SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DEVA ADRENALIN 1 mg/ml solution for IM/IV/SC/Intraocular injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml ampoule contains:
Active ingredient:
Epinephrine 1 mg

Excipients:
Sodium chloride 9 mg
See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM
Solution for IM/IV/SC and intraocular injection
Clear, transparent solution free from visible particles in a colorless glass ampoule

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
DEVA ADRENALIN is indicated for the following conditions:

- Cardiac arrest and cardiopulmonary resuscitation

If artificial respiration and open or closed chest compressions are ineffective, DEVA ADRENALIN can be administered intravenously, intracardiac, or endotracheally after sodium bicarbonate has been administered intravenously.

- Anaphylactic shock and acute allergic reactions

It is used as a physiological antagonist of histamine in cases of angioedema, drug and serum reactions, insect stings, and other allergens. It should not be administered subcutaneously if shock is present.

Additionally, an H1 receptor antagonist (chlorpheniramine) should be administered intravenously to the patient in shock.

- Stopping capillary (superficial) bleeding in the skin and mucous membranes

Administered locally as a solution.

- Extending the duration of action of local anesthetics

It is added by dentists as a vasoconstrictor.

- Initiation and maintenance of mydriasis during intraocular surgery

It is indicated for the initiation and maintenance of mydriasis during intraocular surgery.

4.2 Posology and method of administration
Dosage/frequency and duration of administration:
- Anaphylaxis:

If the cause of the allergy is a drug administered subcutaneously or intramuscularly, DEVA ADRENALIN injection can be administered at the same sites to delay and reduce absorption.

The initial doses of DEVA ADRENALIN should be small and can be increased if necessary. However, the dose given at one time should not exceed 1 mg.

DEVA ADRENALIN is injected intramuscularly or subcutaneously into the anterolateral aspect of the thigh. The injection can be repeated every 5 to 10 minutes as needed. For intramuscular administration, a sufficiently long needle (at least 1/2 inch to 5/8 inch) should be used to ensure the injection is administered into the muscle. With repeated doses titrated according to effect, the patient is clinically monitored for the severity of the allergic reaction and the potential cardiac effects of the drug.

Repeated injections into the same area should be avoided, as the resulting vasoconstriction may cause tissue necrosis.

Adults and children weighing 30 kg or more: 0.3 to 0.5 mg (0.3 to 0.5 ml) of undiluted DEVA ADRENALIN is administered intramuscularly or subcutaneously in the anterolateral aspect of the thigh, up to a maximum of 0.5 mg (0.5 ml) per injection. if necessary, the dose may be repeated every 5 to 10 minutes.

Children under 30 kg: 0.01 mg/kg (0.01 ml/kg) of undiluted DEVA ADRENALIN administered intramuscularly or subcutaneously in the anterolateral part of the thigh up to a maximum of 0.3 mg (0.3 ml), if necessary, the dose may be repeated every 5 to 10 minutes.

- Dosage in case of cardiac arrest:

For cardiac resuscitation in adults, 0.5-1 mg (0.5-1 ml) of DEVA ADRENALIN diluted is injected intravenously or intracardiac. The intravenous route is preferred to avoid interfering with cardiac massage. 1-2 mg (1-2 ml) of DEVA ADRENALIN is instilled into the trachea via an endotracheal tube after being mixed with 10 ml of sterile distilled water, or 0.3 mg (0.3 ml) of DEVA ADRENALIN is administered subcutaneously after the initial intravenous injection, or it is administered as an intravenous infusion at a rate of 1-4 mcg/min.

- Dosage for initiating and maintaining mydriasis during intraocular surgery:

Epinephrine must be diluted before intraocular use. To create an epinephrine concentration between 1:100,000 and 1:1,000,000 (10 mcg/ml to 1 mcg/ml), dilute 1 ml of epinephrine 1 mg/ml in 100 to 1000 ml of ophthalmic irrigation solution (1:1000) is diluted. The irrigation solution is used as required for the surgical procedure.

After dilution in an ophthalmic irrigation solution, epinephrine can also be injected intracameral as a 0.1 ml bolus dose at a dilution of 1:100,000 to 1:400,000 (10 mcg/ml to 2.5 mcg/ml).

