SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ADRENALINE S.A.L.F. 1 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection contains:
Adrenaline (Epinephrine) 1 mg

Excipients with known effect
Sodium chloride 8mg/1ml
Sodium metabisulphite 1mg/ml
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is clear, colourless, almost colourless or slightly yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADRENALINE S.A.L.F. 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 S.A.L.F. 1 mg/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 S.A.L.F. 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.
However, the presence of sulphites and the possibility of allergic reactions do not prevent use of the medicinal product for the treatment of severe allergic reactions or in other emergency situations. The possibility that the patient may develop adverse reactions to sulphites should be considered in asthmatics who show a deterioration in respiratory function after administration of the solution (see section *4.4 Special warnings and precautions for use*).
Use of this medicinal product is contraindicated in patients with cardiac insufficiency, cardiac dilatation, coronary insufficiency and in most patients with cardiac arrhythmias, as this would further increase the need for oxygen of the myocardium.
The use of adrenaline is generally contraindicated in cases of hyperthyroidism and in the presence of serious hypertension as these patients are more susceptible to the adverse effects of this medicinal product.
Use should be avoided in patients with phaeochromocytoma, as they may develop severe hypertension.
The medicinal product is also contraindicated in patients with organic brain damage, such as cerebral arteriosclerosis, and in patients with angle-closure glaucoma.
Adrenaline should be avoided in patients undergoing anaesthesia with halogenated hydrocarbons (chloroform, trichloroethylene) or cyclopropane. Adrenaline should be used with extreme caution with other halogenated hydrocarbon anaesthetics, such as halothane. Combination with this medicinal product can cause serious arrhythmias (see section *4.5 Interaction with other medicinal products and other forms of interaction*).

Administration of adrenaline is contraindicated during labour. During the last month of pregnancy and during labour, adrenaline inhibits uterine tone and contractions.
There are, however, no absolute contraindications in extremely serious situations.

4.4 Special warnings and precautions for use

Adrenaline should be administered with special caution in patients with cerebrovascular insufficiency and in patients with heart disease such as angina pectoris or myocardial infarction, in patients with chronic pulmonary disease and in patients with urinary difficulty due to prostatic hypertrophy.
The hypokalaemic effect of adrenaline may be potentiated by other drugs that cause potassium loss, such as corticosteroids, diuretics, aminophylline or theophylline, and periodic checks are therefore advisable.
Hypokalaemia may increase susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides (see section *4.5 Interaction with other medicinal products and other forms of interaction*).
In diabetic patients, doses should be monitored and special caution exercised due to the possible adverse reactions that may occur, particularly in relation to metabolic changes.
Special caution is recommended in elderly patients who are more prone to the adverse effects of this medicinal product.
Repeated local injections can cause necrosis at the injection site due to vascular vasoconstriction. Injection sites should be alternated.
This medicine should not be injected intramuscularly into the buttocks, as adrenaline-induced vasoconstriction reduces the oxygen tension of tissues, enabling anaerobic *Clostridium welchii* which may be present on the buttocks to multiply and lead to gas gangrene. Due to its vasoconstrictive properties, adrenaline should not be administered into peripheral areas of the body, such as fingers and toes, ear lobe, nose or penis.
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.

Changes in laboratory test results
It should be borne in mind that epinephrine (adrenaline) can alter the values of the following blood test results: increased glucose, falsely increased bilirubin values, increased cholesterol, increased lactic acid (in the form of lactate) and uric acid (urate) - possibly by renal efferent vasoconstriction - and reduced insulin. Although increases in the lactic acid concentration are generally small, adrenaline overdose may be associated with lactic acidosis.

Furthermore, as approximately 40% of adrenaline is metabolised to vanillylmandelic acid, urinary vanillylmandelic acid excretion increases if adrenaline is administered.
After adrenaline administration, the determination of catecholamines in urine will also be altered.

Use in sports
Adrenaline is a substance which may give a positive result in anti-doping tests and its use is considered prohibited in competition. However, the use of adrenaline is permitted when administered in association with local anaesthetics or in preparations for local use, for example for nasal or ophthalmological administration.

