Epinephrine Injection USP 1mg/1ml

1. Name of the medicinal product

Epinephrine Injection USP 1mg/1ml Taj Pharma

2. Qualitative and quantitative composition

Each ml contains:

Epinephrine as the Epinephrine Hydrochloride	1mg
Sodium Chloride	9mg
Water for injection	q.s

Sodium Hydroxide or Hydrochloric Acid for pH adjustment
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Clear, colourless, sterile, aqueous solution, intended for parenteral administration to human beings.

4. Clinical particulars

4.1 Therapeutic indications

Adrenaline is a direct-acting sympathomimetic agent.

Adrenaline may be used to provide rapid relief of severe hypersensitivity reaction to drugs and other allergens, and in the emergency treatment of anaphylactic shock.

4.2 Posology and method of administration

Posology

Severe hypersensitivity reactions, anaphylactic shock

IM Injection:

Adults: The usual dose is 500 micrograms (0.5ml of adrenaline 1/1000). If necessary, this dose may be repeated several times at 5-minute intervals according to blood pressure, pulse and respiratory function.

Half doses of adrenaline may be safer for patients who are taking amitriptyline, imipramine or a beta blocker.

Paediatric population

The following doses of adrenaline 1/1,000 are recommended:

Age	Dose
Over 12 years	0.5 mg IM (0.5ml 1:1000 solution)
6 - 12 years	0.3 mg IM (0.3ml 1:1000 solution)
6 months - 6 years	0.15 mg IM (0.15ml 1:1000 solution)
Under 6 months	0.01mg/kg IM (0.01ml/kg 1:1000 solution)

If necessary, these doses may be repeated at 5-15 -minute intervals according to blood pressure, pulse and respiratory function.

Elderly

The dosage is the same as for younger adults but particular caution is required when administering adrenaline to elderly patients (see section 4.4).

Renal impairment

Adrenaline should be used with caution in patients with severe renal impairment (see section 4.4).

Method of Administration

Adrenaline Injection BP. 1/1000 (1mg/ml) may be administered undiluted by S.C. or IM injection. In the shocked patient, the intramuscular route is recommended as

absorption from the intramuscular site is more rapid and reliable than from the subcutaneous site.

A small volume syringe should be used.

4.3 Contraindications

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

Adrenaline should not be used during labour or, with local anaesthesia of peripheral structures including digits and ear lobe.

Use in the presence of ventricular fibrillation, cardiac dilatation, coronary insufficiency, organic brain disease or atherosclerosis, except in emergencies where the potential benefit clearly outweighs the risk.

Use if solution is discoloured.

4.4 Special warnings and precautions for use

Adrenaline should be used with caution in patients with hyperthyroidism, diabetes mellitus, phaeochromocytoma, narrow angle glaucoma, hypokalaemia, hypercalcaemia, severe renal impairment, prostatic adenoma leading to residual urine, cerebrovascular disease, organic brain damage or arteriosclerosis, in elderly patients, 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. Anginal pain may be induced when coronary insufficiency is present.

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

Prolonged administration may produce 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.

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.

Adrenaline 1 in 1000 should not be diluted to 1 in 10,000 for use in cardiac resuscitation - when the 1 in 10,000 strength of adrenaline is required for this indication a “ready to use” preparation should be selected.

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. Intramuscular injections of Adrenaline into the buttocks should be avoided because of the risk of tissue necrosis.

The IM route is generally preferred in the initial treatment of anaphylaxis, the IV route is generally more appropriate in the Intensive Care Unit (ICU) or Emergency Department (ED) setting. Epinephrine injection 1:1000 (1mg/ml) is not suitable for IV use. If the epinephrine1:10000 (0.1mg/ml) injection is not available, epinephrine injection 1:1000 must be diluted to 1:10000 before IV use. The IV route for

injection of epinephrine must be used with extreme caution and is best reserved for specialists familiar with IV use of epinephrine (adrenaline).

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

The presence of sodium metabisulphite 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. 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-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).

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.

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; a reversal of the pressor effects of Adrenaline may result in further lowering of blood pressure.

Other drugs:

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

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, extra systoles and louder heart sounds.

