SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml of solution contains:
Dopamine hydrochloride 40 mg.

Each ampoule of 5 ml contains:
200 mg of Dopamine hydrochloride.

Excipients with known effect:
Each 1ml of solution contains 3.54 mg of sodium and 1 mg of potassium metabisulfite.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear solution and not more intensely colored than B6 or Y6 solution.

4. CLINICAL INFORMATION

4.1 Therapeutic indications
Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml is used for the treatment of states of shock of different nature:
- Post myocardial infarction cardiogenic shock, a shock caused by a heart attack,
- Surgical shock, caused by a surgical operation,
- Hypovolemic or haemorrhagic shock, caused by a decrease in blood volume due to a hemorrhage,
A shock is characterized by a sharp decrease in blood pressure in response to a reduced blood flow in the organism.

4.2 Posology and method of administration
Hypovolaemia should be fully corrected, if possible, before dopamine hydrochloride is used.
Dopamine hydrochloride MUST be diluted before administration to the patient. Dilution should be made just prior to administration.
For dilution instructions and shelf life after dilution see clause 6.6. Dopamine hydrochloride should be given via an infusion pump or another suitable metering device to control the rate of flow in drops per minute. The initial rate is 2 to 5 µg per kg body mass per minute, gradually increased by 5 to 10 µg per kg per minute according to the patient's blood pressure, cardiac output and urine output. Up to 20 to 50 µg per kg per minute may be required in seriously ill patients. A reduction in urine flow, without hypotension, may indicate a need to reduce the dose. To avoid tissue necrosis dopamine hydrochloride is best administered into a large lumen vein. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. More suitable sites should be used as rapidly as possible.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
It must not be used in patients with pheochromocytoma or hyperthyroidism and cannot be administered in the presence of untreated tachyarrhythmias and ventricular fibrillation.
Cyclopropane and halogenated hydrocarbon anesthetics should not be used together with dopamine.

4.4 Special warnings and precautions for use
Excessive administration of potassium-free solutions may cause significant hypokalemia. Intravenous administration of these solutions may cause fluid and/or solute overload, resulting in dilution of serum electrolyte concentrations, hyperhydration, congestive states or pulmonary edema.
Before treatment with dopamine hydrochloride, hypovolemia should be corrected with appropriate amounts of blood or plasma according to the indications.
During therapy with dopamine hydrochloride, it is necessary to control urine flow, cardiac output and blood pressure.
Should a disproportionate increase in diastolic blood pressure (i.e. a significant wrist pulse decrease) occur, the infusion should be reduced and the patient should be observed carefully in order to prevent a predominant undesired vasoconstrictor activity.
Dopamine hydrochloride should be infused into the largest veins, if possible, to avoid extravasation into adjacent tissues. Extravasation may cause necrosis and sores. Therefore, infusion rate should be checked.
Ischemia is reversible by infiltration of the affected area with 10 ml - 15 ml of saline solution containing 5 mg to 10 mg of phentolamine mesylate. When an extravasation occurs, a syringe with a small diameter hypodermic needle should be used to allow free infiltration of phentolamine in the ischemic zone.
Patients with previous occlusive vascular disease (atherosclerosis, arterial embolism, Raynaud's disease, cold sores, diabetic endarteritis and Buerger's disease) should be carefully observed for any change in color or temperature of the skin at the extremities. If you observe some variation in this regard and you believe that this may be the result of impaired circulation in extremities, it is necessary to evaluate the benefits of continuing the infusion with dopamine hydrochloride and the risks of a possible necrosis.
This condition can be reversed, by decreasing or stopping the infusion.
As an antidote for peripheral ischemia, in order to prevent sores and necrosis, it is advisable to infiltrate 10 or 15 ml of saline solution containing 5 or 10 mg of phentolamine as quickly as possible.
Patients treated with monoamine oxidase inhibitors (MAOIs) require a substantial reduction in the dosage (at least 1/10 of the normal dosage).
Do not add alkaline solutions to Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml.
Dextrose solutions should be used with caution in patients with a history of subclinical or manifested diabetes mellitus. Since the effect of dopamine is not known in case of reduced renal and hepatic function, in these patients careful monitoring is needed.
To avoid an inappropriate state of hypotension, dopamine infusion should be stopped gradually.
Keep the medicine out of the sight and reach of children.