- Other administration methods and dosages:

As a local hemostatic, epinephrine solutions at concentrations of 1:50,000 (0.002%) to 1:1,000 (0.1%) are applied to skin, mucous membranes, and tissue surfaces as wet dressings or sprays. Epinephrine is added to local anesthetic solutions at a ratio of 1:500,000-1:50,000. The most commonly used concentration is 1:200,000.

DEVA ADRENALIN 1 mg/ml IM/IV/SC/Intraocular Injection Solution, 1 ampoule containing 1000 ml diluted with 5% Dextrose Intravenous Infusion Solutionto prepare an infusion solution with a concentration of 0.001 mg/ml, or with 5% Dextrose + 0.9% NaCl Intravenous Infusion Solution to prepare an infusion solution with a concentration of 0.001 mg/ml by diluting the contents of 1 ampoule in 1000 ml.

Method of administration:
DEVA ADRENALIN can be administered subcutaneously or intramuscularly. If administered intramuscularly, the gluteal muscles should not be used. (This area of skin may be colonized by anaerobic microorganisms, and the vasoconstrictor effect of DEVA ADRENALIN may cause hypoxia, accelerating the development of *Clostridium welchii* infection.)

In emergencies, DEVA ADRENALIN can be diluted and administered as a very slow intravenous injection. In cases of cardiac arrest, diluted epinephrine solution can be administered by intracardiac injection or endotracheal instillation. When injected into the heart, cardiac massage should also be performed. This ensures that the drug enters the coronary circulation. Epinephrine aerosol can be administered by oral inhalation using a vaporizer or IPPB device.

Epinephrine solutions used for this purpose are more concentrated and should not be injected systemically. DEVA ADRENALIN can be diluted and applied locally to the skin, mucosa, and tissue surfaces. Wet dressings or sprays are used for this purpose. The epinephrine dose is expressed by the amount of epinephrine in epinephrine salts.

Additional information for specific populations:
Renal impairment:
No data available.

Hepatic impairment:
No data available.

Pediatric population:
- Anaphylaxis:

Clinical usage data supports weight-based dosing for the treatment of anaphylaxis in pediatric patients, and other reported clinical experience with epinephrine suggests that adverse reactions seen in children are similar in nature and magnitude to those expected and reported in adults.

- Dosage in case of cardiac arrest:

In children, 0.005-0.01 mg/kg DEVA ADRENALIN is injected intracardially or 0.01 mg/kg DEVA ADRENALIN is administered intravenously. For this purpose, a ready-made ampoule with a concentration of 1:10,000 should be used. This prevents dilution errors.

Not for use in children under 2 years of age. Not recommended for use in children under 12 years of age except in emergencies.

- Dosage for initiating and maintaining mydriasis during intraocular surgery:

The safety and efficacy of epinephrine (at a dilution of 1:100,000 to 1:400,000) for the initiation and maintenance of mydriasis during intraocular surgery in pediatric patients has been

established. The use of epinephrine for the initiation and maintenance of mydriasis during intraocular surgery in pediatric patients is supported by adequate and well-controlled studies in adults and uncontrolled studies in pediatric patients.

Geriatric population:
The recommended dose for adults is applied with caution.

- Dosage for initiating and maintaining mydriasis during intraocular surgery:

No general difference has been observed between the elderly and other patients regarding its use for the initiation and maintenance of mydriasis during intraocular surgery.

4.3 Contraindications
This product is contraindicated in patients with hypersensitivity to the active substance or any of the excipients listed in Section 6.1.

Since this product is designed for use in life-threatening emergencies, contraindications are relative.

- Use on fingers, toes, ears, nose, genital area, or buttocks due to the risk of ischemic tissue necrosis.
- Do not use if the color of the solution has changed.

4.4 Special warnings and precautions for use
This product is for emergency use only, and patients require medical supervision after administration.