Important information about some of the ingredients
This medicine may rarely cause severe hypersensitivity reactions and bronchospasm because it contains sodium metabisulfite.
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

- *Adrenergic blockers*
  Due to antagonism with adrenaline, adrenergic blockers and adrenaline should not be administered in combination, except in the case of adrenaline intoxication. Concomitant administration of adrenaline and beta-blockers, such as propranolol, causes an increase in blood pressure due to vasoconstriction, followed by reflex bradycardia and occasionally arrhythmias. The bronchodilator effect is also inhibited. In contrast, after the administration of cardioselective beta-blockers, such as metoprolol, blood pressure and heart rate are minimally affected. Low doses of cardioselective beta-blockers seem not to interfere with adrenaline- induced bronchodilation, although the effect at higher doses has not been established.

- *General anaesthetics such as chloroform, halothane or cyclopropane*
  These anaesthetics may sensitise the myocardial tissue. This increase in cardiac irritability may result in the occurrence of ventricular arrhythmias, tachycardia and ventricular fibrillation (see section *4.3 Contraindications*).

- *Cardiac glycosides*
  Concomitant administration with digitalis glycosides increases the possibility of ventricular arrhythmias due to additive effects. In addition, adrenaline has a hypokalaemic effect which may increase susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides (see section *4.4 Special warnings and precautions for use*).

- *Drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, aminophylline or theophylline*
  The hypokalaemic effect of adrenaline is potentiated and it is recommended that patients have their plasma potassium concentrations monitored (see section *4.4 Special warnings and precautions for use*).

- *Antidepressants*
  This concerns mainly tricyclic antidepressants, which decrease adrenaline reuptake at the adrenergic endings, with an intense pressor response.

- *Catechol-O-methyltransferase (COMT) inhibitors*
  Adrenaline is metabolised to a large extent by the enzyme catechol-O-methyltransferase or COMT. The combination of adrenaline and a COMT inhibitor may potentiate the chronotropic and arrhythmogenic effects of adrenaline.

- *Guanethidine*
  The combination of guanethidine and adrenaline may cause a severe hypertensive reaction. If possible, combined administration should be avoided. However, if they are used concomitantly, blood pressure should be monitored.

- *Monoamine oxidase inhibitors (MAOIs)*
  MAO metabolises and inactivates adrenaline. However, MAOIs do not markedly potentiate the effects of adrenaline. In spite of this, it is not advisable to administer MAOIs and adrenaline in combination.

- *Hypoglycaemic drugs*
  Due to antagonism with respect to adrenaline, which induces hyperglycaemia, higher doses of insulin or synthetic hypoglycaemic agents are required.

4.6 Fertility, pregnancy and lactation

Pregnancy
FDA pregnancy category C.
No adequate and well-controlled studies have been conducted in humans. However, animal studies have demonstrated that adrenaline produces teratogenic effects when administered at doses several times higher than the human doses. The use of this medicinal product during pregnancy is only accepted if the potential benefits justify the possible risks to the foetus.
If used during pregnancy, adrenaline may cause anoxia to the foetus. It is not recommended for use during labour, as its relaxing effect on the muscles of the uterus may delay the second stage by inhibiting spontaneous or oxytocin-induced contractions, and may even cause a prolonged period of uterine atony with haemorrhage if doses are high.

Lactation
Adrenaline is excreted in breast milk. Due to the potential risk of serious adverse effects in the infant, it is recommended that breast-feeding be discontinued or administration be avoided.

4.7 Effects on ability to drive and use machines
Not relevant.

4.8 Undesirable effects
The most common undesirable effects are cardiovascular and nervous system disorders, which occur in up to 10% of patients.
It should be borne in mind that the occurrence and severity of these effects depend on the route of administration, with the subcutaneous and intramuscular routes having a lower incidence than the intravenous and intracardiac routes.

- *Common (≥ 1/100 to < 1/10)*
Nervous system disorders: fear, anxiety, throbbing headache, dyspnoea, sweating and nausea, vomiting, trembling and dizziness.
Cardiovascular disorders: tachycardia, palpitations, pallor, a (modest) increase in blood pressure. These manifestations are not serious and disappear with rest, calm and reassurance of the patient.

- *Uncommon (≥ 1/1,000 to < 1/100)*
Cardiovascular disorders: hypertension, which could lead to cerebral haemorrhage or acute cardiac insufficiency with pulmonary oedema, angina pectoris (even with doses common in patients with coronary insufficiency), ventricular arrhythmias, tachycardia and ventricular fibrillation, which can be fatal.
Difficulty urinating, necrosis at the injection site, metabolic acidosis and renal failure have also been reported in some cases.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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
Symptoms
An overdose of adrenaline can cause sudden increases in blood pressure and tachycardia, which may occur after an initial phase of transient bradycardia. Potentially fatal arrhythmias can also occur.
The adverse reactions to adrenaline are of short duration due to its rapid inactivation by the body, and the treatment of these adverse reactions is therefore supportive.
Administration of a quick-acting alpha-blocker, such as phentolamine, followed by a beta-blocker, such as propranolol, has been shown to counteract the pressor and arrhythmogenic effects of adrenaline.

