SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

EPIPEN® AUTO-INJECTOR Solution for injection

EPIPEN® JUNIOR AUTO-INJECTOR Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0,3 mL of EPIPEN AUTO-INJECTOR contains: Epinephrine (adrenaline) 0,3 mg.

Excipients with known effect: Sodium metabisulfite (E223) 0,5 mg/dose, sodium chloride 1,8 mg/dose.

Each 0,3 mL of EPIPEN JUNIOR AUTO-INJECTOR contains: Epinephrine (adrenaline) 0,15 mg.

Excipients with known effect: Sodium metabisulfite (E223) 0,5 mg/dose, sodium chloride 1,8 mg/dose.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (auto-Injector, disposable automatic injection device)

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Use as an adjunct in the treatment of severe anaphylactic or life-threatening reactions. EPIPEN and EPIPEN JUNIOR are to be used only when prescribed by a doctor for patients who are highly allergic and in danger of developing a life-threatening reaction.

EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS are intended as emergency treatment and should not substitute any medical care to be implemented at a later stage.

EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g. order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g. triatoma, mosquitos), allergen immunotherapy, foods, medicines, diagnostic testing substances (e.g. radio contrast media)

and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

EPIPEN and EPIPEN JUNIOR 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.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse 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.

EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

4.2 Posology and method of administration

Posology

EPIPEN or EPIPEN JUNIOR should be administered immediately in the case of the development of a life-threatening reaction.

Selection of the appropriate dosage strength (EPIPEN 0,3 mg or EPIPEN JUNIOR 0,15 mg) is determined according to patient body weight.

- Patients greater than or equal to 30 kg: EPIPEN 0,3 mg
- Patients 15 to 30 kg: EPIPEN JUNIOR 0,15 mg

The medical practitioner should consider using other forms of injectable epinephrine (adrenaline) if lower doses are felt to be necessary for small children.

An initial dose should be administered as soon as symptoms of anaphylaxis are recognised. 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 administered 5 – 15 minutes after the first injection. It is recommended that patients are prescribed two EPIPEN AUTO INJECTORS which they should carry at all times.

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

Method of administration

EPIPEN and EPIPEN JUNIOR are for single dose administration only and the unused portion must be discarded.

Inject EPIPEN or EPIPEN JUNIOR intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. Instruct caregivers of young children who are prescribed an EPIPEN or EPIPEN JUNIOR 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 (see section 4.4).

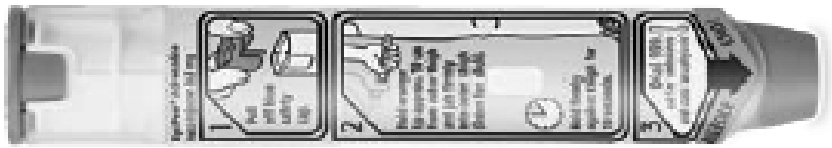
Each EPIPEN or EPIPEN JUNIOR contains a single dose of epinephrine for single-use injection. Since the doses of epinephrine delivered from EPIPEN or EPIPEN JUNIOR are fixed, consider using other forms of injectable epinephrine if doses lower than 0,15 mg are deemed necessary.

The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which EPIPEN or EPIPEN JUNIOR is indicated. With severe persistent anaphylaxis, repeat injections with an additional EPIPEN or EPIPEN JUNIOR may be necessary. More than two sequential doses of epinephrine should only be administered under direct medical supervision (see section 4.4).

The epinephrine solution in the clear window of the EPIPEN AUTO-INJECTOR should be inspected visually for particulate matter and discoloration. Epinephrine is light sensitive and should be stored in the carrier tube provided to protect it from light.

Never put thumb, fingers or hand over orange tip. The needle comes out of the orange tip.

Do not remove blue safety release until ready to use.



Blue safety cap **Orange tip**

A dose of 0,3 mL (0,23 – 0,37 mL) injection fluid is automatically injected intramuscularly by the auto-injector.

Grasp unit with the orange tip pointing downward, form a fist around the unit (orange tip down). With your other hand, pull off the blue safety release.

Diagram 1

Hold the orange tip near outer thigh. **DO NOT INJECT INTO BUTTOCK.** Take the shaft firmly in the hand with the orange plastic tip directed to the upper thigh whilst pushing hard against the skin until the mechanism releases the injection needle. The device should be held in position for at least 3 seconds.

Remove the unit from thigh (the orange needle cover will extend to cover needle).

After this the device is removed from the thigh and the injection area massaged for 10 seconds.

A clinical practitioner should be consulted as soon as possible, and the used device taken along if you need a second injection.

Intravascular injection should be avoided at all costs.

4.3 Contraindications

There are no absolute contraindications to the use of EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS in a life-threatening situation.

4.4 Special warnings and precautions for use

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

Emergency treatment

EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS are intended for immediate administration as emergency supportive therapy and are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.

Injection-related complications

EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS should only be injected into the anterolateral aspect of the thigh (see section 4.2).

