

NEW ZEALAND DATA SHEET

EPIPEN®

1. Product Name

EPIPEN 300 µg Adrenaline (epinephrine*) Auto-Injector

* in some countries, adrenaline is known as epinephrine

2. Qualitative and Quantitative Composition

Each auto-injector delivers a single 300 microgram (µg) intramuscular dose of adrenaline (epinephrine) from Adrenaline Injection 1:1,000 USP (0.3 mL).

Excipient(s) with known effect: contains sulfites.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Solution for injection in an auto-injector (prefilled, disposable automatic injection device) for intramuscular use. The injection is a clear, colourless solution.

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*

Dose

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 mL, 1:1000).

Children (15 to 30 kg): Intramuscular injection of EPIPEN JR.Auto-Injector containing 0.15 mg adrenaline injection (0.3 mL, 1:2000).

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).

Method of administration

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).
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.

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 including anaphylactic symptoms and bronchospasm in certain susceptible

persons, especially those with a history of asthma. 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).

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, severe renal impairment, hypercalcaemia, hypokalaemia, 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.

In patients with a thick sub-cutaneous fat layer (> 20 mm skin to muscle distance under maximum compression), 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 in such individuals (see Section 4.2).

Hold leg firmly during injection. Lacerations, bent needles, and embedded needles have been reported when adrenaline 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 Interaction with other medicines and other forms of interaction

Central nervous system and other medicines

The effects of adrenaline may be potentiated by tricyclic antidepressants, levothyroxine sodium, thyroid hormones, monoamine oxidase inhibitors (MAO inhibitors), catechol-O-methyl transferase inhibitors (COMT inhibitors), theophylline, oxytocin, parasympatholytic some antihistamines (e.g. diphenhydramine, dexchlorpheniramine, chlorpheniramine and tripeleminamine) levodopa and alcohol.

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. It may be necessary for diabetic patients receiving adrenaline to increase their dosage of insulin or oral hypoglycaemic drugs.

4.6 Fertility, pregnancy and lactation

Pregnancy (Category A)

Australian Pregnancy Categorisation Definition of Category A: Drugs which have been taken by 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 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.

Breast-feeding

Adrenaline is not orally bioavailable. Adrenaline is excreted in breast milk but would not be expected to have any effect on the nursing infant.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

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 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). Adverse events experienced as a result may include increased heart rate, local reactions including injection site pallor, coldness or hypoesthesia 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 adrenaline has been injected into the thigh of young children who are uncooperative and kick or move during the injection (see section 4.4).

Rare cases of serious skin and soft tissue infections, including necrotising fasciitis and myonecrosis caused by Clostridia (gas gangrene), at the injection site have been reported from post-marketing experience. Injection into the buttock has resulted in cases of gas gangrene (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

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, raising cardiac rate, cardiac output and coronary circulation. 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.

5.2 Pharmacokinetic properties

Absorption

The onset of action is rapid and of short duration. The plasma half-life of adrenaline is about 2.5 minutes. However, following subcutaneous or intramuscular administration, local vasoconstriction retards absorption, so that the effects occur insidiously and last much longer than the half-life would predict.

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 inactivated in the liver and tissues 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.

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.

Clinical Trials

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 individualised for delivery to the 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. However, overall adrenaline exposure from 0 to 30 minutes ($AUC_{0-30min}$) for all groups of subjects receiving EpiPen exceeded exposures resulting from syringe delivery. 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

Carcinogenesis, mutagenesis and impairment on fertility

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 carcinogenic and mutagenic potential or the effect on fertility have not been conducted. As adrenaline is a substance that naturally occurs in the body, it is unlikely that this drug would have any detrimental effects on fertility. This should not prevent the use of adrenaline under the conditions noted under section 4.1.

6. Pharmaceutical Particulars

6.1 List of excipients

EPIPEN Auto-Injector also contains

- sodium chloride
- sodium metabisulfite
- hydrochloride acid
- water for injection.

6.2 Incompatibilities

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.

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

Oxidation can be inhibited by addition of antioxidants. The solution darkens in colour upon exposure to air or light.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Adrenaline is light sensitive and should be stored in the carrier tube provided. The carrier tube is not waterproof.

Store below 25°C. Temperature excursions between 15°C to 25°C permitted. Do not refrigerate. Protect from light.

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 a rubber diaphragm, which has been inserted into an aluminum hub with an attached stainless steel needle, at the other end. The glass cartridge contains the product.

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 and other handling

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.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Medicines Schedule

Restricted Medicine

8. Sponsor Details

Viatrix Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatrix.co.nz
Telephone 0800 168 169

9. Date of First Approval

07 Feb 1997

10. Date of Revision of the Text

18 April 2023

*Australasian Society of Clinical Immunology and Allergy
Anaphylaxis emergency medication - Adrenaline (Epinephrine) Injector Prescription, ASCIA 2022
https://www.allergy.org.au/images/stories/anaphylaxis/2022/ASCIA_HP_Guidelines_Adrenaline_Injector_Prescription_2022.pdf (Accessed February 2022).

Summary table of changes

| Section | Summary of new information |
|---------|---|
| 4.4 | Added more detail on thick sub-cutaneous fat layer |
| 10 | Updated to the latest version of the ASCIA 2022 guideline |

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