The IM route is generally preferred for the initial treatment of anaphylaxis, while the IV route is generally more appropriate in an intensive care unit or emergency department setting. If epinephrine 0.1 mg/ml (1:10000) injection is not available, epinephrine 1 mg/ml (1:1000) solution must be diluted to 0.1 mg/ml (1:10000) before IV use. The IV route should be used with extreme caution for epinephrine injection and is best reserved for specialists familiar with IV epinephrine administration.

Epinephrine; hyperthyroidism, *diabetes mellitus*, narrow-angle glaucoma, pheochromocytoma, hypertension, hypokalemia, hypercalcemia, severe renal failure, prostatic adenoma causing residual urine, cerebrovascular disease, elderly patients, patients in shock (except anaphylactic shock), organic heart disease or cardiac dilatation (severe angina pectoris, obstructive cardiomyopathy, hypertension), as well as arrhythmia, organic brain damage, or cerebral arteriosclerosis. Anginal pain may be triggered in the presence of coronary insufficiency.

Epinephrine should be used with caution during the second stage of labor (see Section 4.6).

Epinephrine may cause or exacerbate hyperglycemia; blood glucose should be monitored, especially in diabetic patients.

Repeated local application may cause necrosis at the injection sites.

Prolonged use may cause metabolic acidosis, renal necrosis, and tachyphylaxis.

Epinephrine should be avoided or used with extreme caution in patients anesthetized with halothane or other halogenated anesthetics due to the risk of triggering ventricular fibrillation. Accidental intravascular injection may cause cerebral hemorrhage due to a sudden increase in blood pressure.

To assess the response to epinephrine, the patient should be monitored as soon as possible for parameters such as pulse, blood pressure, ECG, and pulse oximetry.

The best site for IM injection is the anterolateral aspect of the middle third of the thigh. The needle used for injection must be long enough to ensure that epinephrine is injected into the muscle.

Damage caused by undiluted intraocular solution
Epinephrine must be diluted before intraocular use. Other epinephrine products containing sodium bisulfite have been associated with corneal endothelial damage when used at undiluted concentrations (1 mg/ml) in the eye. Although DEVA ADRENALIN does not contain sulfite or preservatives, it should still be used with caution.

DEVA ADRENALIN contains less than 1 mmol (23 mg) of sodium per dose; i.e., it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
Sympathomimetic agents/Oxytocin
Epinephrine should not be administered concomitantly with oxytocin or other sympathomimetic agents due to the potential for additive effects and increased toxicity.

Alpha-adrenergic blocking agents
Alpha blockers such as phentolamine antagonize the vasoconstrictive and hypertensive effects of epinephrine.

Beta-adrenergic blocking agents
Severe hypertension and reflex bradycardia may occur with non-selective beta-blocking drugs such as propranolol due to alpha-mediated vasoconstriction.

Beta blockers, especially non-cardioselective agents, also antagonize the cardiac and bronchodilator effects of epinephrine. Patients with severe anaphylaxis who are using non-cardioselective beta blockers may not respond to epinephrine treatment.

General anesthetics
Administration of epinephrine to patients receiving halogenated hydrocarbon general anesthetics, which increase cardiac irritability and render the myocardium sensitive to epinephrine, may cause arrhythmias such as ventricular premature contractions, tachycardia, or fibrillation (see Section 4.4).

Antidepressant agents
Tricyclic antidepressants such as imipramine may enhance the effects of epinephrine, particularly on heart rhythm and rate.

Non-selective MAO inhibitors
They generally moderately increase the blood pressure-raising effect of epinephrine.

Selective MAO-A inhibitors
Linezolid (by extrapolation from non-selective MAO inhibitors): Risk of increased blood pressure.

Antihypertensive agents
Epinephrine reverses the antihypertensive effects of adrenergic neuron blockers, such as guanethidine, with a risk of severe hypertension. Epinephrine raises blood pressure and may antagonize the effects of antihypertensive drugs.

Phenothiazines
Epinephrine should not be used to prevent circulatory collapse or hypotension caused by phenothiazines: the reversal of epinephrine's blood pressure-raising effects may cause blood pressure to drop even further.

Other medicinal products
Epinephrine should not be used in patients receiving high doses of other drugs that sensitize the heart to arrhythmias (e.g., cardiac glycosides). Some antihistamines (e.g., diphenhydramine) and thyroid hormones may increase the effects of epinephrine, particularly on heart rhythm and rate.

