SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dilute Adrenaline (Epinephrine) 1:10,000 Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the solution for injections contains 100 micrograms of Adrenaline (Epinephrine) as the Acid Tartrate.

Excipient with known effect

Each ml of Adrenaline 1:10,000 Injection contains 1mg of sodium metabisulfite (E223) and 2.695 mg or 0.117 mmol of sodium

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless and practically free from particles

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardiopulmonary Resuscitation
Acute Anaphylaxis when intramuscular route has been ineffective**.**

4.2 Posology and method of administration

Posology

Cardiopulmonary Resuscitation

Adults and children over 12 years

1 in 10,000 (1mg in 10ml) is recommended in a dose of 10ml (1mg), by **central intravenous injection**. The procedure for Cardiopulmonary Resuscitation is given in the algorithm which reflects the recommendations of the European Resuscitation Council and the Resuscitation Council (UK).

If venous access is not available, intraosseous (IO) route is recommended.

The dose may be repeated at 3 minute intervals.

Paediatric population under 12 years

It is not recommended.

Elderly

It should be used with great caution in these patients who may be more susceptible to the cardiovascular side effects of adrenaline.

Acute life threatening allergic reactions/Acute Anaphylaxis

For specialist use only (see section 4.4)

Adults

Administer IV Adrenaline as a bolus. Titrate IV Adrenaline using 50 microgram boluses according to response.

A dose of 50 micrograms is equivalent to 0.5ml.

If repeated adrenaline doses are needed, start an IV adrenaline infusion with reference to local guidelines on the preparation and infusion of adrenaline.

Paediatric population

Administer IV Adrenaline as a bolus. There is no evidence on which to base a dose recommendation in children. Titrate the dose according to response. A child may respond to a dose as small as 1 microgram/kg.

Method of administration

Intraveneous or Intraosseous Injection

4.3 Contraindications

These should be regarded as relative and not absolute contraindications in life threatening emergency situations.

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

Adrenaline 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 injection is contraindicated in patients with narrow angle glaucoma. Adrenaline 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., aAdrenaline is contraindicated for use in fingers, toes, ears, nose or genitalia. Adrenaline should not be used during the second stage of labour (see pregnancy and lactation).

4.4 Special warnings and precautions for use

For adults: for the treatment of anaphylaxis, IV Adrenaline should only be used by those experienced in the use and titration of vasopressors (e.g. anaesthetist, emergency physicians, intensive care doctors).

For children: for the treatment of anaphylaxis, IV Adrenaline should only be administered to children in specialist paediatric settings by those familiar with its use (e.g. paediatric anaesthetists, paediatric emergency physicians, paediatric intensivists) and if the patient is monitored and if IV access is already available.

Constant vigilance is needed to ensure that the correct strength is used. **Anaphylactic shock kits need to make a very clear distinction between the 1 in 10,000 strength and the 1 in 1000 strength Adrenaline solution.**

Patients who are given IV adrenaline must be monitored. The Resuscitation Council (UK) advises continuous ECG and pulse oximetry and frequent non-invasive blood pressure measurements as a minimum Intramuscular administration of Adrenaline (1:1000) is preferred for the management of anaphylactic shock. It is also important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

IM injection 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 1 in 10,000 contains sodium metabisulfite that can cause allergic-type reactions, including anaphylaxis and life-threatening or less severe asthmatic episodes, in certain susceptible individuals.

In the treatment of anaphylaxis and in other patients with a spontaneous circulation, intravenous adrenaline can cause life-threatening hypertension, tachycardia, arrhythmias and myocardial ischaemia.

Adrenaline should be used with caution in elderly patients.

The risk of toxicity is increased if the following conditions are pre-existing

- Hyperthyroidism
- Hypertension

•Structural cardiac disease, cardiac arrhythmias, severe obstructive cardiomyopathy,

• Coronary insufficiency

• Phaeochromocytoma,

• Hypokalaemia

• Hypercalcaemia

• Severe renal impairment

• Cerebrovascular disease, organic brain damage or arteriosclerosis

• Patients taking Monoamine oxidase (MAO) inhibitors (see section 4.5)

• Patients taking concomitant medication which results in additive effects, or sensitizes the myocardium to the actions of sympathomimetic agents (see section 4.5)

Adrenaline may increase intra-ocular pressure in patients with narrow angle glaucoma.

