Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

EpiPen 300 micrograms solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 1 mg adrenaline (epinephrine). A single dose (0.3 ml) contains 300 micrograms (0.3 mg) adrenaline.

Excipients with known effect: Sodium metabisulfite (E223) 0.5 mg/dose, sodium chloride 1.8 mg/dose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (Auto-Injector).

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

EpiPen (adrenaline) Auto-Injectors are indicated in the emergency treatment of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens, as well as idiopathic or exercise induced anaphylaxis.

4.2 Posology and method of administration

Posology
Paediatric population
Usual paediatric dose is 0.01 mg/kg body weight. However, the prescribing physician has the option of prescribing more or less than these amounts based on careful assessment of each individual patient and recognizing the life-threatening nature of reactions for which this is being described. A dosage below 150 micrograms cannot be administered with EpiPen adrenaline Auto-Injector. The physician should consider using other forms of injectable adrenaline if lower doses are felt to be necessary for small children.

Children and adolescents over 30 kg weight:
The usual dose is 300 micrograms for intramuscular use.

*Children between 15 kg and 30 kg in weight**:
The usual dose is 150 micrograms for intramuscular use.
* For these patients EpiPen Junior Auto-Injector containing 150 micrograms adrenaline per dose is available.

Children below 15 kg in weight:
The suitability of EpiPen Junior has to be judged individually. The use in children weighing less than 7.5 kg is not recommended unless in a life-threatening situation and under medical advice.

Adults
The usual dose is 300 micrograms for intramuscular use.

An initial dose should be administered as soon as symptoms of anaphylaxis are recognized.

In the absence ofclinical improvement or if deterioration occurs, a second injection with an additional EpiPen Auto-Injector may be administered 5 - 15 minutes after the first injection. It is recommended that patients are prescribed two EpiPen pens which they should carry at all times.

The physician prescribing an EpiPen Auto-Injector must ensure that the patient understands the indications for use and the correct method of application.
Therefore, the physician should discuss the patient information leaflet, the correct handling of the Auto-Injector and the possible symptoms of an anaphylactic shock in detail with the patient.

Method of administration
EpiPen Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

For intramuscular administration into the anterolateral thigh, not the buttock. It is designed to inject through clothing or directly through the skin.
See section "6.6 Special precautions for disposal and other handling".

The patient/carer should be informed that following each use of EpiPen:

- They should call for immediate medical assistance, ask for an ambulance and state "anaphylaxis" **even if symptoms appear to be improving** (see section 4.4).
- Conscious patients should preferably lie flat with feet elevated but sit up if they have breathing difficulties. Unconscious patients should be placed on their side in the recovery position.
- The patient should if possible remain with another person until medical assistance arrives.

4.3 Contraindications

There are no known absolute contraindications to the use of EpiPen during an allergic emergency.

4.4 Special warnings and precautions for use

All patients who are prescribed EpiPen should be thoroughly instructed to understand the indications for the use and the correct method of administration (see section 6.6). It is strongly advised also to educate the patient's immediate associates (e.g. parents, caregivers, teachers) for the correct usage of the EpiPen in case support is needed in the emergency situation.

The patient should be instructed to dial 112, ask for ambulance, state anaphylaxis to seek emergency medical assistance immediately after administering the first dose in order to have close monitoring of the anaphylactic episode and further treatment as required.

The Auto-Injectors should be injected into the anterolateral aspect of the thigh. Patients should be advised not to inject into the buttock.

In case of injection performed by a caregiver, immobilization of the patient's leg should be ensured during injection to minimize the risk of leg laceration, bent needle or other injuries.
The product is for single use only and in no case the used pen should be reused.

Adrenaline is ordinarily administered with extreme caution to patients who have a heart disease. Adrenaline should only be prescribed to those patients, but also those suffering from diabetes, hyperthyroidism, hypertension and elderly individuals if the potential benefit justifies the potential risk. There is a risk of adverse reactions following epinephrine administration in patients with high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia and hypokalaemia. In patients with Parkinson's disease, epinephrine may be associated with a transient worsening of Parkinson symptoms such as rigidity and tremor.

The patient/carer should be informed about the possibility of biphasic anaphylaxis which is characterised by initial resolution followed by recurrence of symptoms some hours later.

Patients with concomitant asthma may be at increased risk of a severe anaphylactic reaction.

Accidental injection into hands or feet resulting in peripheral ischaemia has been reported. Patients may need treatment following the accidental injection.

In patients with thick sub-cutaneous fat layer, there is a risk for adrenaline not reaching the muscle tissue resulting in a suboptimal effect (see section 5.2). A second injection with an additional EpiPen may be needed (see section 4.2).

EpiPen contains sodium metabisulfite which may rarely cause severe hypersensitivity 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 EpiPen should be used.

