SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adrenaline 1:1000 (1mg/mL) Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 1 mg of adrenaline (epinephrine) as adrenaline tartrate.

Excipients with known effect:

sodium metabisulfite 0.1 mg / mL

sodium chloride 8.0 mg / mL

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

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or slightly yellow, sterile solution with a pH of 2.8 - 3.6 and an osmolarity of 250 - 280 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute anaphylaxis

Cardiopulmonary resuscitation

4.2 Posology and method of administration

Acute anaphylaxis

The **intramuscular (IM) route** is the route of choice for most individuals who have to be given adrenaline for the management of acute anaphylaxis, using the doses in table 1.

In general, the recommended dose of adrenaline is 0.01 mg per kilogram of body weight (10 micrograms/kg).

For adults, the usual recommended dose of adrenaline is 0.5 mg (500 micrograms).

For children, when the weight is not known, the table below, showing recommended doses according to age, can be advised:

Table 1. *Dose of IM injection of Adrenaline (epinephrine) Injection BP 1 in 1000 for a severe anaphylactic reaction*

Age	Dose	Volume of adrenaline 1 in 1000 (1 mg/mL)
Adult	500 micrograms (0.5mg)	0.5 mL
Child > 12 years	500 micrograms (0.5 mg)	0.5 mL
Child 6 – 12 years	300 micrograms (0.3 mg)	0.3 mL
Child 6 months - 6 years	150 micrograms (0.15 mg)	0.15 mL
Under 6 months	10 micrograms/kg (0.01 mg/kg)	0.01 mL/kg
If necessary, these doses may be repeated several times at 5 – 15 minutes intervals according to blood pressure, pulse and respiratory function. A small volume syringe should be used.		

When the patient is severely ill and there is real doubt about adequacy of the circulation and absorption from the IM injection site, Adrenaline 1:1000 (1mg/mL) Solution for injection may be given by intravenous injection (IV).
Intravenous adrenaline should only be administered by those experienced in the use and titration of vasopressors in their normal clinical practice (see section 4.4). In the case of intravenous adrenaline, the dose must be titrated using 50 microgram boluses according to response. This dose can only be administered using a 1 in 10,000 solution (i.e. a 1:10 mL dilution of the contents of the ampoule). Do not give the undiluted 1:1000 adrenaline solution IV.
If repeated adrenaline doses are needed, an IV adrenaline infusion is recommended, with the rate titrated according to response in the presence of continued haemodynamic monitoring.

Cardiopulmonary resuscitation

Adults
1 mg adrenaline by the intravenous or intraosseous route repeated every 3-5 minutes until return of spontaneous circulation. If injected through a peripheral line, it must be followed by flush of at least 20 mL of fluid and elevation of the extremity for 10–20 seconds to facilitate delivery of the medicinal product to the central circulation.

Paediatric population
The recommended intravenous or intraosseous dose of adrenaline in children is 10 micrograms/kg. Depending on weight, such doses may need to be administered using a 1 in 10,000 solution (i.e. a 1:10 mL dilution of the contents of the ampoule).

Subsequent doses of adrenaline may be given every 3–5 min. The maximum single dose is 1 mg.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

This product is for emergency use only and medical supervision of the patients is necessary after administration.

The IM route is generally preferred in the initial treatment of anaphylaxis, the intravenous (IV) route is generally more appropriate in the Intensive Care Unit (ICU) or Emergency Department (ED) setting. Adrenaline (epinephrine) injection 1:1000 (1 mg/mL) is not suitable for IV use. If the adrenaline (epinephrine) 1:10000 (0.1 mg/mL) injection is not available, adrenaline (epinephrine) injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for injection of adrenaline must be used with extreme caution and is best reserved for specialists familiar with IV use of adrenaline.

Adrenaline should only be administered with great caution in:
elderly patients, patients with hyperthyroidism, diabetes mellitus, phaeochromocytoma, narrow angle glaucoma, hypokalaemia, hypercalcaemia, severe renal impairment and prostatic adenoma leading to residual urine, cerebrovascular disease, organic brain damage, arteriosclerosis, coronary insufficiency, in patients with shock (other than anaphylactic shock) and in organic heart disease or cardiac dilatation (severe angina pectoris, obstructive cardiomyopathy, hypertension) as well as most patients with arrhythmias (e.g. ventricular fibrillation). Anginal pain maybe induced when coronary insufficiency is present.

Adrenaline may increase intra-ocular pressure in patients with narrow angle glaucoma.
Adrenaline may cause or exacerbate hyperglycaemia, blood glucose should be monitored, particularly in diabetic patients.

Repeated local administration may produce necrosis at the sites of injection.

The best site for IM injection is the anterolateral aspect of the middle third of the thigh. The needle used for injection needs to be sufficiently long to ensure that the adrenaline is injected into muscle. Intramuscular injections of Adrenaline 1:1000 (1mg/mL) Solution for injection into the buttocks should be avoided because of the risk of tissue necrosis.