Adrenaline usually 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 drug may cause a prolonged period of uterine atony with haemorrhage.

Parenteral Adrenaline should not be used during the second stage of labour.

Breast-feeding

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

Adrenaline should not be used in pregnancy unless clearly necessary.

4.7 Effects on ability to drive and use machines

Adrenaline has moderate influence on the ability to drive and use machines. The patients' ability to drive and use machines may be affected by the anaphylactic reaction, as well as by possible adverse reactions to adrenaline.

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.

Frequencies are defined using the following convention: not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Undesirable effects**
Immune system disorders	Not Known	Anaphylaxis, possibly with severe bronchospasm (See section 4.4).
Metabolism and nutrition disorders	Not Known	Hypokalaemia, metabolic acidosis (see section 4.4). Inhibition of insulin secretion and hyperglycaemia even with low

		doses, gluconeogenesis, glycolysis, lipolysis and ketogenesis.
Psychiatric disorders	Not Known	Psychotic states, Anxiety, fear, confusion, irritability, insomnia
Nervous system disorders	Not Known	Headache, dizziness, tremors, restlessness 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.
Cardiac disorders	Not Known	Disturbances of cardiac rhythm and rate may result in palpitation and tachycardia. Chest pain/angina may occur. 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) Stress cardiomyopathy (such as Takotsubo syndrome) Adrenaline causes E.C.G. changes including a decrease in T-Wave amplitude in all leads in normal subjects.
Vascular disorders	Not Known	Hypertension (with risk of cerebral haemorrhage). Coldness of extremities may occur even with small doses of Adrenaline.
Respiratory, thoracic and mediastinal disorders	Not Known	Dyspnoea, Pulmonary oedema may occur after excessive doses or in extreme

		sensitivity.
Gastrointestinal disorders	Not Known	Dry mouth, Reduced appetite, nausea, vomiting, hypersalivation.
Renal and urinary disorders	Not Known	Difficulty in micturition, urinary retention.
General disorders and administration site conditions	Not Known	Sweating, weakness. Repeated injections of Adrenaline can cause local ischaemic 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.

4.9 Overdose

Symptoms

After overdosage or inadvertent intravenous administration of usual intramuscular subcutaneous doses of Adrenaline, systolic and diastolic blood pressure rise sharply; venous pressure also rises. Cerebrovascular or other haemorrhages and hemiplegia may result, especially in elderly patients. Pulmonary oedema may occur.

Adrenaline overdosage causes transient bradycardia followed by tachycardia and may cause other potentially fatal cardiac arrhythmias. Kidney failure, metabolic acidosis and cold white skin may also occur.

Treatment

Because Adrenaline is rapidly inactivated in the body, treatment of acute toxicity is mainly supportive.

The pressor effects of Adrenaline may be counteracted by an immediate intravenous injection of a quick-acting alpha-adrenoreceptor blocking agent, such as 5-10mg of phentolamine mesylate, followed by a beta-adrenoreceptor blocking agent, such as 2.5 - 5mg of propranolol. Arrhythmias, if they occur, may be counteracted by propranolol injection.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline.

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 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. In resuscitation procedures it is used to increase the efficacy of basic life support. It is a positive cardiac inotrope.

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.

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 Metabisulphite

Sodium Chloride

Sodium Hydroxide

Hydrochloric acid

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 2 years

After reconstitution: Not applicable

After first opening: 2 years*

*If only part of an ampoule is used, the remainder should be discarded.

6.4 Special precautions for storage

Do not store above 25°C

Keep in outer carton

6.5 Nature and contents of container

1ml, clear One point cut (OPC) glass ampoules, glass type 1. borosilicate glass, packed in cardboard cartons to contain 10 x 1ml ampoules.

7.Manufactured in India by:

TAJ PHARMACEUTICALS LTD.

Mumbai, India

Unit No. 214.Old Bake House,

Maharashtra chambers of Commerce Lane,

Fort, Mumbai - 400001

at:Gujarat, INDIA.

Customer Service and Product Inquiries:

1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)

Monday through Saturday 9:00 a.m. to 7:00 p.m. EST
E-mail: tajgroup@tajpharma.com