Emergency treatment and antidotes
If there is a sudden increase in blood pressure, vasodilators such as nitrites can be administered. Angina attacks are treated with sublingual nitroglycerin, while ventricular fibrillation requires the use of an electrical defibrillator.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cardiac stimulants, excluding cardiac glycosides: adrenergic and dopaminergic agents.
ATC code: C01C A
Adrenaline is a sympathomimetic amine. It has vasoconstrictor, positive chronotropic and inotropic, bronchodilator and hyperglycaemic activity.

Mechanism of action
Adrenaline acts by binding to its (α and β) receptors on a large number of body systems: cardiovascular, bronchial, gastrointestinal, renal, uterine, ocular, nervous system, metabolism and blood composition. Although some of these actions have no therapeutic application, they should be borne in mind as they may be related to the occurrence of adverse effects.

Pharmacodynamic effects
Actions on the cardiovascular system
The effects depend on the route of administration and the dose.

Effects on blood pressure
Adrenaline causes an increase in blood pressure due to its positive inotropic, positive chronotropic and vasoconstrictor actions.
Low doses of adrenaline (0.1 µg/kg) may cause blood pressure to fall because β2 receptors, which cause vasodilation, are more sensitive to adrenaline. The pulse rate at first accelerates but, as the blood pressure rises, is slowed by compensatory vagal discharge.

Vascular effects
Adrenaline causes vasoconstriction mainly of precapillary sphincters and smaller arterioles, although it also affects the veins and large arteries. Adrenaline administration decreases cutaneous blood flow.

Cardiac effects
Adrenaline is a very potent cardiac stimulant. It acts directly on the β1 receptors of the myocardium, increasing the heart rate and rhythm. The myocardium is more excitable, systole is shorter and cardiac contraction is more forceful, cardiac output is enhanced and the work of the heart and its oxygen consumption are also markedly increased.
In addition, adrenaline causes an increase in coronary circulation.

Action on the bronchial system
Adrenaline acts on β2 receptors, causing relaxation of the smooth muscle, and on α receptors, contracting the vessels of the bronchial mucosa, thereby decreasing congestion and oedema. Adrenaline acts via cyclic AMP, which activates a kinase chain, and by inhibiting degranulation of mast cells.

Action on the gastrointestinal tract
Catecholamines have depressant effects on the gastrointestinal muscles (β1 and α effects).

Action on the kidney and urinary tract
Adrenaline causes a marked reduction in renal blood flow (vasoconstriction of the afferent and efferent glomerular arterioles, α effect), while the volume of glomerular filtrate is unchanged. Urine volume is generally unchanged. Adrenaline relaxes the (detrusor) muscle of the bladder and contracts the sphincter, and may therefore contribute to retention of urine in the bladder.

Action on the uterus
During the last month of pregnancy and during labour, adrenaline inhibits uterine tone and contractions.

Action on the eye
Adrenaline produces mydriasis (stimulation of the radial fibres of the iris, α effect) and has the property of decreasing intraocular pressure in normal individuals and especially in glaucoma.

Action on the nervous system
Adrenaline can cause restlessness and apprehension due rather to the occurrence of tachycardia or palpitations than to direct action on the central nervous system.
Adrenaline is able to facilitate neuromuscular junction transmission.

Metabolic actions
Adrenaline causes a large number of changes in metabolism.

The injection of adrenaline produces hyperglycaemia (and sometimes glycosuria). It inhibits the secretion of insulin and increases the secretion of glucagon. Muscle glycogen is also converted into lactic acid, which passes into the blood, thereby increasing the blood lactate level.

Furthermore, adrenaline increases the concentration of free fatty acids in blood by stimulating β1 receptors in adipocytes. The calorigenic action of adrenaline (increase in metabolism) is reflected by an increase of 20-30% in oxygen consumption after administration of the usual doses.

Actions on blood composition
Adrenaline can reduce circulating plasma volume and therefore increase erythrocyte and plasma protein concentrations. This effect has been observed in the presence of shock, haemorrhage, hypotension and anaesthesia.
In addition, it produces a decrease in the number of eosinophils in the circulating blood and causes aggregation of blood platelets.