- **Do not inject intravenously.** Large doses or accidental intravenous injection of EPIPEN or EPIPEN JUNIOR may result in cerebral haemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine (adrenaline) if there is such inadvertent administration.
- **Do not inject into buttock.** Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis. 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.
- **Do not inject into digits, hands or feet.** Since epinephrine is a strong vasoconstrictor, should the patient accidentally inject him or herself, in the hands, feet, fingers or toes; immediate hospitalization together with the appropriate treatment is recommended.

- **Hold leg firmly during injection.** Lacerations, bent needles, and embedded needles have been reported when EPIPEN and EPIPEN JUNIOR have been injected into the thigh of young children who are uncooperative and kick or move during an injection. To minimize 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.

In patients with a thick subcutaneous fat layer, there is 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).

Serious infections at the injection site

Rare cases of serious skin and soft tissue infections, including necrotizing fasciitis and myonecrosis caused by *Clostridia* (gas gangrene), have been reported at the injection site following epinephrine 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 epinephrine injection site.

Allergic reactions associated with sulfite

The presence of a sulfite in this medicine should not deter administration of the medicine for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine (adrenaline) is the preferred treatment for serious allergic reactions or other emergency situations even though EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS 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.

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

The alternatives to using EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS in a life-threatening situation may not be satisfactory.

Disease interactions

Some patients may be at greater risk for developing adverse reactions after epinephrine administration.

Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EPIPEN or EPIPEN JUNIOR to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

Patients with heart disease

EPIPEN and EPIPEN JUNIOR AUTO-INJECTORS should be administered with caution in patients who have heart disease, including patients with cardiac dysrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on medicines that may sensitise the heart to dysrhythmias e.g. digitalis, diuretics, or anti-dysrhythmics, administration of EPIPEN or EPIPEN JUNIOR AUTO-INJECTORS may precipitate or aggravate angina pectoris as well as produce ventricular dysrhythmias.

Other patients and diseases

Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, elderly individuals, pregnant women and children under 25 kg body weight as they may theoretically be at greater risk of developing adverse reactions.

There is a risk of adverse reactions following epinephrine (adrenaline) administration in patients with high intraocular pressure, severe renal impairment, prostatic adenoma leading to residual urine, hypercalcaemia and hypokalaemia. Patients with Parkinson’s disease may notice a transient worsening of symptoms.

The epinephrine (adrenaline) solution should be checked every 14 days to make sure the solution in the autoinjector is clear and colourless. Replace the auto-injector if the solution is discoloured (pinkish or brown colour), cloudy, or contains particles.

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

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

Children under 15 kg in body weight should be carefully monitored for signs of epinephrine (adrenaline) overdosage (see section 4.9).

4.5 Interaction with other medicines and other forms of interaction

Patients who receive EPIPEN or EPIPEN JUNIOR while concomitantly taking cardiac glycosides, diuretics, or anti-dysrhythmics (including digitalis and quinidine) should be observed carefully for the development of cardiac dysrhythmias.

The effects of EPIPEN and EPIPEN JUNIOR may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, thyroid hormones (such as levothyroxine sodium), catechol-O-methyl-transferase inhibitors (COMT-inhibitors), theophylline, oxytocin, parasympatholytics, levodopa, alcohol and certain antihistamines, notably chlorpheniramine, tripelennamine and diphenhydramine.

The cardio-stimulating and bronchodilating effects of EPIPEN and EPIPEN JUNIOR are antagonised by beta-adrenergic blocking medicines, such as propranolol.

The vasoconstricting and hypertensive effects of EPIPEN and EPIPEN JUNIOR are antagonized by rapidly acting vasodilators or alpha-adrenergic blocking medicines, such as phentolamine. If prolonged hypotension follows such measures, it may be necessary to administer another pressor medicine, such as levarterenol.

Ergot alkaloids may also reverse the pressor effects of EPIPEN and EPIPEN JUNIOR.

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

The β-stimulating effect can be inhibited by simultaneous treatment with β-blocking medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of the acute effect of epinephrine in pregnant women. In animal reproductive studies, epinephrine administered by the subcutaneous route to rabbits, mice and hamsters during the period of organogenesis was teratogenic at doses 7 times and higher than the maximum recommended human intramuscular and subcutaneous dose on a mg/m2 basis. Epinephrine is the first-line medication of choice for the treatment of anaphylaxis during pregnancy in humans. Epinephrine (adrenaline) should be used for treatment of anaphylaxis during pregnancy in the

same manner as it is used in non-pregnant patients.

Breastfeeding

There is no information on the presence of epinephrine in human milk, the effects on breastfed infants, or the effects on milk production. Epinephrine (adrenaline) is the first line-medication of choice for treatment of anaphylaxis; it should be used in the same manner in breastfeeding and non-breastfeeding patients.

Fertility

As epinephrine (adrenaline) is a substance that naturally occurs in the body, it is unlikely that this medicine would have any detrimental effect on fertility.

