280.00 mm

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AUSTRALIAN PRODUCT INFORMATION

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*Adrenaline (epinephrine)**

1 NAME OF THE MEDICINE

** In some countries, adrenaline is known as epinephrine.*

Adrenaline (epinephrine)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

EpiPen 300 µg/0.3 mL Adrenaline Auto-Injector for Intramuscular Injection of Adrenaline for the Emergency Treatment of Anaphylactic Reactions. Delivers a single 300 microgram (µg) intramuscular dose of adrenaline from Adrenaline Injection USP 0.3 mg/0.3 mL.

The EpiPen device provides adrenaline for intramuscular auto-injection in a sterile solution prepared from adrenaline with the aid of hydrochloric acid in Pyrogen Free Water.

The EpiPen Auto-Injector contains 2 mL Adrenaline Injection USP 0.3 mg/0.3 mL and is designed to deliver a single 0.3 mL dose of 300 µg.

Each 0.3 mL dose contains 300 µg adrenaline as the active ingredient. The inactive ingredients are 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite and hydrochloric acid to adjust pH. The pH range is 2.2-5.0.

Excipients with known effect:

Contains sulfites.

3 PHARMACEUTICAL FORM

Refer to Section 2 – Qualitative and quantitative composition.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the emergency treatment of anaphylaxis (acute severe allergic reactions) due to insect stings, or bites, foods, drugs or other allergens.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage:

Selection of the appropriate dosage strength is determined according to patient body weight and this decision should be based on careful assessment of the individual patient and recognition of the life-threatening nature of reactions for which EpiPen is prescribed.

Adults (≥ 30 kg): Intramuscular injection of EpiPen Auto-Injector containing 0.3 mg adrenaline injection (0.3 mg/0.3 mL)

Children (15 to 30 kg): Intramuscular injection of EpiPen Jr. Auto-Injector containing 0.15 mg adrenaline injection (0.15 mg/0.3 mL)

The doctor or pharmacist may choose to recommend more or less than this amount*. With severe persistent anaphylaxis, repeat injections with an additional EpiPen Auto-Injector may be necessary.

To manage severe anaphylaxis, repeat EpiPen injections may be necessary. Each EpiPen Auto-Injector is used once only. The EpiPen dose may be repeated every 5 to 15 minutes if symptoms recur or have not subsided (see **Section 4.9 OVERDOSE**).

Use of Adrenaline:

1. Before using, check to make sure the solution in the Auto-Injector is not brown in colour. If it is discoloured or contains a precipitate, do not use, since these changes indicate that the effectiveness of the drug product may be decreased.
2. The delivered dose of the EpiPen Auto-Injector should be injected intramuscularly into the anterolateral aspect of the thigh, through clothing if necessary. The EpiPen Auto-Injector should be pushed firmly into the outer mid-thigh until a "click" is heard or felt and it should then be held firmly against the thigh for approximately 3 seconds to ensure the dose is delivered. Instruct caregivers of young children who are prescribed an EpiPen and who may be uncooperative and kick or move during an injection to hold the leg firmly in place and limit movement prior to and during an injection.
3. DO NOT INJECT INTRAVENOUSLY. Every effort should be made to avoid inadvertent intravascular administration (see **Section 4.9 OVERDOSE**).
4. **Appropriate steps should be taken to ensure that the patient thoroughly understands the indications and use of this device. The EpiPen Auto-Injector should not be used for demonstration purposes. An EpiPen Training Device is available to assist with patient education and practice. The healthcare professional, educator or caregiver should regularly review in detail with the patient, the package leaflet provided inside the EpiPen Auto-Injector carton, which includes usage instructions for the EpiPen Auto-Injector.**
5. Patients should be instructed to dispose of the device safely after use by placing the used Auto-Injector in a sharps disposal unit.

The EpiPen Auto-Injector is intended for immediate self-administration. It is designed as emergency supportive therapy only and is not a replacement or substitute for subsequent medical or hospital care.

4.3 CONTRAINDICATIONS

Contraindications are relative as this product is intended for use in life-threatening emergencies.

Adrenaline should not be used in patients with certain types of arrhythmia, cerebral arteriosclerosis and where vasopressor drugs are contraindicated e.g. thyrotoxicosis.