Hypokalemia
The hypokalemic effect of epinephrine may be potentiated by other drugs that cause potassium loss, including corticosteroids, diuretics that increase potassium excretion, aminophylline, and theophylline.

Hyperglycemia
Epinephrine-induced hyperglycemia may cause loss of blood sugar control in diabetic patients treated with insulin or oral hypoglycemic agents.

Additional information for specific populations:
No data available.

Pediatric population:
No data available.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category: C

Women of childbearing potential/Birth control (Contraception)
There is insufficient data available. Therefore, the potential risk to humans is unknown.

Pregnancy
Teratogenic effects have been observed in animal studies.

Epinephrine crosses the placenta. There are findings of a slight increase in the incidence of congenital anomalies. Epinephrine injection may cause anoxia, fetal tachycardia, cardiac irregularities, extrasystoles, and increased heart sounds. Epinephrine generally inhibits spontaneous or oxytocin-induced uterine contractions, which may delay the second stage of labor. When taken in doses sufficient to reduce uterine contractions, the drug may cause prolonged uterine atony with bleeding. Therefore, parenteral epinephrine should not be used during the second stage of labor.

Lactation
Epinephrine passes into breast milk. Mothers who receive epinephrine injections should avoid breastfeeding.

Reproductive ability/Fertility
The effect of epinephrine on fertility is unknown.

4.7 Effects on the ability to drive and use machines
It is recommended that individuals affected by the administration of DEVA ADRENALIN refrain from operating vehicles or machinery.

4.8 Undesirable effects
The side effects of epinephrine are primarily related to the stimulation of both alpha and beta adrenergic receptors. The occurrence of undesirable effects depends on the individual sensitivity of the patient and the relevant dose.

Metabolic and nutritional disorders
Unknown: Hyperglycemia, hypokalemia, metabolic acidosis

Psychiatric disorders
Unknown: Anxiety, irritability, fear, hallucinations

Nervous system disorders
Unknown: Headache, tremor, dizziness, syncope

Epinephrine increases rigidity and tremor in patients with Parkinson's syndrome.

Eye disorders
Unknown: Mydriasis

Epinephrine products containing sodium bisulfite have been associated with corneal endothelial damage when used at undiluted concentrations (1 mg/ml) for the eye. Although DEVA ADRENALIN does not contain sulfite or preservatives, it should still be used with caution.

Cardiac disorders
Unknown: Palpitations, tachycardia
At high doses or in epinephrine-sensitive patients: cardiac dysrhythmia (sinus tachycardia, ventricular fibrillation/cardiac arrest), acute angina attacks, and acute myocardial infarction.

Vascular diseases
Unknown: Pallor, coldness in the extremities

For patients on high doses or those sensitive to epinephrine: hypertension (with risk of cerebral hemorrhage), vasoconstriction (e.g., cutaneous, in the extremities, or in the kidneys)

Respiratory, thoracic and mediastinal disorders
Unknown: Dyspnea

Gastrointestinal diseases
Unknown: Nausea, vomiting

General disorders and disorders related to the application site
Unknown: Sweating, fatigue

Repeated local injections may cause necrosis in the injection sites as a result of vascular constriction.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and treatment
Overdose of epinephrine or accidental intravenous administration may cause severe hypertension. This may result in potentially fatal cerebral, cardiac, or vascular events (e.g., cerebral hemorrhage, dysrhythmias such as transient bradycardia followed by tachycardia that may lead to arrhythmia, myocardial necrosis, acute pulmonary edema, renal failure).

The effects of epinephrine can be prevented by administering fast-acting vasodilators, fast-acting alpha-adrenergic receptor blocking agents (e.g., phentolamine), or beta-adrenergic receptor blocking agents (e.g., propranolol), depending on the patient's condition. However, due to the short half-life of epinephrine, treatment with these drugs may not be necessary. In cases of prolonged hypotensive reactions, another vasopressor agent such as norepinephrine may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Adrenergic and dopaminergic agents, epinephrine
ATC code: C01CA24
Epinephrine is a naturally occurring catecholamine secreted by the adrenal medulla in response to exertion or stress. It is a sympathomimetic amine that is a potent agonist of both alpha and beta adrenergic receptors, and therefore its effects on target organs are complex. It is used for the rapid relief of hypersensitivity reactions to allergies or idiopathic or exercise-induced anaphylaxis. Epinephrine causes glucose to be released into the circulation, and oxygen consumption increases. Blood flow to the kidneys, mucosa, and skin decreases.

