

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Adrenaline Injection BP 1/1000 (1mg/1ml)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains adrenaline acid tartrate BP equivalent to 1mg of adrenaline

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

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.

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.

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

Age	Dose
Over 12 years	500 micrograms (0.5ml) 250 micrograms (0.25ml) if child is small or prepubertal
6 - 12 years	250 micrograms (0.25ml)
6 months - 6 years	120 micrograms (0.12ml)
Under 6 months	50 micrograms (0.05ml)

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

4.3 Contraindications

- 1) Use during labour
- 2) Use with local anaesthesia of peripheral structures including digits, ear lobe.
- 3) 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.
- 4) 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.

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 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.

Lactation:

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

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.

Immune system disorders:

Anaphylaxis, possibly with severe bronchospasm (See section 4.4).

Metabolism and nutrition disorders:

Hypokalaemia, metabolic acidosis (see section 4.4).

Inhibition of insulin secretion and hyperglycaemia even with low doses, gluconeogenesis, glycolysis, lipolysis and ketogenesis.

Psychiatric disorders:

Psychotic states, Anxiety, fear, confusion, irritability, insomnia

Nervous system disorders

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:

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)

Adrenaline causes E.C.G. changes including a decrease in T-Wave amplitude in all leads in normal subjects.

Vascular disorders:

Hypertension (with risk of cerebral haemorrhage).

Coldness of extremities may occur even with small doses of Adrenaline.

Respiratory disorders:

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

Gastrointestinal disorders:

Dry mouth, Reduced appetite, nausea, vomiting, hypersalivation.

Renal and urinary disorders:

Difficulty in micturition, urinary retention.

General disorders and administrative site conditions:

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.

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 overdose 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.

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 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

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 Metabisulphite
Sodium Chloride
Sodium Hydroxide
Hydrochloric acid
Water for Injections

6.2 Incompatibilities

Do not admix with other agents unless compatibility is known.

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 Ph.Eur. borosilicate glass, packed in cardboard cartons to contain 10 x 1ml ampoules.

6.6 Special precautions for disposal

For S.C. or I.M. injection.
Use as directed by the physician.
Keep out of reach of children.
If only part used, discard the remaining solution.

7 MARKETING AUTHORISATION HOLDER

Antigen International Limited
Roscrea
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 02848/5909R

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

30/01/1991 / 19/05/2003

10 DATE OF REVISION OF THE TEXT

04/02/2011