Prolonged administration may induce metabolic acidosis, renal necrosis and adrenaline-fastness or tachyphylaxis.

Adrenaline should be avoided or used with extreme caution in patients undergoing anaesthesia with halothane or other halogenated anaesthetics, in view of the risk of inducing ventricular fibrillation.
Adrenaline should not be used with local anaesthesia of peripheral structures including digits, ear lobe.

Do not mix with other agents unless compatibility is known.

Adrenaline should not be used during the second stage of labour (See Section 4.6).

Accidental intravascular injection may result in cerebral haemorrhage due to the sudden rise in blood pressure.

Monitor the patient as soon as possible (pulse, blood pressure, ECG, pulse oximetry) in order to assess the response to adrenaline.

Sodium metabisulfite, one of the excipients of this medicinal product, may rarely cause severe hypersensitivity reactions and bronchospasm. The presence of sodium metabisulphite in parenteral adrenaline and the possibility of allergic-type reactions should not deter use of the medicinal product when indicated for the treatment of serious allergic reactions or for other emergency situations.

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

The product should be inspected visually for particles and colour of solution prior to administration. Only clear colourless or slightly yellow solution free from particles or precipitates should be used.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetic agents/ oxytocin

Adrenaline should not be administered concomitantly with oxytocin or other sympathomimetic agents because of the possibility of additive effects and increased toxicity.

Alpha-adrenergic blocking agents

Alpha-blockers such as phentolamine antagonise the vasoconstriction and hypertension effects of adrenaline. This effect may be beneficial in adrenaline overdose (see Section 4.9).

Beta-adrenergic blocking agents

Severe hypertension and reflex bradycardia may occur with non-cardioselective beta-blocking agents such as propranolol, due to alpha-mediated vasoconstriction. Beta-

blockers, especially non-cardioselective agents, also antagonise the cardiac and bronchodilator effects of adrenaline. Patients with severe anaphylaxis who are taking non-cardioselective beta-blockers may not respond to adrenaline treatment.

General Anaesthetics

Administration of adrenaline in patients receiving halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitise the myocardium to adrenaline may result in arrhythmias including ventricular premature contractions, tachycardia or fibrillation (see Section 4.4).

Prophylactic administration of lignocaine or prophylactic administration of propranolol 0.05 mg/kg may protect against ventricular irritability if adrenaline is used during anaesthesia with a halogenated hydrocarbon anaesthetic.

Antihypertensive agents

Adrenaline specifically reverses the antihypertensive effects of adrenergic neurone blockers such as guanethidine, with the risk of severe hypertension. Adrenaline increases blood pressure and may antagonise the effects of antihypertensive medicinal products.

Antidepressant agents

Tricyclic antidepressants such as imipramine inhibit reuptake of directly acting sympathomimetic agents, and may potentiate the effect of adrenaline, increasing the risk of development of hypertension and cardiac arrhythmias.

Although monoamine oxidase (MAO) is one of the enzymes responsible for adrenaline metabolism, MAO inhibitors do not markedly potentiate the effects of adrenaline.

Phenothiazines

Phenothiazines block alpha-adrenergic receptors. Adrenaline should not be used to counteract circulatory collapse or hypotension caused by phenothiazines since a reversal of the pressor effects of adrenaline may result in further lowering of blood pressure.

Other medicinal products

Adrenaline should not be used in patients receiving high dosage of other medicinal products (e.g. cardiac glycosides) that can sensitise the heart to arrhythmias. Some antihistamines (e.g. diphenhydramine) and thyroid hormones may potentiate the effects of adrenaline, especially on heart rhythm and rate.

Hypokalaemia

The hypokalaemic effect of adrenaline may be potentiated by other medicinal products that cause potassium loss, including corticosteroids, potassium-depleting diuretics, aminophylline and theophylline.

Insulin or oral hypoglycaemic agents

Adrenaline-induced hyperglycaemia may lead to loss of blood sugar control in diabetics treated with insulin or oral hypoglycaemic agents.

4.6 Fertility, pregnancy and lactation

Pregnancy

Adrenaline crosses the placenta. There is some evidence of a slightly increased incidence of congenital abnormalities. Injection of adrenaline may cause anoxia, foetal tachycardia, cardiac irregularities, extrasystoles and louder heart sounds.

Adrenaline inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labour. In dosage sufficient to reduce uterine contractions, the medicinal product may cause a prolonged period of uterine atony with haemorrhage. Parenteral adrenaline should not be used during the second stage of labour.

Breastfeeding

Adrenaline is distributed into breast milk. Breast-feeding should be avoided in mothers receiving an injection of Adrenaline 1:1000 (1mg/mL) Solution for injection.