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

Patients should be warned regarding related allergens and should be investigated whenever possible so that their specific allergens can be characterised.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is indicated in patients receiving drugs that may sensitise the heart to arrhythmias, including digitalis and quinidine. The effects of adrenaline may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors (MAO-inhibitors) and catechol -O-methyl transferase inhibitors (COMT inhibitors), thyroid hormones, theophylline, oxytocin, parasympatholytics, certain antihistamines (diphenhydramine, chlorpheniramine), levodopa and alcohol.

Adrenaline inhibits the secretion of insulin, thus increasing the blood glucose level. It may be necessary for diabetic patients receiving adrenaline to increase their dosage of insulin or oral hypoglycaemic drugs.

Observe. The ß-stimulating effect can be inhibited by simultaneous treatment with ß -blocking drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy
Clinical experience in the treatment of pregnancy is limited.

Adrenaline should be used during pregnancy only if the potential benefit justifies the potential risk for the foetus.

Breast-feeding
Adrenaline is not orally bioavailable; any adrenaline excreted in breast milk would not be expected to have any effect on the nursing infant.

Fertility
As adrenaline is a substance that naturally occurs in the body, it is unlikely that this drug would have any detrimental effects on fertility.

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, since patients will be affected by symptoms of the anaphylactic shock.

4.8 Undesirable effects

Side effects associated with adrenaline's alpha and beta receptor activity may include symptoms such as tachycardia and hypertension as well as undesirable effects on the central nervous system.

Evaluation of undesirable effects is based on the following frequency information:

- Very common (≥ 1/ 10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥1/10,000 to < 1/1,000)
- Very rare (< 1 / 10,000)
- Not known (Frequency cannot be estimated from the available data).

Organ System	Frequency	Adverse drug reaction
Infections and infestations	Frequency not known	Injection site infection *

Psychiatric disorders	Frequency not known	Anxiety
Nervous system disorders	Frequency not known	Headache, dizziness, tremor
Cardiac disorders	Rare	Stress cardiomyopathy
	Frequency not known	Tachycardia, cardiac arrhythmia, palpitations, angina pectoris, ventricular fibrillation
Vascular disorders	Frequency not known	Hypertension, pallor, peripheral ischaemia following accidental injection of the pens in hands or feet
Respiratory, thoracic and mediastinal disorders	Frequency not known	Respiratory difficulties
Gastrointestinal disorders	Frequency not known	Nausea, vomiting
Skin and subcutaneous tissue disorders	Frequency not known	Hyperhidrosis
General disorders and administration site conditions	Frequency not known	Asthenia
Injury, poisoning and procedural complications	Frequency not known	Accidental needle injury[#]

accidental injections or inappropriate use can lead to injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury
* rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by Clostridia (gas gangrene) are known from post-marketing experience

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdose or inadvertent intravascular injection of adrenaline may cause cerebral haemorrhage resulting from a sharp rise in blood pressure. Fatalities may also result from pulmonary oedema because of peripheral vascular constriction together with cardiac stimulation.
Pulmonary oedema may be treated with α-blocking agents such as phentolamine. In case of arrhythmias these may be treated with β-blocking agents.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac stimulants excl. cardiac glycosides, adrenergic and dopaminergic agents.
ATC code: C01CA24.

Adrenaline is a catecholamine which stimulates the sympathetic nervous system (both alpha and beta receptors) by which cardiac rate, cardiac output and coronary circulation is raised. Adrenaline through its action on beta receptors on bronchial smooth muscles causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnoea.
Adrenaline is rapidly inactivated and much of the dose of adrenaline is accounted for by excretion of metabolites in the urine.

5.2 Pharmacokinetic properties

Adrenaline is a naturally occurring substance produced by the adrenal medulla and secreted in response to exertion or stress. It is rapidly inactivated in the body mostly by the enzymes COMT and MAO. The liver is rich in these enzymes and is an important, although not essential, tissue in the degradation process. Much of the dose of adrenaline is accounted for by excretion of metabolites in the urine.

The plasma half-life of adrenaline is about 2.5 min. However, by subcutaneous or intramuscular routes, local vasoconstriction retards absorption, so that the effects occur insidious and last much longer than the half-life would predict. Gently massage the injection area is advised.