Adrenaline is also contraindicated in shock (other than anaphylactic shock) in patients or during general anaesthesia with halogenated hydrocarbons or cyclopropane.

Clinical conditions where special precautions are advised and interactions with other medicines are described in further detail in **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

A severe anaphylactic reaction is a life-threatening emergency and administration of EpiPen is not intended as a substitute for immediate medical care. In conjunction with the administration of adrenaline, the patient should seek immediate medical or hospital care. More than two sequential doses of adrenaline should only be administered under direct medical supervision.

The presence of anaphylactic shock should be confirmed before administering EpiPen, as EpiPen is only indicated for the treatment of anaphylaxis. Anaphylaxis 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, dyspnoea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

For these reasons, auto-injectors should always be carried by such persons in situations of potential risk.

EpiPen Adrenaline Auto-Injector contains sodium metabisulfite, a sulfite, which may itself cause allergic-type reactions 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 for serious allergic reactions even if the patient is sulfite-sensitive.

DO NOT INJECT INTRAVENOUSLY as cerebral haemorrhage may occur due to a sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of adrenaline if there is such inadvertent administration.

Use with caution in patients with ventricular fibrillation, cerebral arteriosclerosis, prefibrillatory rhythm, tachycardia, myocardial infarction, phenothiazine-induced circulatory collapse and prostatic hypertrophy.

Adrenaline should not be used in the presence of cardiac dilation.

Adrenaline causes ECG changes including a decrease in T-wave amplitude in all leads of normal persons. Caution should be taken when administering in the presence of cardiac dilation.

Adrenaline should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease or hypertension.

Adrenaline can cause potentially fatal ventricular arrhythmias including fibrillation, especially in patients with organic heart disease or those receiving other drugs that sensitise the heart to arrhythmias (see **Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Anginal pain may be induced by adrenaline in patients with coronary insufficiency.

Use with caution in patients with pre-existing conditions whereby the use of vasopressor drugs is contraindicated (e.g. thyrotoxicosis).

Administer with caution to the elderly, and to individuals with diabetes, cardiovascular disease, hypertension, organic brain damage, narrow angle glaucoma, hyperthyroidism and psychoneurosis. In patients with Parkinsonism the drug increases rigidity and tremor.

Syncope has occurred following administration to asthmatic children.

EpiPen should not be injected into the hands, feet, ears, nose, buttocks or the genitalia as it may result in loss of blood flow to the affected area and may not provide effective treatment of anaphylaxis. Treatment should be directed at vasodilatation in addition to further treatment of anaphylaxis. If an accidental injection into one of these areas occurs, specialist medical advice must be sought immediately. Ensure the product is kept well clear of the face.

Additionally, injection into the buttock has been associated with Clostridial infections (gas gangrene). Cleansing with alcohol does not kill bacterial spores, and therefore, does not lower this risk.

Rare cases of serious skin and soft tissue infections, including necrotising fasciitis and myonecrosis caused by Clostridia (gas gangrene), have been reported at the injection site following adrenaline injection for anaphylaxis. *Clostridium* spores can be present on the skin and introduced into the deep tissue with subcutaneous or intramuscular injection. While cleansing with alcohol may reduce presence of bacteria on the skin, alcohol cleansing does not kill *Clostridium* spores. To decrease the risk of *Clostridium* infection, do not inject EpiPen into the buttock. Advise patients to seek medical care if they develop signs or symptoms of infection, such as persistent redness, warmth, swelling, or tenderness, at the adrenaline injection site.

Hold leg firmly during injection. Lacerations, bent needles, and embedded needles have been reported when EpiPen has been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimise the risk of injection related injury when administering EpiPen to young children, instruct caregivers to hold the child's leg firmly in place and limit movement prior to and during injection.

Despite these concerns, adrenaline is essential 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 adrenaline should be used.

Use in the Elderly

No data available.

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Central nervous system and other medicines

The effects of adrenaline may be potentiated by tricyclic antidepressants, levothyroxine sodium, thyroid hormones, monoamine oxidase inhibitors and some antihistamines (e.g. diphenhydramine, dexchlorpheniramine, chlorpheniramine and tripelennamine).

Other sympathomimetic agents

Adrenaline should not be administered with other sympathomimetic agents because of the danger of additive effects and increased toxicity.

