

SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. Trade Name of the Medicinal Product

EpiPen[®] Adrenaline (Epinephrine) Auto-Injector 0.3mg

2. Qualitative and Quantitative Composition

Per 1 ml:

<u>Active ingredient</u>	<u>Quantity / Unit</u>	<u>Reference Standards</u>
Adrenaline (Epinephrine)	1.0 mg	BP/USP

3. Pharmaceutical Form

Solution for injection in an Auto-Injector (prefilled, disposable automatic injection device) for intramuscular use.

Clinical Particulars

4.1. Therapeutic Indications

EpiPen Auto-Injectors are automatic injection devices containing adrenaline for allergic emergencies. The Auto-Injectors should be used only by a person with a history or an acknowledged risk of an anaphylactic reaction. The Auto-Injectors are indicated in the emergency treatment of allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs and other allergens as well as idiopathic or exercise induced anaphylaxis. Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhoea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritis, rashes, urticaria or angioedema.

For these reasons Auto-Injectors should always be carried by such persons in situations of potential risks.

Adrenaline is considered the first line drug of choice for allergic emergencies. Adrenaline effectively reverses the symptoms of rhinitis, urticaria, bronchospasm and hypotension because it is a pharmacological antagonist to the effects of the chemical mediators on smooth muscles, blood vessels and other tissues. Adrenaline is recommended as the initial and primary therapeutic agent in the treatment of anaphylaxis by every recognised authority in allergy, and its appropriate use in these circumstances is widely documented in the medical literature.

4.2. Posology and Method of Administration

The EpiPen Auto-Injector is for adult intramuscular administration. It is designed for easy use by the lay person and has to be considered as first aid. EpiPen Auto-Injector delivers a single dose 0.3 ml injection equal to 0.3 mg adrenaline when activated. Usual adrenaline adult dose for allergic emergencies is 0.3 mg. For paediatric use the appropriate dosage may be 0.15 mg or 0.30 mg depending upon the body weight of the patient (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 recognising the life-threatening nature of reactions for which this is being described.

The physician should consider using other forms of injectable adrenaline if lower doses are felt to be necessary for small children.

In the absence of clinical improvement or if deterioration occurs after the initial treatment, a second injection with an additional EpiPen Auto-Injector may be necessary. The repeated injection may be administered after about 5 – 15 minutes.

As EpiPen is designed as emergency treatment only, the patient should be advised always to seek medical help immediately.

A physician who prescribes EpiPen Auto-Injector should take appropriate steps to ensure that the patient understands the indications and use of this device thoroughly. The physician should review with the patient or any other person who might be in a position to administer EpiPen Auto-Injector to a patient experiencing anaphylaxis, in detail, the patient instructions and operation of the EpiPen Auto-Injector.

Administration:

Inject the delivered dose of the EpiPen Auto-Injector (0.3 ml equal to 0.3 mg) into the anterolateral aspect of the thigh, through clothing if necessary. See detailed instructions for use, point 6.6.

4.3. Contra-indications

There are no known absolute contraindications to the use of EpiPen Auto-Injector during an allergic emergency. Clinical conditions where special precautions are advised and drug interactions are prescribed in sections 4.4 and 4.5.

4.4. Special Warnings and Precautions for Use

Patients must be instructed in the proper use of EpiPen Auto-Injectors. See section 6.6.

Adrenaline is ordinarily administered with extreme caution to patients who have a heart disease. Use of adrenaline with drugs that may sensitise the heart to arrhythmias, e.g., digitalis, mercurial diuretics, or quinidine, ordinarily is not recommended. Anginal pain may be induced by adrenaline in patients with coronary insufficiency.

Hyperthyroid individuals (hyperfunction of the thyroid gland), individuals with cardiovascular disease, hypertension (raised blood pressure), or diabetes, elderly individuals, pregnant women, and children under 30 kg body weight using EpiPen Auto-Injector may theoretically be at greater risk of developing adverse reactions after adrenaline administration.

Accidental injection into the hands or feet may result in loss of blood flow to the affected area and should be avoided. If there is an accidental injection into these areas, advise the patient to go immediately to the nearest emergency room or hospital casualty department for treatment.

The patient should be instructed to check the contents of the glass cartridge in the Auto-Injector periodically through the viewing window of the unit to make sure the solution is clear and colourless. The Auto-Injector should be discarded if discoloured or contains a precipitate. For emergency treatment use of an EpiPen Auto-Injector with discoloured contents may be recommended rather than to postpone the treatment.

The Auto-Injectors should ONLY be injected into the anterolateral aspect of the thigh. Patients should be advised NOT to inject into the buttock. Large doses or accidental intravenous injection of adrenaline may result in cerebral haemorrhage due to sharp rise in blood pressure. Directions for proper use of the Auto-injectors must be followed in order to avoid intravenous injection. Rapidly acting vasodilators can counteract the marked pressor effects of adrenaline.

The adrenaline solution contains sodium metabisulfite, a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using adrenaline in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations.

Despite these concerns, adrenaline is essentially for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen Auto-Injector to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which this life-saving medication should be used.

4.5. Interactions with other Medicaments and other forms of Interaction

Caution is indicated in patients receiving drugs that may sensitise the heart to arrhythmias, including digitalis, mercurial diuretics or quinidine. The effects of adrenaline may be potentiated by tricyclic antidepressants and mono amine oxidase inhibitors.

Pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug, such as levarterenol.

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.

4.6. Pregnancy and Lactation

Adrenaline has been used for years in the treatment of allergic emergencies and its use is well documented in the literature. No clinical trials were performed in conjunction with this application. As adrenaline is a substance that naturally occurs in the body, it is unlikely that this drug would have any detrimental effects on fertility.

Adrenaline should be used during pregnancy only if the potential benefit justifies the potential risk to fetus.

4.7. Effects on Ability to Drive and Use Machines

The patients' ability to drive and use machines may be affected by the anaphylactic reaction, as well as by possible adverse reactions to adrenaline.

4.8. Undesirable Effects

Repeated dose toxicity studies were not performed in conjunction with this application. Side effects associated with adrenaline's alpha and beta receptor activity may include palpitations, tachycardia, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety. Cardiac arrhythmias may follow administration of adrenaline.

Accidental injection into hands or fingers resulting in peripheral ischaemia has been reported. Patients may need treatment following accidental injection. See section 4.4.

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 edema because of peripheral vascular constriction together with cardiac stimulation.

Pressor effects of adrenaline may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measures, it may be necessary to administer another pressor drug, such as levarterenol.

If an adrenaline overdose induces pulmonary edema that interferes with respiration, treatment consists of a rapidly acting alpha-adrenergic blocking drug such as phentolamine and/or intermittent positive-pressure respiration.

Adrenaline overdose can also cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Treatment of arrhythmias may consist of administration of beta-adrenergic blocking drugs.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Adrenaline is one of the catecholamines which are a group of sympathomimetic amines containing a catechol moiety. Adrenaline activates an adrenergic receptive mechanism on effector cells and imitates all actions of the sympathetic nervous system except those on the arteries of the face and sweat glands. Adrenaline acts on both alpha and beta receptors and is the most potent alpha receptor activator.

The strong vasoconstrictor action of adrenaline through its effect on alpha adrenergic receptors acts quickly to counter vasodilation and increased vascular permeability which can lead to loss of intravascular fluid volume and hypotension during anaphylactic reactions. Adrenaline through its action on beta receptors on bronchial smooth muscles causes bronchial smooth muscle relaxation which alleviates wheezing and dyspnea. Adrenaline also alleviates pruritis, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis.

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.

According to Remington's Pharmaceutical Sciences, 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 insidiously and last much longer than the half-life would predict. Massage around the injection area is advised.

5.3. Preclinical Safety Data

Adrenaline has been utilised in the treatment of allergic emergencies for many years. No preclinical studies have been performed in connection with this application.

Pharmaceutical Particulars

6.1. List of Excipients

Sodium Chloride

Sodium Metabisulfite
Hydrochloric Acid
Water for Injection

6.2. Incompatibilities

Adrenaline and its salts are rapidly destroyed in solution with oxidising agents. The solution darkens in colour upon exposure to air or light.

6.3. Shelf Life

The expiration period for the EpiPen Auto-Injector is 18 months from the date of manufacture. The expiry date is indicated on the label, and EpiPen Auto-Injector should not be used after this date. Replace the Auto-Injector by expiration date or earlier if the solution is discoloured or contains a precipitate. Check the solution periodically through the viewing window of the unit to make sure the solution is clear and colourless.

Shelf life after opening: The Auto-Injectors must be discarded immediately after use.

6.4. Special Precautions for Storage

Adrenaline is sensitive to light. Keep the auto-injector in the outer carton. Do not store above 25 °C. Do not refrigerate or freeze.

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:

Glass cartridge container:

Type I, Borosilicate Glass - complies with USP and Ph. Eur

Diaphragm - Stopper:

PH 701/50/Black (butyl rubber plunger) - complies with USP and Ph. Eur.

Needle - Hub - Sheath:

Materials compatible with adrenaline injection

Needle: Siliconised Type 304 stainless steel

Hub: Anodized 3003 aluminium alloy

Sheath: Synthetic polyisoprene

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

Pack sizes: 1 Auto-injector and 2 Auto-Injectors

6.6. Instruction for Use/Handling

Do not remove grey safety cap until ready for use.

Under no circumstances place the black end of the EpiPen Auto-Injector on or near your thumbs, fingers or hands. Accidental injection into hands or fingers 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 the black 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 Auto-Injector 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 on the outer portion of the thigh. When EpiPen Auto-Injector is jabbed against the thigh, it releases a spring activated plunger, pushing the concealed needle into the thigh muscle and expelling a dose of adrenaline:

1. Grasp EpiPen Auto-Injector in dominant hand, with thumb closest to grey safety cap.
2. With the other hand pull off grey safety cap.
3. Hold the EpiPen Auto-Injector in a distance of approximately 10 cm away from the outer thigh. The black 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 in place for 10 seconds. The EpiPen Auto-Injector should be removed and safely discarded.
6. Massage the injection area for 10 seconds.

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

Administrative Data

7. Marketing Authorisation Holder

ALK-Abelló A/S,
Bøge Allé 6-8,
DK 2970 Hørsholm,
Denmark

8. Marketing Authorization Number

PL 10085/0012

9. Date of First Authorisation/Renewal of Authorisation

28th of March 1996

10. Date of (Partial) Revision of the Text

25th July 2008