SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Adrenaline (Epinephrine) Injection BP (1:1000) for Anaphylaxis

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains 1mg Adrenaline (Epinephrine) as the Acid Tartrate

3 PHARMACEUTICAL FORM
Solution for Injection

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Anaphylaxis or Acute Allergy (Angioedema)

4.2 Posology and method of administration
The intramuscular (IM) route is recommended by the UK 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 subcutaneous route for adrenaline is not recommended for treatment of an anaphylactic reaction as it is less effective.

Dosage:
Adults:
500 micrograms (0.5ml) of 1:1000 adrenaline solution

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.

Children:
Volume of 1:1000 adrenaline to be administered is shown in brackets
12 years: 500 micrograms IM (0.5ml i.e. same as adult dose)
300 micrograms (0.3ml if the child is small or pre-pubertal)
6 -12 years: 300 micrograms (0.3ml)
6 months - 6 years:  150 micrograms (0.15ml)
<6 months:  150 micrograms (0.15ml)

Repeat the IM adrenaline dose if there is no improvement in the patient’s condition. Further doses can be given at about 5-minute intervals according to the patient’s response.

The IM route for adrenaline is stated by the UK Resuscitation Council as the route of choice for most healthcare providers.

There is a much greater risk of causing harmful side effects by inappropriate dosage or misdiagnosis of anaphylaxis when using IV adrenaline. This is why the IM route is recommended for most healthcare providers.

The UK Resuscitation Council advises the IV adrenaline for anaphylaxis should be administered by those experienced in the use and titration of vasopressors in their normal clinical practice (e.g. anaesthetists, emergency physicians or intensive care doctors).

Intravenous administration of adrenaline for anaphylaxis requires the use of a 1:10000 adrenaline solution.

Do not give the undiluted 1:1000 adrenaline intravenously.

4.3 Contraindications
Adrenaline/epinephrine is contraindicated in patients with shock (other than anaphylactic shock), organic heart disease, or cardiac dilatation, as well as most patients with arrhythmias, organic brain damage, or cerebral arteriosclerosis. Adrenaline/epinephrine injection is contraindicated in patients with narrow angle glaucoma. Adrenaline/epinephrine is contraindicated for use during general anaesthesia with chloroform, trichloroethylene, or cyclopropane, and should be used cautiously, if at all, with other halogenated hydrocarbon anaesthetics. Adrenaline/epinephrine is contraindicated for use in fingers, toes, ears, nose or genitalia.

Adrenaline/epinephrine should not be used during the second stage of labour (see pregnancy and lactation).

4.4 Special warnings and precautions for use
IM injection of adrenaline/epinephrine into the buttocks should be avoided because of the risk of tissue necrosis. Prolonged use of adrenaline/epinephrine can result in severe metabolic acidosis because of elevated blood concentrations of lactic acid.

Adrenaline/Epinephrine Injection 1 in 1000 BP contains sodium metabisulphite that 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/epinephrine 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.
Care should be exercised in patients who suffer from diabetes mellitus, hypertension and hyperthyroidism.

4.5 Interaction with other medicinal products and other forms of interaction

- Sympathomimetic agents: Adrenaline/epinephrine should not be administered concomitantly with other sympathomimetic agents because of the possibility of additive effects and increased toxicity.

- Alpha and beta blocking agents: The cardiac and bronchodilating effects of adrenaline/epinephrine are antagonised by β-adrenergic blocking drugs such as propranolol, and the vasoconstriction and hypertension caused by high doses of adrenaline/epinephrine are antagonised by alpha-adrenergic blocking agents such as phentolamine.

- Because of their alpha-adrenergic blocking properties, ergot alkaloids can reverse the pressor response to adrenaline.

- General anaesthetics (see also contraindications) Administration of adrenaline/epinephrine in patients receiving cyclopropane or halogenated hydrocarbon general anaesthetics that increase cardiac irritability and seem to sensitize the myocardium to adrenaline/epinephrine may result in arrhythmias including ventricular premature contractions, tachycardia, or fibrillation.

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

Other Drugs:

- Adrenaline/epinephrine should not be used in patients receiving high dosage of other drugs (e.g. cardiac glycosides) that can sensitise the heart to arrhythmias. Tricyclic antidepressants such as imipramine, some antihistamines (e.g. diphenhydramine) and thyroid hormones may potentiate the effects of adrenaline/epinephrine, especially on heart rhythm and rate. Although monoamine oxidase (MAO) is one of the enzymes responsible for adrenaline/epinephrine metabolism, MAO inhibitors do not markedly potentiate the effects of adrenaline/epinephrine.

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

- Insulin and other hypoglycaemic agents: Because adrenaline/epinephrine may cause hyperglycaemia, diabetic patients receiving adrenaline/epinephrine may require increased dosage of insulin or oral hypoglycaemic agents.

- Clonidine may increase the risk of hypertension.

- Dopexamine may enhance the action of adrenaline.

- Entacapone may enhance the action of adrenaline.

- Antipsychotics antagonise the hypertensive effect of sympathomimetics.
• Doxapram: Increased risk of hypertension when sympathomimetics are given with doxapram.

• Ergotamine and Methylsergide: There is an increased risk of ergotism if sympathomimetics are given with these drugs.

• Oxytocin: Concomitant use with adrenaline may increase the vasopressor effect and thus a risk of hypertension may develop. (see also Section 4.6)

4.6 Pregnancy and lactation

Adrenaline/epinephrine 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/epinephrine may cause anoxia to the foetus. For this reason parenteral adrenaline/epinephrine should not be used during the second stage of labour. Adrenaline/epinephrine should only be used during pregnancy if the potential benefits justify the possible risks to the foetus. Adrenaline/epinephrine is distributed into breast milk. Breast-feeding should therefore be avoided in mothers receiving Adrenaline/Epinephrine Injection.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

• Hyperglycaemia.