Alpha-adrenergic blocking agents

Alpha-adrenergic blocking agents such as ergot alkaloids and phentolamine can reverse the pressor response to adrenaline.

Beta-adrenergic blocking agents

Patients taking non-selective beta-blocking drugs when administered adrenaline for the treatment of an anaphylactic reaction may experience severe hypertension and bradycardia. Propranolol inhibits the bronchodilator effect of adrenaline. The risk of cardiac arrhythmias is higher when adrenaline is given to patients receiving digoxin or quinidine.

General anaesthetics

Halothane and other anaesthetics such as cyclopropane and trichlorethylene increase the risk of adrenaline-induced ventricular arrhythmias and acute pulmonary oedema if hypoxia is present.

Hypoglycaemic agents

Adrenaline-induced hyperglycaemia may lead to loss of blood sugar control in diabetic patients treated with hypoglycaemic agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Studies of adrenaline after repeated exposure in animals to evaluate the effect on fertility have not been conducted. This should not prevent the use of adrenaline under the conditions noted under **Section 4.1 THERAPEUTIC INDICATIONS.**

Use in Pregnancy

Pregnancy Category: A

Adrenaline has been given to a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Adrenaline may delay the second stage of labour by inhibiting contractions of the uterus.

Use with caution in pregnant women whose maternal blood pressure is in excess of 130/80.

Use in Lactation

Adrenaline is excreted in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Common symptomatic adverse events include anxiety, apprehensiveness, restlessness, tachycardia, respiratory difficulty, tremor, weakness, dizziness, headache, dyspnoea, cold extremities, sweating, pallor, nausea, vomiting, sleeplessness, hallucinations, palpitations, respiratory difficulties, fear and flushing or redness of face and skin. Psychomotor agitation, disorientation, impaired memory and psychosis may occur.

Potentially fatal ventricular arrhythmias, including ventricular fibrillation may occur and severe hypertension may lead to cerebral haemorrhage and pulmonary oedema.

Angina may occur in patients with coronary artery disease.

Rare cases of stress cardiomyopathy have been reported in patients treated with adrenaline.

The potential for adrenaline to produce these types of adverse effects does not contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the hands, fingers or feet may result in loss of blood flow to the affected area (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). Adverse events experienced as a result may include increased heart rate, local reactions including injection site pallor, coldness or hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discolouration, erythema or skeletal injury.

Lacerations, bent needles, and embedded needles have been reported when EpiPen has been injected into the thigh of young children who are uncooperative and kick or move during the injection (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Injection into the buttock has resulted in cases of gas gangrene (see **Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems (or at https://nzphvc.otago.ac.nz/reporting for New Zealand).

4.9 OVERDOSE

Effects

Overdosage 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.

Cardiac arrhythmias may lead to ventricular fibrillation and death.

Repeated administration of adrenaline can result in severe metabolic acidosis because of elevated blood concentration of lactic acid.

Treatment

Adrenaline is rapidly inactivated in the body and treatment of acute toxicity is mainly supportive. If necessary, the combined alpha and beta mediated effects of adrenaline may be counteracted by labetalol. Individually, alpha mediated effects may be counteracted by phentolamine whilst beta mediated effects may be counteracted by beta blocking agents.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or the National Poisons Information Centre on +64 800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Adrenaline is a sympathomimetic drug, acting on both alpha and beta receptors. Through its action on alpha adrenergic receptors, adrenaline lessens the vasodilatation and increased vascular permeability that occurs during anaphylaxis, which can lead to a loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, adrenaline causes bronchial smooth muscle relaxation that helps alleviate bronchospasm, wheezing and dyspnoea that may occur during anaphylaxis. Other major effects are increased systolic blood pressure, reduced diastolic pressure, tachycardia, hyperglycaemia and hypokalaemia. It is a powerful cardiac stimulant. It has vasopressor properties, an antihistaminic action and is a bronchodilator. Adrenaline also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxant effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The onset of action is rapid and of short duration. After intravenous infusion the half-life is approximately 5 to 10 minutes.

Distribution

Adrenaline is rapidly distributed to the heart, spleen, several glandular tissues and adrenergic nerves. It is approximately 50% bound to plasma proteins.

