ADRENALINE INJECTION

1. Name of the medicinal product

Adrenaline (Epinephrine) 1mg/ml (1:1000) solution for injection.

2. Qualitative and quantitative composition

Each 1 mL ampoule contains 1 mg Adrenaline

3. Pharmaceutical form

Sterile Solution for Injection (injection)

Clear, colourless sterile solution, free from visible particulates.

4. Clinical particulars

4.1 Therapeutic indications

Adrenaline (Epinephrine) 1 mg/ml (1:1000) Solution for Injection may be used in the emergency treatment of

• anaphylaxis

• acute allergic reactions

4.2 Posology and method of administration

This medicinal product will be administered by a trained healthcare professional.

The intramuscular (IM) route is recommended by the EU Resuscitation Council as the most appropriate for most individuals who have to give adrenaline to treat an anaphylactic reaction. The patient should be monitored as soon as possible (pulse, blood pressure, ECG, pulse oximetry). This will help monitor the response to adrenaline.

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.

The subcutaneous route for adrenaline is not recommended for treatment of an anaphylactic reaction as it is less effective.

Adults:

The usual dose is 0.5 mg (0.5ml of adrenaline 1mg/ml (1:1000)). If necessary, this dose may be repeated several times at 5-minute intervals according to blood pressure, pulse and respiratory function.

Elderly:

There are no specific dosage regimes for adrenaline injection in elderly patients. However, Adrenaline should be used with great caution in these patients who may be more susceptible to the cardiovascular side effects of adrenaline.

Paediatric population

The following doses of Adrenaline (Epinephrine) 1 mg/ml (1:1000) Solution for Injection are recommended:

Age	**Dose**
Over 12 years	0.5 mg IM (0.5ml 1mg/ml (1:1000) solution) 0.3 mg IM (0.3ml 1mg/ml (1:1000) solution) if the child is small or pre-pubertal)
6 - 12 years	0.3 mg IM (0.3ml 1mg/ml (1:1000) solution)
6 months - 6 years	0.15 mg IM (0.15ml 1mg/ml (1:1000) solution)

Under 6 months	0.01mg/kg IM (0.01ml/kg 1mg/ml (1:1000) solution)

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.

Do not give Adrenaline (Epinephrine) 1mg/ml (1:1000) solution for injection intravenously.

Intravenous administration of adrenaline for anaphylaxis requires the use of a 1:10,000 adrenaline solution (please refer section 4.4 for intravenous use).

4.3 Contraindications

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

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

• Use in fingers, toes, ears, nose genitalia or buttocks owing to the risk of ischaemic tissue necrosis.

• Do not use if solution is discoloured.

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.

Adrenaline (Epinephrine) 1 mg/ml (1:1000) Solution for Injection 1mg/ml (1:1000) is not suitable for IV use.

The IM route is generally preferred in the initial treatment of anaphylaxis, the IV route is generally more appropriate in the Intensive Care Unit or Emergency Department setting. Adrenaline (Epinephrine) 1mg/ml (1:1000) solution for injection is not suitable for IV use. If the adrenaline 0.1 mg/ml (1:10000) injection is not available, Adrenaline 1mg/ml (1:1000) solution must be diluted to 0.1 mg/mL (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 be used with caution in patients with hyperthyroidism, diabetes mellitus, narrow angle glaucoma, phaeochromocytoma, hypertension, hypokalaemia, hypercalcaemia, severe renal impairment, prostatic adenoma leading to residual urine, cerebrovascular disease, elderly patients, patients with shock (other than anaphylactic shock), organic heart disease or cardiac dilatation, (severe angina pectoris, obstructive cardiomyopathy, hypertension), as well as most patients with arrhythmias, organic brain damage or cerebral arteriosclerosis. Anginal pain may be induced when coronary insufficiency is present.

Adrenaline should be used with caution during the second stage of labour (See Pregnancy and Lactation).

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.

Prolonged administration may induce metabolic acidosis, renal necrosis and 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.

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.

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. .

Adrenaline Injection contains sodium metabisulfite that can cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals.

The presence of sodium metabisulfite in parenteral Adrenaline and the possibility of allergic-type reactions should not deter use of the drug when indicated for the treatment of serious allergic reactions or for other emergency situations.

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.

Beta-adrenergic blocking agents:

Severe hypertension and reflex bradycardia may occur with non-selective beta-blocking drugs 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).

Antidepressant agents:

Tricyclic antidepressants such as imipramine may potentiate the effects of adrenaline, especially on heart rhythm and rate.

Non-selective MAO inhibitors:

increased pressor action of adrenaline, usually moderate.

Selective MAO-A inhibitors:

Linezolid (by extrapolation from non-selective MAO inhibitors): Risk of aggravation of pressor action.

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 drugs.

Phenothiazines:

Adrenaline should not be used to counteract circulatory collapse or hypotension caused by phenothiazines: a reversal of adrenaline's pressor effects resulting in further lowering of blood pressure may occur.

