SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Adrenaline Sintetica 1 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains: epinephrine (adrenaline) 1 mg

Excipients with known effect

Each ml of solution for injection contains sodium 3.4 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colorless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adrenaline Sintetica 1 mg/ml is indicated in the following situations:

- Spasm of the airways in acute asthma attacks.
- Rapid relief of allergic reactions to drugs or other substances.
- Emergency treatment of anaphylactic shock.
- Cardiac arrest and cardiopulmonary resuscitation (physical measures should be used first).

4.2 Posology and method of administration

Adrenaline Sintetica 1mg/ml solution for injection can be administered by intramuscular (I.M.), subcutaneous (S.C.) and intravenous (I.V.) injection, and in extremely serious cases and if the intravenous route is not practicable, via the intracardiac route.

The intravenous and intracardiac routes must be used in the hospital setting, after dilution of the solution in 0.9% sodium chloride solution and under cardiac monitoring. Adrenaline Sintetica 1 mg/ml will be administered by healthcare personnel. It must be diluted in 0.9% sodium chloride solution to 1:10,000 before I.V. or intracardiac administration. To prevent degradation by light or oxidation, it is recommended that the product be used immediately after dilution. The dosage and route of administration depend on the diagnosis and the clinical condition of patients. In an emergency situation, a rapid route of absorption should be used.

Acute asthma attacks, allergic reactions and anaphylactic shock
The usual dose for the treatment of acute asthma attacks and allergic reactions in adults is 0.3-0.5 mg (0.3-0.5 ml) by I.M. or subcutaneous injection, with the I.M. route being the quickest and most effective. In the case of anaphylactic shock, the I.M. route or, in very serious cases and in the hospital setting, the I.V. route must be used. If necessary, the administration can be repeated after 15-20 minutes and then at intervals of 4 hours. In serious conditions, the dose can be increased up to 1 mg (1 ml).

In elderly patients, the recommended doses are the same as for adults, but special caution is needed.

The usual dose for children is 0.01 mg (0.01 ml) per kg of body weight either by intramuscular or subcutaneous injection up to a maximum dose of 0.5 mg (0.5 ml). If necessary, the administration can be repeated after 15-20 minutes and then at intervals of 4 hours.

Cardiac arrest and cardiopulmonary resuscitation
For the treatment of cardiac arrest and cardiopulmonary resuscitation, the recommended dose of epinephrine (adrenaline) is 1 mg by intravenous injection which must be administered after dilution in 0.9% sodium chloride solution to 1:10,000 and can be repeated every 3-5 minutes as many times as necessary.

In children, the standard dose is 0.01 mg/kg by intravenous injection, which can be repeated every 5 minutes if necessary.

When the intravenous route is not practicable, the intracardiac route can be used (using the same diluted solution). However, it should be borne in mind that this route presents serious risks and should only be used if the intravenous route is persistently inaccessible.

The lowest dose that produces relief should be used. For acute asthma attacks, low doses administered at the outset are more effective than higher doses administered later. Patients who frequently receive adrenaline (and other sympathomimetics), such as asthmatic patients, may develop tolerance and therefore require increased doses to achieve the same therapeutic effect. In advanced cases, this may lead to resistance or refractoriness to the clinical effects of this medicinal product.

4.3 Contraindications

- Hypersensitivity to adrenaline, sympathomimetics 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.

4.4 Special warnings and precautions for use

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.
Intramuscular injections of Adrenaline into the buttocks should be avoided because of the risk of tissue necrosis.

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).

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.

Important information about some of the ingredients of Adrenaline Sintetica 1 mg/ml

This medicine contains less than 23 mg sodium (1 mmol) per ampoule; that is to say essentially "sodium-free".

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-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 Sintetica 1 mg/ml. 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

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: drenergic and dopaminergic agents, adrenaline.
ATC code: C01CA24

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,
Hydrochloric acid 1N,
Water for injection.

6.2 Incompatibilities

Adrenaline may be inactivated in alkaline solutions or in the presence of oxidising agents such as sodium bicarbonate, halogens, permanganates, chromates, nitrates, nitrites and salts of easily reducible metals such as iron, copper and zinc. If adrenaline and sodium bicarbonate need to be administered, they should be injected separately.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution
For microbiological reasons, the solution for infusion must be used within 24 hours after opening.

Shelf life after first opening of the pack
The product does not contain a preserving agent. For microbiological reasons, the product should be administered immediately after opening.

6.4 Special precautions for storage

Store in the original package below 25ºC. Protect from light.

In case of prolonged administration (e.g. infusion), it must be performed protected from light.

6.5 Nature and contents of container

Clear glass ampoules.
Each pack contains 10 ampoules of 1 ml.

6.6 Special precautions for disposal and other handling

Single-use containers. Discard any unused contents remaining after administration.
This medicinal product should only be used if the container is undamaged and the solution is clear.
Any unused medicinal product and all materials that have come into contact with it should be disposed of in accordance with local requirements.

7. LICENCE HOLDER

CTS Ltd., 4 Haharash St., Hod-Hasharon, 4524075.

8. MANUFACTURER

Sintetica SA, VIA Penate 5, CH-6850 Mendrisio, Switzerland

9. REGISTRATION NUMBER

166-60-35988
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