Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Adrenaline (Epinephrine) 1:1,000 Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains Adrenaline (Epinephrine)
Acid Tartrate equivalent to 1mg Adrenaline (Epinephrine)

Excipients with known effect:
Sodium Metabisulphate (E223)

This medicinal product contains 3.389 mg/ml (0.147mmoles/ml) of sodium, less than 1 mmol sodium (23 mg) per ml, i.e. essentially 'sodium- free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear colourless sterile solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adrenaline Injection may be used to relieve bronchial spasm in acute attacks of asthma. It may also be used to provide rapid relief of hypersensitivity reactions to drugs and other allergens, and in the emergency treatment of anaphylactic shock. Adrenaline Injection may be used in follow-up treatment in cardiopulmonary resuscitation.

4.2 Posology and method of administration

Posology

Adults: The usual dose is 0.3 to 0.5mg (0.3 to 0.5ml). If necessary, this may be repeated at 15 to 20 minute intervals for two doses, then subsequently every four hours as required. A dose of 1mg (1ml) can be given as a single injection in severe allergic reactions and anaphylactic shock.

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

Age	Dose
Over 12 years	0.5mg IM (0.5ml 1:1000 solution)
6-12 years	0.3mg IM (0.3ml 1:1000 solution)
6 months – 6 years	0.15mg 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.

A small volume syringe should be used.

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).

Cardiopulmonary Resuscitation
As follow-up treatment in cardiopulmonary resuscitation, a subcutaneous dose of 0.3mg (0.3ml) may be given after intravenous or intracardiac administration of the 1:10,000 dilution.

Method of administration
Adrenaline Injection is for subcutaneous, intramuscular injection or intravenous injection after dilution.

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, ear lobe.

Use in the presence of ventricular fibrillation.

Adrenaline should not be used in the presence of cardiac dilatation, coronary insufficiency, organic brain disease or arteriosclerosis, 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 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.

Adrenaline should only be administered with great caution in:
elderly patients, patients with hyperthyroidism, diabetes mellitus, phaeochromocytoma, narrow angle glaucoma, hypokalaemia, hypercalcaemia, severe renal impairment and prostatic adenoma leading to residual urine, cerebrovascular disease, organic brain damage, 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 maybe induced when coronary insufficiency is present.

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

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).

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 administration may induce 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.

Monitor the patient as soon as possible (pulse, blood pressure, ECG, pulse oximetry) in order to assess the response to adrenaline.

This medicinal product contains 3.389 mg sodium per ml. i.e. essentially sodium free.

Sodium metabisulphite, one of the excipients of this medicinal product, may rarely cause severe hypersensitivity reactions and bronchospasm. 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 interactions

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-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. Adrenaline should not be used to counteract circulatory collapse or hypotension caused by phenothiazines since 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 diabetics 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, extrasystoles and louder heart sounds.
Adrenaline 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

Not applicable.

4.8 Undesirable effects

The adverse effects of adrenaline are related 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 Inhibition of insulin secretion (even with low doses) Hyperglycaemia (even with low doses) Gluconeogenesis Glycolysis, Lipolysis Ketogenesis
Psychiatric disorders	Not known	Psychotic states Anxiety Fear Confusional state Irritability Insomnia
Nervous system disorders	Not known	Headache Dizziness Tremor Restlessness
Cardiac disorders	Not known	Disturbances of cardiac rhythm and rate Palpitation Tachycardia Chest pain/ angina potentially fatal ventricular arrhythmias Fibrillation Stress cardiomyopathy (such as Takotsubo syndrome) Decrease in T-wave amplitude
Vascular disorders	Not known	Hypertension (with risk of cerebral haemorrhage) Coldness of extremities

Respiratory disorders	Not known	Dyspnoea Pulmonary oedema
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

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.

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).

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

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.

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: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Possible signs of overdosage include restlessness, confusion, pallor, tachycardia, bradycardia, cardiac arrhythmias and cardiac arrest.

Treatment is primarily symptomatic and supportive. Prompt injection of a rapidly-acting alpha-adrenoceptor blocking agent such as phentolamine, followed by a beta-blocker such as propranolol, has been tried to counteract the pressor and arrhythmogenic effects of adrenaline. A rapidly-acting vasodilator such as glycetyl trinitrate has also been used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: adrenergic and dopaminergic agents, adrenaline.

ATC code: CO1 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 pruritis, urticaria and angioedema associated with anaphylaxis.

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 chloride
Sodium Metabisulphite
Sodium Hydroxide
Hydrochloric Acid
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened: 18 months.
The product should be used immediately after opening.

6.4 Special precautions for storage

Keep the ampoule in the outer carton in order to protect from light.
Do not store above 25°C.

6.5 Nature and contents of container

1 ml, clear glass ampoules, glass type I Ph. Eur.

Pack size: 10 x 1 ml ampoules.

6.6 Special precautions for disposal and other handling

Single use only.
If only part used, discard the remaining solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/035/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1979

Date of last renewal: 1st April 2009

10 DATE OF REVISION OF THE TEXT

November 2021