Adrenaline should be used with caution in patients with prostatic hyperplasia with urinary retention.

Adrenaline may cause or exacerbate hyperglycaemia, blood glucose should be monitored, particularly in diabetic patients.

Adrenaline should not be used during the second stage of labour (See Section 4.6).

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.

This medicinal product contains 2.695 mg or 0.117 mmol of sodium per ml of solution for injection: to be taken into consideration by patients on strict sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Volatile halogen anaesthetics: severe ventricular arrhythmia (increase in cardiac
excitability).

Imipramine antidepressants: paroxysmal hypertension with the possibility of
arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

Serotoninergic-adrenergic antidepressants: paroxysmal hypertension with the
possibility of arrhythmia (inhibition of the entry of sympathomimetics into sympathetic fibres).

Sympathomimetic agents: concomitant administration of other sympathomimetic agents may increase toxicity due to possible additive effects.

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.

Alpha-adrenergic blocking agents: Alpha-blockers antagonise the vasoconstriction and hypertension effects of adrenaline, increasing the risk of hypotension and tachycardia.

Beta-adrenergic blocking agents: Severe hypertension and reflex bradycardia may occur with non-cardioselective beta-blocking agents. Beta-blockers, especially noncardioselective agents, also antagonise the cardiac and bronchodilator effects of adrenaline.

Insulin or oral hypoglycaemic agents: 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:

Teratogenic effect has been demonstrated in animal experiments.

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.

Lactation:

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

Fertility:
No information available concerning 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

Frequencies are defined using the following convention: very common (>1/10), common (>1/100 to <1/10), uncommon (>1/1000 to<1/100), rare (>1/10000 to<1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Undesirable effects**
Metabolism and nutrition disorders:	Not known	Hyperglycaemia, hypokalaemia, metabolic acid
Psychiatric disorders	Not known	Anxiety, nervousness, fear, hallucinations
Nervous system disorders	Not known	Headache, tremors, dizziness, syncope
Eye disorders	Not known	Mydriasis
Cardiac disorders	Not known	Palpitations, tachycardia. In high dosage or for patients sensitive to adrenaline: cardiac dysrhythmia (sinus tachycar ventricular fibrillation/cardiac arrest), Acute angina attacks, and risk of acute myocard infarction.
Vascular disorders	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:	Not known	Dyspnoea
Gastrointestinal disorders	Not known	Nausea, vomiting
General disorders and administration site conditions	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 suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 adreno-receptor blocking agents (e.g. phentolamine), or beta adreno-receptor blocking agents (e.g. propanolol). 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 direct acting sympathomimetic agent, which exerts effects on both αand β adrenoceptors. It exhibits little selectivity towards α^1 and α^2 receptors but is significantly more selective to β^2 than β^1. Major effects include increased systolic blood pressure, reduced diastolic blood pressure, vasoconstriction, bronchodilation tachycardia, hyperglycaemia and hypokalaemia.

5.2 Pharmacokinetic properties

Pharmacologically active concentrations of adrenaline are not achieved following oral administration as it is rapidly oxidised and conjugated in the gastrointestinal mucosa and the liver. Absorption from subcutaneous tissue is slow due to local vasoconstriction; effects are produced within 5 minutes. Absorption is more rapid after intramuscular injection than after subcutaneous injection.

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

Adrenaline is rapidly inactivated in the body, mostly in the liver by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO). Most of a dose of adrenaline is excreted as metabolites in urine.

After intravenous administration, the plasma half-life is about 2-3 minutes.

5.3 Preclinical safety data

There are no preclinical 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
Citric Acid monohydrate
Sodium Citrate Dihydrate
Sodium Metabisulfite
Dilute hydrochloric acid
Water for Injections

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

12 months

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze
Keep in the original container.

6.5 Nature and contents of container

Sterile aqueous solution in glass (Type 1) ampoules.
Pack sizes: 10 x 1ml, 10 x 5ml and 10 x 10ml ampoules

6.6 Special precautions for disposal

Protect from light.

The glass ampoule is for single patient use only. Discard the ampoule after use.

7 MARKETING AUTHORISATION HOLDER

Macarthys Laboratories Ltd
T/A Martindale Pharma
Bampton Road
Harold Hill
Romford
Essex RM3 8UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 01883/0065

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/11/2002

10 DATE OF REVISION OF THE TEXT

09/01/2018