mg/0,3ml Solution for Injection

This leaflet was last approved: dd/mm/yyyy. Anapen is a registered trade mark

AU2500/11/0000/01
Module 4
Labelling

Anapen® 500 micrograms in 0.3ml solution for injection
in a pre-filled syringe
Adrenaline (Epinephrine) autoinjector 1:600
Single dose intramuscular injection

- Deliver one single dose (0.3ml) of 500 micrograms of Adrenaline (Epinephrine).
- Solution for injection. Each auto-injector contains: Adrenaline (Epinephrine) 500 micrograms/0.3ml
- List of excipients: Sodium metabisulphite (E223), Sodium chloride, hydrochloric acid (For pH adjustment). Water for injections.
- Marketing authorisation holder: Lincoln Medical Ltd., Unit B Wilton Business Centre, Wilton Salisbury, SP2 6AG, UK
- Distributor: Lincoln Medical Ltd., Salisbury, SP2 6AH, UK
- MCA Ref: PL 1991/00003. PA 10729/00009
- POM (Prescription Only Medication). Suitable for use by medical professionals.
**Anapen® 500 micrograms in 0.3 ml solution for injection (pre-filled syringe)**

- Adrenaline (Epinephrine) autoinjector 1:600
- DELIVERS ONE SINGLE DOSE (0.3 ml) of 500 micrograms Adrenaline (Epinephrine)

1. Remove BLACK needle shield.
2. Remove GREY safety cap from red firing button.
3. Hold the needle end of the Anapen Auto-injector against outer thigh. Press red button so it clicks and HOLD FOR 10 SECONDS. Gently massage the injection site.
Module 5  
Scientific discussion during initial procedure

I. INTRODUCTION  

Based on the review of the data on quality, safety and efficacy, the RMS and CMS countries considered that the application for Anapen 500 micrograms in 0.3ml solution for injection in a pre-filled syringe in the emergency treatment for acute allergic reactions (anaphylaxis) caused by peanuts or other foods, drugs, insect bites or stings, and other allergens as well as exercise-induced or idiopathic anaphylaxis, could be approved.

A national marketing authorisation was granted in the UK on 1 June 2009. This application was made under Article 10a of 2001/83/EC (well-established use), with the UK as RMS and Austria, Germany, Greece, France, Ireland, the Netherlands and Sweden as CMS countries.

Anapen 500 micrograms in 0.3ml solution for injection in a pre-filled syringe contains adrenaline. Adrenaline (epinephrine) is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha and beta adrenergic receptors and its effects on target organs are, therefore, complex. It is the medicinal product of choice to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise induced anaphylaxis.

Adrenaline (epinephrine) has a strong vasoconstrictor action through alpha adrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacotoxicological features in anaphylactic shock. Through its stimulation of bronchial beta adrenergic receptors, adrenaline (epinephrine) has a powerful bronchodilator action which alleviates wheezing and dyspnoea. Adrenaline (epinephrine) also alleviates pruritus, urticaria and angioedema associated with anaphylaxis.

No new preclinical or clinical studies were conducted, which is acceptable given that this application is submitted under Article 10a of 2001/83/EC, a well-established use application. All preclinical and clinical data submitted are in the form of literature references.

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 this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Anapen 500 micrograms in 0.3ml solution for injection (pre-filled syringe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Epinephrine (C01C A 24)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Solution for injection (500 micrograms in 0.3ml)</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/0516/003/MR</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Austria, Germany, Greece, France, Ireland, the Netherlands and Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 18813/0003</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Lincoln Medical Ltd, Unit 8 Wilton Business Centre, Wilton, Salisbury, SP2 0AH, United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

S. Active substance

Epinephrine

INN: Epinephrine
Chemical name: \((R)-4-(1\text{-hydroxy-2-(methylamino)ethyl})\text{benzene-1,2-diol}\)
Structure:

\[
\begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{N} \\
\text{C} \\
\end{array}
\]

Physical form: white or off-white, crystalline substance.
Solubility: very slightly soluble in water and alcohol.
Molecular formula: \(\text{C}_9\text{H}_{13}\text{NO}_3\)
Molecular weight: 183.21

Epinephrine is the subject of a European Pharmacopoeia monograph.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance epinephrine.

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

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance epinephrine. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer.

The specifications and typical analytical test results are provided and are satisfactory.

Satisfactory specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

An appropriate retest period has been proposed based on stability data submitted for the active substance epinephrine.
P. Medicinal Product

Other Ingredients
Other ingredients consist of pharmaceutical excipients sodium chloride, sodium metabisulphite (E223), hydrochloric acid and water for injections. All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin.

Product development
The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid.

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

In-process controls are satisfactory based on process validation data and controls on batches of the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis for all working standards used have been provided and are satisfactory.

Container-Closure System
Anapen 500 micrograms in 0.3ml Solution for Injection consists of a pre-filled syringe contained in a single-use, auto-injection device.

The product is packaged in a type I, glass syringe sealed by a rubber plunger at one end, and at the other end by a rubber needle shield.

Specifications and certificates of analysis for the packaging types used have been provided. All primary product packaging complies with European Pharmacopoeia monograph 3.2.1 (glass containers for pharmaceutical use).

Anapen is supplied in units of 1. The product contains a solution of 0.3ml.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years for the product has been set with the storage precautions ‘Do not store above 25°C’ and ‘To protect from light, store in original package’.

ADMINISTRATIVE

Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SmPC)
This is pharmaceutically satisfactory.
Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

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.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS
This application for Anapen 500 micrograms in 0.3ml Solution for Injection was submitted according to Article 10a of Directive 2001/83/EC, a well-established use application.

No new pre-clinical data have been supplied with this application and none are required for applications of this type.

III.3 CLINICAL ASPECTS
CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed and none are required for this application, as this application was submitted according to Article 10a of Directive 2001/83/EC, a well-established use application.

EFFICACY
No new data have been provided and none are required for this application.

SAFETY
No new data have been provided and none are required for this application.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORM (MAA FORM)
This is satisfactory.
SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
This is clinically satisfactory.

DISCUSSION
A bioequivalence study with the reference product is not required for this product and can be justified as this product contains a well-known, widely used active substance (epinephrine).

MEDICAL CONCLUSION
The grant of a marketing authorisation is recommended for this application.

IV OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT
QUALITY
The important quality characteristics of Anapen 500 micrograms in 0.3ml Solution for Injection 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.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
Epinephrine is a well-known drug and has been used for many years. No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted from literature references support the applicant’s claim that this product is a well-known substance and can be used for the proposed indications.

Extensive clinical experience with epinephrine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY**

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