Adrenaline 1:1000 (1mg/mL) Solution for injection should not be used in pregnancy unless clearly necessary.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The side effects of adrenaline are related to the stimulation of both alpha- and beta-adrenergic receptors. The occurrence of undesirable effects depends on the sensitivity of the individual patient and the dose involved.

Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000), not known (cannot be estimated from the available data).

System organ class	Undesirable effects (Frequency unknown)
Metabolism and nutrition disorders	Hypokalaemia Metabolic acidosis Hyperglycaemia (even with low doses)
Psychiatric disorders	Psychotic states Anxiety Fear Confusional state Irritability Insomnia
Nervous system disorders	Headache Dizziness Tremor Restlessness
Cardiac disorders	Disturbances of cardiac rhythm and rate Palpitation Tachycardia Chest pain/ angina Potentially fatal ventricular arrhythmias Fibrillation Electrocardiogram T-wave amplitude decreased
Vascular disorders	Hypertension (with risk of cerebral haemorrhage) Coldness of limbs
Respiratory, thoracic and mediastinal disorders	Dyspnoea Pulmonary oedema
Gastrointestinal disorders	Dry mouth Decreased appetite Nausea Vomiting Hypersalivation
Renal and urinary disorders	Difficulty in micturition Urinary retention
General disorders and administration site conditions	Sweating Weakness

In patients with Parkinsonian Syndrome, adrenaline increases rigidity and tremor. Subarachnoid haemorrhage and hemiplegia have resulted from hypertension, even following subcutaneous administration of usual doses of adrenaline.

Adrenaline can cause potentially fatal ventricular arrhythmias including fibrillation, especially in patients with organic heart disease or those receiving other medicinal products that sensitise the heart to arrhythmias (see section 4.5).

Pulmonary oedema may occur after excessive doses or in extreme sensitivity.

Repeated injections of Adrenaline 1:1000 (1mg/mL) Solution for injection can cause necrosis as a result of vascular constriction at the injection site. Tissue necrosis may also occur in the extremities, kidneys and liver.

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 Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Possible signs of overdosage include restlessness, confusion, pallor, tachycardia, bradycardia, cardiac arrhythmias and cardiac arrest. Treatment is primarily symptomatic and supportive. Prompt injection of a rapidly-acting alpha-adrenoceptor blocking agent such as phentolamine, followed by a beta-blocker such as propranolol, has been tried to counteract the pressor and arrhythmogenic effects of adrenaline. A rapidly-acting vasodilator such as glycetyl trinitrate has also been used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline,

ATC code: C01CA24

Adrenaline is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine which is a potent stimulant of both alpha- and beta- adrenergic receptors and its effects on target organs are therefore complex. It is used to provide rapid relief of hypersensitivity reactions to allergies or to idiopathic or exercise-induced anaphylaxis.

Adrenaline has a strong vasoconstrictor action through alpha- adrenergic stimulation. This activity counteracts the vasodilatation and increased vascular permeability leading to loss of intravascular fluid and subsequent hypotension, which are the major pharmacological features in anaphylactic shock.

Adrenaline stimulates bronchial beta-adrenergic receptors and has a powerful bronchodilator action. Adrenaline also alleviates pruritis, urticaria and angioedema associated with anaphylaxis.

5.2 Pharmacokinetic properties

Adrenaline has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site.

Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Much of a dose of adrenaline is excreted as metabolites in urine. The plasma half-life is about 2-3 minutes. However, when given by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption so that the effects may last longer than the half-life suggests.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Sodium metabisulfite (E223)

Water for injections

6.2 Incompatibilities

Adrenaline 1:1000 (1mg/mL) Solution for injection must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened ampoules: 24 months.

After dilution:

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and when diluted to 0.1 mg/mL in sodium chloride 0.9 % would normally not be longer than 24 hours at 2 to 8° C, 3 hours at 23-27 °C when exposed to light, or 6 hours at 23 to 27 °C when protected from light.

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.

Store below 25 °C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber coloured glass ampoules.

Pack size: Box × 5 ampoules × 1 mL
Box × 10 ampoules × 1 mL
Box × 25 ampoules × 1 mL
Box × 50 ampoules × 1 mL

6.6 Special precautions for disposal

Dilution

For intravenous administration, Adrenaline 1:1000 (1mg/mL) Solution for injection must be diluted to a 1 in 10,000 solution (a 1:10 dilution of the contents of the ampoule) with sodium chloride 0.9 %.

Handling

Single use only.

If only part used, discard the remaining solution.

Do not remove ampoule from the carton until ready to use.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

BRADEX S.A.
27 Asklipiou street,
14568 Kryoneri,
Greece

8 MARKETING AUTHORISATION NUMBER(S)

PL 43946/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/05/2021

10 DATE OF REVISION OF THE TEXT

06/03/2022