Other medicinal products:

Adrenaline should not be used in patients receiving high dosage of other drugs (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 drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, aminophylline and theophylline.

Hyperglycaemia:

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A teratogenic effect has been demonstrated in animal studies.

Adrenaline crosses the placenta. There is some evidence of a slightly increased incidence of congenital abnormalities. Injection of adrenaline may cause anoxia, fetal tachycardia, cardiac irregularities, extra systoles and louder heart sounds. Adrenaline usually inhibits spontaneous or oxytocin induced contractions of the uterus and may delay the second stage of labour. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with haemorrhage. For this reason, parenteral adrenaline should not be used during the second stage of labour.

Adrenaline should only be used during pregnancy if the potential benefits outweigh the possible risks to the fetus.

Breast-feeding

Adrenaline is distributed into breast milk. Breast-feeding should be avoided in mothers receiving adrenaline injection.

Fertility

No data are available with respect to the impact of adrenaline on fertility.

4.7 Effects on ability to drive and use machines

Not applicable in normal conditions of use

4.8 Undesirable effects

The adverse events of adrenaline mainly relate 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.

Metabolism and nutrition disorders:

Frequency not known: hyperglycaemia, hypokalaemia, metabolic acidosis.

Psychiatric disorders:

Frequency not known: anxiety, nervousness, fear, hallucinations.

Nervous system disorders:

Frequency not known: headache, tremors, dizziness, syncope.

In patients with Parkinsonian Syndrome, Adrenaline increases rigidity and tremor.

Eye disorders:

Frequency not known: mydriasis.

Cardiac disorders:

Frequency not known: palpitations, tachycardia. In high dosage or for patients sensitive to adrenaline: cardiac dysrhythmia (sinus tachycardia, ventricular fibrillation/cardiac arrest), acute angina attacks, and risk of acute myocardial infarction.

Vascular disorders:

Frequency not known: pallor, coldness of the extremities. In high dosage or for patients sensitive to adrenaline: hypertension (with risk of cerebral haemorrhage), vasoconstriction (for example cutaneous, in the extremities or kidneys)

Respiratory, thoracic and mediastinal disorders:

Frequency not known: dyspnoea.

Gastrointestinal disorders:

Frequency not known: nausea, vomiting.

General disorders and administration site conditions:

Frequency not known: sweating, weakness

Repeated local injections may produce necrosis at sites of injection as a result of vascular constriction.

Reporting of suspected adverse reactions

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.

4.9 Overdose

Over dosage or inadvertent intravenous administration of adrenaline may produce severe hypertension. Cerebral, cardiac or vascular accidents which could be potentially fatal may occur as a result (cerebral haemorrhage, dysrhythmias such as transient bradycardia followed by tachycardia that may result in arrhythmia, myocardial necrosis, acute pulmonary oedema, renal insufficiency)

The effects of adrenaline may be counteracted, depending on the condition of the patient, by administration of quick-acting vasodilators, of quick-acting alpha-adrenoreceptor blocking agents (e.g. phentolamine), or beta-adrenoreceptor blocking agents (e.g. propranolol). However, due to the short half-life of adrenaline, treatment with these medicines may not be necessary. In case of prolonged hypotensive reaction, administration of another vasopressive agent such as noradrenaline may be required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline.

ATC code: C01 CA 24

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 causes glucose to be released into circulation, oxygen consumption is increased. Blood flow to the kidneys, mucosa and skin is reduced.

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 pruritus, urticaria and angioedema associated with anaphylaxis.

The overall effect of adrenaline depends on the dose used, and may be complicated by the homeostatic reflex responses.

5.2 Pharmacokinetic properties

Absorption

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. 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.

Biotransformation

Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).

Elimination

Much of a dose of adrenaline is excreted as metabolites in urine. The onset of action and peak effect after injection is rapid, and the duration short (1 - 2 hours). Elimination is mainly via metabolism of the liver and sympathetic nerve endings, with a small amount excreted unchanged in the urine.

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 Incompatibilities

Adrenaline/epinephrine is rapidly denatured by oxidising agents and alkalis including sodium bicarbonate, halogens, nitrates, nitrites, and salts of iron, copper and zinc.

6.2 Shelf life

3 years.

6.3 Special precautions for storage

Keep ampoules in original carton in order to protect from light.

Do not freeze

Do not store above 30°C.
KEEP MEDICINES OUT OF REACH OF CHILDREN.

6.4 Nature and contents of container

0.5, 1, 2, 5, 10 ml in type 2 colourless OPC (one point cut) glass ampoules. Fusion sealed.

Packed into cartons of 10 ampoules.

Not all pack sizes may be marketed

6.5 Special precautions for disposal and other handling

For single use only. If only part used, discard the remaining solution.

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

7. Manufacturer:
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