



## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **PRODUCT SUMMARY**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Adrenaline (Epinephrine) Injection BP 1 in 1000.

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ml of solution for injection contains 1 mg of adrenaline (epinephrine) as the acid tartrate.

#### **3. PHARMACEUTICAL FORM**

Sterile Injection.

#### **4. Clinical Particulars**

##### **4.1 Therapeutic indications**

Adrenaline Injection BP 1 in 1000 may be used in the treatment of acute allergy and anaphylactic shock.

## 4.2 Posology and method of administration

The **intramuscular route** is the preferred choice for most individuals who have to be given adrenaline for the management of an anaphylactic reaction.

The following adrenaline doses are advised by the Working Group of the Resuscitation Council (UK).

Dose of <b>intramuscular</b> injection of Adrenaline (Epinephrine) Injection BP 1 in 1000 for a severe anaphylactic reaction		
Age	Dose	Volume of adrenaline <b>1 in 1000</b> (1mg/ml)
Child under 6 years	150 micrograms	0.15 ml <sup>1</sup>
Child 6 – 12 years	300 micrograms	0.3 ml
Child > 12 years	500 micrograms	0.5 ml <sup>2</sup>
Adult	500 micrograms	0.5 ml

These doses may be repeated several times if necessary at 5 – minute intervals according to blood pressure, pulse, and respiratory function.

1. Use suitable syringe for measuring small volume
2. 300 micrograms (0.3ml) if child is small or prepubertal

There is lack of robust evidence for the doses recommended in children: the recommended doses are based on what is considered to be safe and practical.

## 4.3 Contraindications

Hypersensitivity to adrenaline, sodium metabisulphite or any of the other ingredients.

Adrenaline 1 in 1000 should not be used in fingers, toes, ears, nose or genitalia owing to the risk of ischaemic tissue necrosis.

## 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.

Adrenaline should be used cautiously, if at all, during general anaesthesia with halogenated hydrocarbon anaesthetics (See section 4.5).

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.

Prolonged use of Adrenaline can result in severe metabolic acidosis because of elevated blood concentrations of lactic acid.

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 Interactions with other medicinal products and other forms of interactions**

##### *Sympathomimetic agents:*

Adrenaline should not be administered concomitantly with 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).

*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 (see above). 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. Hypokalaemia may result in increased susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides.

*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**

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. If used during pregnancy, Adrenaline may cause anoxia to the foetus. 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 justify the possible risks to the foetus.

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

#### **4.7 Effects on ability to drive and use machines**

None noted.

#### **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:*

Hyperglycaemia, hypokalaemia, metabolic acidosis (see section 4.4).

*Psychiatric disorders:*

Anxiety

### *Nervous system disorders*

Headache, dizziness, tremors

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.

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:*

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

### *Gastrointestinal disorders:*

Nausea, vomiting.

### *Renal and urinary disorders:*

Difficulty in micturition, urinary retention.

### *General disorders and administrative site conditions:*

Sweating, weakness.

Repeated injections of Adrenaline can cause 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 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 5-10 mg of phentolamine mesylate, followed by a beta-adrenoreceptor blocking agent, such as 2.5 - 5 mg 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.

## **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 information other than that which is included in the Summary of Product Characteristics.

## **6. Pharmaceutical Particulars**

### **6.1 List of excipients**

Sodium Metabisulphite Ph. Eur.  
Sodium Chloride Ph. Eur.  
Sodium Hydroxide Ph. Eur.  
Water for Injections Ph. Eur.  
Hydrochloric Acid Ph. Eur.

### **6.2 Incompatibilities**

Adrenaline is rapidly denatured by oxidising agents and alkalis including sodium bicarbonate, halogens, nitrates, nitrites and salts of iron, copper and zinc. Adrenaline may be mixed with 0.9% Sodium Chloride injection but is incompatible with 5% sodium chloride injection. The stability of Adrenaline in 5% dextrose injection decreases when the pH is greater than 5.5.

### **6.3 Shelf life**

24 months.

### **6.4 Special precautions for storage**

Store at less than 25 C and protect from light.

**6.5 Nature and contents of container**

Clear glass ampoules of 1 ml. Packed in cardboard cartons to contain 10 ampoules x 1 ml.

**6.6 Instructions for use, handling and disposal**

Use as directed by the Physician.

**ADMINISTRATIVE DATA**

**7. MARKETING AUTHORISATION HOLDER**

hameln pharmaceuticals ltd  
Gloucester  
UK

**8. MARKETING AUTHORISATION NUMBER**

PL 01502/0024

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

14<sup>th</sup> December 1978 / 23<sup>rd</sup> August 2001

**10. DATE OF (PARTIAL) REVISION OF TEXT**

06/08/09