4.7 Effects on ability to drive and use machines

The patient's ability to drive and use machines may be affected by the anaphylactic reaction as well as by possible adverse reactions to epinephrine (adrenaline).

Therefore, it is not recommended that patients drive or use machines following the administration of EPIPEN and EPIPEN JUNIOR.

4.8 Undesirable effects

a. Summary of the safety profile

Side effects associated with adrenaline's alpha and beta-receptor activity may include symptoms such as palpitations, tachycardia and hypertension as well as undesirable effects on the central nervous system, sweating, nausea and vomiting, respiratory difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, nervousness and anxiety. Cardiac arrhythmias may follow administration of adrenaline.

Tabulated list of adverse reactions

Frequency 'Not known' (Frequency cannot be estimated from the available data)

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequency not known	Injection site infection.*
Endocrine disorders	Frequency not known	Hypersalivation, altered metabolism

		including disturbances of glucose metabolism.
Psychiatric disorders	Frequency not known	Psychotic states, anxiety.
Nervous system disorders	Frequency not known	Fear, restlessness, insomnia, confusion, irritability, headaches, apprehensiveness, dizziness, tremor.
Cardiac disorders	Less frequent	Stress cardiomyopathy.
	Frequency not known	Tachycardia, cardiac arrhythmias including fatal ventricular fibrillation, anginal pain, palpitations, cardiac arrest, hypotension with dizziness and fainting.
Vascular disorders	Less frequent	Cerebral haemorrhage.
	Frequency not known	Hypertension, peripheral ischaemia following accidental injection of the pens in hands or feet.
Respiratory, thoracic and mediastinal disorders	Frequency not known	Pulmonary oedema, dyspnoea.
Gastrointestinal disorders	Frequency not known	Loss of appetite, nausea, vomiting.
Skin and subcutaneous tissue disorders	Frequency not known	Hyperhidrosis.
Musculoskeletal, connective tissue and bone disorders	Frequency not known	Tremors, weakness.
Renal and urinary disorders	Frequency not known	Difficulty in micturition, urinary retention.
General disorders and administrative site conditions	Frequency not known	Asthenia, pallor. Accidental injections can lead to injury at the injection site resulting in bruising, bleeding, discoloration,

		erythema or skeletal injury.

* Less frequent_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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/wp-content/uploads/2021/05/2.33_Post-Marketing-Reporting-of-ADRs-to-Human-Medicines-in-SA_Version-8_May2021.pdf.

4.9 Overdose

Epinephrine (adrenaline) is rapidly inactivated in the body and treatment of overdosage is symptomatic and supportive.

Overdosage of epinephrine (adrenaline) may produce extremely elevated arterial pressure, which may result in cerebrovascular haemorrhage, particularly in elderly patients.

Overdosage may also result in fatalities from pulmonary oedema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of a rapidly acting vasodilators or alpha-adrenergic blocking medicine and/or respiratory support. If prolonged hypotension follows such measures, it may be necessary to administer another pressor medicine such as levarterenol.

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

Epinephrine (adrenaline) overdosage can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac dysrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally be atrioventricular block. Treatment of dysrhythmias consists of administration of a beta-blocking medicine such as propranolol.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis and kidney failure. Suitable corrective measures must be taken in such situations.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

A 5.1 Adrenomimetics (sympathomimetics)

Adrenaline is a sympathomimetic agent.

5.2 Pharmacokinetic properties

Epinephrine (adrenaline) 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. Although only small amounts appear in the urine of normal persons, the urine of patients with pheochromocytoma may contain relatively large amounts of epinephrine (adrenaline).

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 (> 20mm skin to muscle distance under maximum compression) had slower epinephrine (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 (AUC0-30min) for all groups of subjects receiving EPIPEN exceeded exposure 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 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. Both inter-subject and intra-subject variability was however high in this study

and therefore robust conclusions cannot be drawn.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium metabisulfite (E223)

Hydrochloric acid (for pH adjustment)

Water for injection

6.2 Incompatibilities

The solution darkens in colour upon exposure to air or light.

6.3 Shelf life

EPIPEN AUTO-INJECTOR: 24 months.

EPIPEN JUNIOR AUTO-INJECTOR: 19 months.

6.4 Special precautions for storage

Store at or below 25 °C, protected from light.

Do not refrigerate.

For single use only. Discard unit after use.

6.5 Nature and contents of container

This pre-filled disposable automatic injection device is designed to deliver a single dose. It consists of a glass cartridge, containing the medicine, sealed by a rubber plunger at one end and by a rubber diaphragm, which has been inserted into an aluminium hub with attached stainless steel needle at the other end.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

8 REGISTRATION NUMBERS

EPIPEN AUTO-INJECTOR: 27/5.1/0063

EPIPEN JUNIOR AUTO-INJECTOR: 38/5.1/0278

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

EPIPEN AUTO-INJECTOR: 22 March 1993

EPIPEN JUNIOR AUTO-INJECTOR: 07 July 2006

10 DATE OF REVISION OF TEXT

06 December 2021