• Anxiety.

• Headache, nausea, vomiting, sweating, tremors, dizziness or restlessness.

• Adrenaline/epinephrine causes ECG changes including a decrease in T-wave amplitude in all leads in normal persons. (16) Disturbances of cardiac rhythm and rate may result in palpitation and tachycardia. Adrenaline/epinephrine can cause potentially fatal ventricular arrhythmias including fibrillation, especially in patients with organic heart disease or receiving other drugs that sensitize the heart to arrhythmias. Subarachnoid haemorrhage and hemiplegia have resulted from hypertension, even following subcutaneous administration of usual doses of adrenaline.

• Dyspnoea.

• Weakness. In patients with Parkinsonian syndrome, adrenaline/epinephrine increases rigidity and tremor.

• Coldness of the extremities may occur even with small doses of adrenaline/epinephrine. Repeated injections of adrenaline/epinephrine 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

After overdose or inadvertent IV administration of usual doses of adrenaline/epinephrine, systolic and diastolic blood pressure rise sharply; venous pressure also rises. Cerebrovascular or other haemorrhage and hemiplegia may result, especially in elderly patients. Because adrenaline/epinephrine is rapidly inactivated in the body, treatment of acute toxicity is mainly supportive.

The pressor effects of adrenaline/epinephrine may be counteracted by an immediate intravenous injection of a quick-acting alpha-adrenoceptor blocking agent, such as 5 - 10mg of phentolamine mesylate, followed by a beta-adrenoceptor blocking agent such as 2.5mg to 5mg of propranolol.

Adrenaline/epinephrine overdosage causes transient bradycardia followed by tachycardia and may cause other potentially fatal cardiac arrhythmias. Arrhythmias, if they occur, may be counteracted by propranolol injection. Kidney failure, metabolic acidosis and cold, white skin may also occur. Pulmonary oedema may be caused by overdosage or extreme sensitivity to adrenaline.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Adrenaline/epinephrine is an active principle of the adrenal medulla which is used as a direct-acting sympathomimetic agent. Adrenaline/epinephrine has a somewhat more marked effect on beta-adrenoceptors than on alpha-adrenoceptors. In addition, its actions vary considerably according to the dose given, and the consequent reflex compensating responses of the body. Adrenaline/epinephrine produces marked and concentration-dependent increases in stroke volume, cardiac output and systemic vascular resistance when arterial plasma concentration is increased from 0.3 to 6nmol/l (0.055 to 1.1pg/l).

In practice, major effects of adrenaline/epinephrine include increased speed and force of cardiac contraction (with lower doses this causes increased systolic pressure yet reduced diastolic pressure since overall peripheral resistance is lowered, but with higher doses both systolic and diastolic pressure are increased as stimulation of peripheral alpha-receptors increases peripheral resistance); blood flow to skeletal muscle is increased (reduced with higher doses); metabolic effects include increased glucose output as well as markedly increased oxygen consumption; blood flow in the kidneys, mucosa, and skin is reduced; there is little direct effect on cerebral blood flow.

5.2 Pharmacokinetic properties

Adrenaline/epinephrine acts rapidly following intramuscular and subcutaneous injection; latter route is sometimes considered to be slower and less reliable for emergency use. Local vasoconstriction can slow absorption, but hastened by massaging injection site.
Adrenaline/epinephrine injected into the body, or released from the adrenal medulla is very rapidly inactivated by processes, which include uptake into adrenergic neurones, diffusion, and enzymatic degradation in the liver and body tissues.

Adrenaline/epinephrine is rapidly distributed into the heart, spleen, several glandular tissues and adrenergic nerves. It is approximately 50% bound to plasma proteins.

Endogenous plasma concentrations of adrenaline/epinephrine in normal subjects are in the range 30 to 160ng/l.

The decline of plasma adrenaline/epinephrine following intravenous infusion has been reported to be biexponential with a mean clearance of 9.4 l/min (range 4.9-14.6 l/min). The half-lives of the fast and slow exponential phases are approximately 3 and 10 minutes respectively.

One of the enzymes responsible for the chemical inactivation of this exogenous or hormonal adrenaline/epinephrine is Catechol-O-methyltransferase (COMT), the other is monoamine oxidase (MAO).

In general:
The metabolites are excreted in the urine mainly as their glucuronide and ethereal sulphate conjugates. About 70-95% of an intravenous dose is excreted in the urine; of the excreted material, about 80% is excreted as O-methyl metabolites and 2% as catechol metabolites, and only 1% is excreted as unchanged drug.

Adrenaline/epinephrine is inactivated by the introduction of a methyl group by COMT. Thus the termination of the pharmacological response of adrenaline/epinephrine (and other catecholamines) is not only dependent on MAO. However, in adrenaline/epinephrine’s role as a neurotransmitter, it is enzymatically regulated by MAO.

Adrenaline/epinephrine crosses the placenta to enter the foetal circulation.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber, which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Chloride
Sodium Metabisulphite
Water for Injections
Dilute Hydrochloric Acid

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

6.3 Shelf life
18 Months

6.4 Special precautions for storage
Keep container in the outer carton
Do not store above 25°C
Do not freeze

6.5 Nature and contents of container
Type 1 Glass prefilled Syringe with needle in situ with rubber needle shield, rubber plunger (Type PH 701/50C)

6.6 Special precautions for disposal
Do not use if the contents of the syringe are discoloured. Do not use if the tamper evident seal is broken or the packaging is damaged. Use once and discard any remaining solution at the end of the session.

7 MARKETING AUTHORISATION HOLDER
Aurum Pharmaceuticals Ltd
Bampton Road
Harold Hill
Romford
Essex
RM3 8UG

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