Epinephrine has a potent vasoconstrictor effect via alpha-adrenergic stimulation. This activity counteracts vasodilation and increased vascular permeability, which are the main pharmacological indicators in anaphylactic shock and lead to intravascular fluid loss and subsequent hypotension.

Epinephrine stimulates bronchial beta-adrenergic receptors and has a potent bronchodilator effect. Epinephrine also alleviates itching, urticaria, and angioedema associated with anaphylaxis.

The overall effect of epinephrine depends on the dose used and can be complicated by homeostatic reflex responses.
Epinephrine causes mydriasis when administered intraocularly or parenterally.

Hypotension associated with septic shock:
Fourteen clinical studies in the literature have documented that epinephrine increases mean arterial pressure (MAP) in patients with hypotension associated with septic shock.

Initiation and maintenance of mydriasis during intraocular surgery:
In randomized, controlled trials, patients undergoing routine cataract extraction were evaluated after receiving intraocular irrigation with epinephrine diluted up to 1:1,666,666 (0.6 mcg/ml) or without epinephrine. Patients were also evaluated after receiving bolus intracameral epinephrine injections diluted at 1:25,000 (40 mcg/ml) and 1: 400,000 (2.5 mcg/ml).

In patients with similar initial pupil diameters, mydriasis was preserved by an average of one to two millimeters better in eyes receiving epinephrine, regardless of the use of preoperative mydriatic agents. Pupil constriction of 5 mm or less occurred in patients who did not receive epinephrine.

The mean heart rate and blood pressure did not show a significant difference between patients receiving epinephrine and controls, and no increase in the incidence of ventricular arrhythmia was observed in patients receiving epinephrine.

5.2 Pharmacokinetic properties
General characteristics
Absorption
Epinephrine has a rapid onset of action following intramuscular administration, and its absorption from the intramuscular site in shock patients is faster and more reliable than from the subcutaneous site. The plasma half-life is approximately 2-3 minutes. However, when administered by subcutaneous or intramuscular injection, local vasoconstriction may delay absorption, so that effects may last longer than the half-life would indicate.

Epinephrine has a rapid onset and short duration of action when administered parenterally or intraocularly.

The extent of systemic exposure in humans at the approved intraocular dose has not been evaluated; however, significant systemic concentrations or plasma exposure of epinephrine are not expected when administered intraocularly.

Distribution
Epinephrine rapidly distributes to the heart, spleen, various glandular tissues, and adrenergic nerves. Approximately 50% binds to plasma proteins. Epinephrine crosses the placenta and enters the fetal circulation.

Biotransformation
Epinephrine is rapidly inactivated in the body, primarily in the liver, by the enzymes catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).

Elimination
Most of the epinephrine dose is excreted in the urine as metabolites. After injection, the onset and peak effect are rapid and short-lived (1-2 hours). Elimination occurs primarily through liver metabolism and sympathetic nerve endings, with a small amount excreted unchanged in the urine.

Linearity/nonlinearity
No data available.

5.3. Preclinical safety data
There is no additional relevant information beyond what is included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injection

6.2 Incompatibilities
It is rapidly denatured by oxidizing agents and alkalis, including adrenaline/epinephrine, sodium bicarbonate, halogens, nitrates, nitrites, and iron, copper, and zinc salts.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 25°C, protected from light.

Do not store in the refrigerator; avoid freezing.

6.5 Nature and contents of container
The primary packaging material for our product is a 2 ml colorless, white-banded, Type I glass ampoule. 10 ampoules are provided in a cardboard box with a separator, along with the package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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2024/350

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorization: 17/09/2024
Date of last renewal:

10. DATE OF REVISION OF THE TEXT