Metabolism

Adrenaline is rapidly metabolised in the liver and tissues.

Excretion

Up to 90% of the intravenous dose is excreted as metabolites in the urine. It crosses the placenta and is excreted in breast milk.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Adrenaline and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a *WP2* bacterial reverse mutation assay. Adrenaline had a moderate degree of mutagenicity and was positive in the DNA Repair test with *B. Subtilis* (REC) assay but was not mutagenic in the *Salmonella* bacterial reverse mutation assay.

Studies of adrenaline after repeated exposure in animals to evaluate the mutagenic potential have not been conducted. This should not prevent the use of adrenaline under the conditions noted under **Section 4.1 THERAPEUTIC INDICATIONS.**

Carcinogenicity

Studies of adrenaline after repeated exposure in animals to evaluate the carcinogenic potential have not been conducted. This should not prevent the use of adrenaline under the conditions noted under **Section 4.1 THERAPEUTIC INDICATIONS.**

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Adrenaline is physically incompatible with alkalis, metals, oxidising agents, sodium warfarin, hyaluronidase and many other drugs; it forms polymers with sodium bicarbonate.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Adrenaline is light sensitive and should be stored in the carrier tube provided.

STORE BELOW 25°C. TEMPERATURE EXCURSIONS BETWEEN 15°C TO 25°C PERMITTED.

DO NOT REFRIGERATE. PROTECT FROM LIGHT.

Before using, check to make sure the solution in the auto-injector is not discoloured. Replace the auto-injector if the solution is discoloured or contains a precipitate.

6.5 NATURE AND CONTENTS OF CONTAINER

The EpiPen Auto-Injector contains 2 mL Adrenaline Injection USP 0.3 mg/0.3 mL and delivers a single 300 µg adrenaline dose.

EpiPen Auto-Injector is available in a single pack or in a pack of 2.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

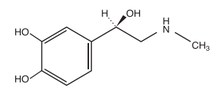
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: (R)-1-(3,4-dihydroxyphenyl)-2-methylaminoethanol

Structural formula:



Molecular formula: $C_9H_{13}NO_3$ Molecular weight: 183.2

CAS Number

CAS Registry No: 51-43-4

Adrenaline is a white odourless crystalline powder, soluble in solutions of mineral acids and alkalis.

Adrenaline solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace the EpiPen Auto-Injector if the adrenaline solution appears discoloured.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 (Pharmacist Only Medicine)

8 SPONSOR

Alphapharm Pty Limited
Level 1, 30 The Bond
30 – 34 Hickson Road
Millers Point NSW 2000
www.mylan.com.au

New Zealand Sponsor:
Mylan New Zealand Limited
Auckland, NZ
Phone: 0800 168 169

9 DATE OF FIRST APPROVAL

20 August 1993

10 DATE OF REVISION

21 October 2019

Made in USA

*Australasian Society of Clinical Immunology and Allergy

Anaphylaxis emergency medication (adrenaline [epinephrine] autoinjector) prescription, ASCIA 2016 http://www.allergy.org.au/images/stories/anaphylaxis/2016/ASCIA_Guidelines_AAI_Prescription_2016.pdf (Accessed July 2019).

Summary Table of Changes

Section Changed	Summary of New Information
All	Remove registered trademark symbol in trade name from body of document
2, 6.5	Change USP reference
4.2	Include 3 second hold time to align with CMI and IFU
4.2, 4.3, 4.4, 4.6, 4.8, 5.3	Correction of heading in reference
4.9	Use TGA suggested text for PIC
8	Update sponsor details
10	Update revision date

EpiPen_pi\Oct19/00

395 mm

CCL

CCL Label
MELBOURNE
120 Merrindale Drive, Croydon South, VIC 3136 Australia
Phone +61 3 9751 7100 www.ccllabel.com

Job No: 181117

Code: LFFS300/7 P1

Version: 1
Operator: JW
16/12/2019 - Prepress Proof Preparation
Proof Generation from supplied files

TERMS AND CONDITIONS
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Date: 2019.12.18 10:31:47 +10'00'

Date:

Keyline/dieline will not print
Inkjet prints are indicative only, and should be matched to relevant pantone colours for printing.

Artwork scale
100% – actual size