5.2 Pharmacokinetic properties
Absorption
When administered by intravenous injection, bioavailability is 100%.
After subcutaneous administration of adrenaline, a relatively slow absorption process takes place. This can be accelerated by massage at the injection site. Adrenaline reaches detectable systemic levels 5-10 minutes after subcutaneous administration and the peak plasma concentration in 20-40 minutes. Absorption is faster and more active after intramuscular administration.
Adrenaline does not act when administered by ingestion or sublingually.

Distribution
Injected adrenaline disappears rapidly from the circulation with an extremely short half-life of approximately 20 seconds. It is distributed to all tissues, especially the heart, liver, kidney and spleen, but only very small amounts reach the brain due to difficulty crossing the blood-brain barrier.
Catecholamines are taken up by nerve endings by active transport and form deposits or pools. There are two types of uptake: neuronal uptake (mainly in organs with extensive sympathetic innervation, such as the heart, vessels and spleen, occurring with low concentrations of catecholamines and by active transport), and extraneuronal uptake (especially in organs such as the liver, kidney, intestine and heart which have a high content of the enzyme catechol-O- methyltransferase, which rapidly inactivates catecholamines, as a result of which they are metabolised rather than stored).

Metabolism or biotransformation
Catecholamines are metabolised mainly by two enzymes, catechol-O-methyltransferase (extraneuronal) and monoamine oxidase (intraneuronal), which lead to their inactivation with the formation mainly of vanillylmandelic acid. These processes take place to a large extent in the liver. The transformations of adrenaline lead to its pharmacological inactivation.

Elimination
Adrenaline and its metabolites are excreted mainly in the urine. The metabolites found in greatest quantity are conjugated metanephrine (around 40%) and vanillylmandelic acid (another 40%). Small amounts of free metanephrine, dihydroxymandelic acid, methoxyhydroxyphenylglycol and unchanged adrenaline (around 5% of the administered dose) are also eliminated.

Fifty per cent of the administered dose is excreted in 6 hours and the rest in 18 hours, and very small amounts are excreted in the faeces.
In patients with phaeochromocytoma, adrenaline is eliminated in the urine in much larger amounts than in healthy subjects.

5.3 Preclinical safety data
No preclinical studies have been performed with ADRENALINE S.A.L.F. 1 mg/ml Solution for Injection.
In acute toxicity studies performed in mice and rats after intravenous administration, LD50 values of 1780 and 82 µg/kg were reached, respectively. After subcutaneous administration, the values obtained in mice and rats were 11100 and 8300 µg/kg, respectively.
In a multiple-dose toxicity study of adrenaline bitartrate administered via the subcutaneous route, the lowest published toxic dose in rats was 76 mg/kg/42 days intermittently, with toxic effects to the heart, liver and intermediary metabolism being observed.
In another repeated-dose toxicity study in rats and mice, the clinical signs related to adrenaline that were observed included increased respiratory rate, respiratory epithelial lesions, uterine atrophy and increased weight of the adrenal glands, heart and liver. At two years, mean body weights and the survival rate were similar for the treated animals and the control group.
It can be concluded from the effects observed in different studies of chronic toxicity in experimental animals that the cardiovascular system and the eyes are target organs for adrenaline toxicity.
Studies of mutagenicity and carcinogenesis have shown negative results.
Reproduction studies have been performed with subcutaneous adrenaline bitartrate in mice, with the results showing negative effects on spermatogenesis.
Some studies in experimental animals have demonstrated foetotoxic and teratogenic effects when adrenaline was administered at doses many times higher than the human doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride,
Sodium metabisulfite,
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
The product should be used immediately after dilution.

Shelf life after first opening of the pack
The product should be administered immediately after opening.

6.4 Special precautions for storage
Store below 25ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container
Glass ampoules.
Each pack contains 5 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. MARKETING AUTHORISATION HOLDER

RAZ PHARMACEUTICS LTD., 6 Hamatechet st., Kadima, Israel.

8. MANUFACTURER

S.A.L.F. S.p.A. Laboratorio Farmacologico, Cenate Sotto (BG), Italy.

REGISTRATION NUMBER
160-10-34515-00

Revised in March 2021 according to MOHs guidelines.

RAZS3124-01

JFIADRERAZ NO-6025A3 r3 Piz