In a pharmacokinetic study in 35 healthy subjects, grouped by varying degrees of thickness in the subcutaneous fat layer of the thigh and stratified by gender, a single 0.3 mg/0.3 ml injection at the anterolateral aspect of the mid-thigh was made with an EpiPen Auto-Injector and was compared in crossover design to a manual syringe-delivered dose with needles individualized for delivery to muscle layer. The results indicate that female subjects with a thick sub-cutaneous fat layer (> 20 mm skin to muscle

distance under maximum compression) had slower adrenaline absorption rate, reflected in a trend to lower plasma exposure in such subjects in the first ten minutes following injection (see section 4.4). However, overall adrenaline exposure from 0 to 30 min ($AUC_{0-30min}$) for all groups of subjects receiving EpiPen exceeded exposures resulting from syringe delivery. Importantly, a trend to higher plasma adrenaline concentrations following EpiPen compared to manual intramuscular injection in healthy subjects who will have well perfused subcutaneous tissue cannot necessarily be extrapolated to patients in established anaphylactic shock in whom there may be diversion of blood from skin to leg muscles. The possibility of existing cutaneous vasoconstriction at the time of injection should be taken into consideration therefore.
Both inter-subject and intra-subject variability was however high in this study and therefore robust conclusions cannot be drawn.

5.3 Preclinical safety data

There is no preclinical data of importance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Metabisulfite (E223)
Hydrochloric Acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities

Adrenaline and its salts are rapidly destroyed in solution with oxidising agents. Oxidation can be inhibited by addition of anti-oxidants. The solution darkens in colour upon exposure to air or light.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the container in the outer carton in order to protect from light. Do not store above 25°C. Do not refrigerate or freeze.

Check the solution periodically through the viewing window of the unit to make sure the solution is clear and colourless. Discard and replace the Auto-Injector if the solution is discoloured or contains a precipitate, or at the latest by expiration date. The expiry date is indicated on the label and the Auto-Injector should not be used after this date.

6.5 Nature and contents of container

The immediate container/closure system consists of a glass cartridge sealed by a rubber plunger at one end and by rubber diaphragm which has been inserted into an aluminium hub with attached stainless-steel needle at the other end. The glass cartridge contains the product.

The Auto-Injector administration device:
<u>Glass cartridge container:</u>
Type I, Borosilicate Glass

<u>Diaphragm - Stopper</u>:
PH 701/5O/Black (butyl rubber plunger)

<u>Needle - Hub -Sheath:</u>
Needle: Siliconised Type 304 stainless steel, exposed and protected needle length after activation approx. 16 mm
Hub: Anodised 3003 aluminium alloy
Sheath: Synthetic polyisoprene

The Auto-Injector contains 2 ml solution for injection. Each Auto-Injector delivers one single dose (0.3 ml) of 300 micrograms adrenaline.

Pack sizes:

1. Auto-Injector.
2. x 1 Auto-Injector.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. The Auto-Injector must be discarded immediately after use.

During instruction of the patient in correct use of the EpiPen the prescribing doctor may use a "EpiPen TRAINER" (contains no solution for injection and no needle).

The EpiPen Auto-Injector contains 2 ml of adrenaline injection 1 mg/ml which is designed to deliver a single dose (0.3 ml) of 300 microgram adrenaline when activated. After activation of the Auto-Injector 1.7 ml remains in the AutoInjector.

Do not remove blue safety cap until ready for use.

Under no circumstances place the orange end of the EpiPen Auto-Injector on or near your thumbs, fingers or hands. Accidental injection into hand or finger resulting in peripheral ischaemia has been reported. See section 4.4.
The EpiPen Auto-Injector should be used on the outer thigh. The injection is activated immediately once the orange end of the EpiPen Auto-Injector comes into contact with any skin or other surface.

The EpiPen Auto-Injectors are designed for easy use by the lay person and has to be considered as a first aid. The AutoInjector should simply be jabbed firmly against the outer portion of the thigh from a distance of approximately 10 cm. There is no need for more precise placement in the outer portion of the thigh. When EpiPen Auto-Injector is jabbed against the thigh, it releases a spring activated plunger, pushing concealed needle into the thigh muscle and expelling a dose of adrenaline:

1. Grasp EpiPen Auto-Injector in dominant hand, with thumb closest to blue safety cap.
2. Remove the blue safety cap by pulling it straight up with the other hand.
3. Hold the EpiPen Auto-Injector in a distance of approximately 10 cm away from the outer thigh. The orange tip should point towards the outer thigh.
4. Jab firmly into the outer thigh, so that the EpiPen Auto-Injector is at a right angle to (at a 90 degree angle) the outer thigh.
5. Hold firmly in place for 3 seconds. The injection is now complete and the viewing window of the Auto-Injector is obscured. The EpiPen Auto-Injector should be removed (the orange needle cover will extend to cover needle) and safely discarded.
6. Gently massage the injection area for 10 seconds.

A small bubble may occur in the EpiPen Auto-Injector. It has no influence on either the use or the efficacy of the product.

Instruction for use is enclosed in the package.

See Section 4.2 for instructions to be conveyed to the patient/carer regarding actions to be taken following each use of EpiPen Auto-Injector.

7 MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23355/011/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th August 2013

Date of last renewal: 24th July 2018

10 DATE OF REVISION OF THE TEXT

June 2023