Warning to athletes: the use of this drug without therapeutic necessity constitutes doping: it may cause doping effects and positivity to anti-doping tests even with therapeutic doses.

Important information about some of the ingredients:
Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml contains potassium metabisulfite; May rarely cause severe hypersensitivity reactions and bronchospasm.
Each ampoule contains less than 1 mmol (23 mg) of sodium, i.e. it is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction
Since dopamine is metabolized by monoamine oxidase (MAO), the inhibition of this enzyme for administration of MAO inhibitors prolongs and enhances the effect of dopamine. Dopamine should be used with extreme caution in patients inhaling cyclopropane or hydrocarbons derived from halogenated anesthetics due to the risk of arrhythmias.
Alpha and Beta Blockers: The cardiac effects of dopamine are antagonized by β-adrenergic blocking agents such as propranolol and metoprolol, while secondary peripheral vasoconstriction at high doses of dopamine is antagonized by α-adrenergic blocking agents. The renal and mesenteric vasodilatation is not antagonized by either α- or β-adrenergic blockers, however, in animals, it is antagonized by haloperidol and other butyrophenones, phenothiazines and opioids.
Phenytoin: Intravenous phenytoin administration in patients treated with dopamine has caused hypotension and bradycardia; some clinicians recommend using phenytoin, if clearly needed, with caution in patients receiving dopamine.
Dopamine may increase the effect of diuretics.
Ergot alkaloids must be avoided, due to the risk of excessive vasoconstriction. Tricyclic antidepressants and guanethidine may potentiate dopamine pressure response.

4.6 Pregnancy and lactation
During pregnancy and lactation the product should be used only if clearly needed, under direct medical supervision.

4.7 Effects on ability to drive and use machines
Dopamine hydrochloride does not affect the ability to drive or use machines.

4.8 Undesirable effects
Below are the possible side effects of dopamine hydrochloride, organized according to MedDRA system-organ classification. There are insufficient data to establish the frequency of each effect listed.

More common:
Cardiac disorders: ectopic heart beats, tachycardia, anginal pain, palpitations.
Gastrointestinal disorders: nausea, vomiting.
Respiratory, thoracic and mediastinal disorders: dyspnea.
Nervous system disorders: headache.
Vascular disorders: hypotension, vasoconstriction.

Less common:
Cardiac disorders: aberrant conduction, bradycardia, widening of QRS complex.
Vascular disorders: hypertension.
Diagnostic tests: azotemia.
Skin and subcutaneous tissue disorders: piloerection.

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
In case of accidental overdose, evidenced by excessive blood pressure, reduce the infusion rate or temporarily discontinue the administration until conditions are stabilized.
Since the activity of dopamine hydrochloride is extremely short, normally no further action is necessary.
If the measures taken were not enough, a short-acting alpha blocker such as phentolamine should be used.
Dopamine may cause local vasoconstriction at the infusion site, so a large-caliber vein should be chosen for infusion. The resulting ischemia is reversible by infiltration of the affected area with 10 ml - 15 ml of saline solution containing 5 mg to 10 mg of phentolamine mesylate. When an extravasation occurs, a syringe with a small diameter hypodermic needle should be used to allow free infiltration of phentolamine in the ischemic zone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Adrenergic and dopaminergic drugs, ATC code: C01CA04.
Dopamine acts as an agonist on specific dopamine receptors and on alpha and beta adrenergic receptors.
It decreases peripheral resistance and causes mesenteric and renal vasodilation.
It increases renal blood flow, glomerular filtration and urinary flow.
As regards the heart, dopamine causes an increased inotropism.
It differs from noradrenaline in the action on the region of the kidneys and from isoproterenol, as it does not increase the heart rate.
The knowledge about cardiovascular activities of dopamine involving the activation of alpha and beta adrenergic receptors, as well as dopaminergic receptors, allows to better modulate the amine infusion, which, depending on the dose, can give effects of vasoconstriction or vasodilation, cardiac stimulation, inhibition of the increase in heart rate, diuresis, natriuresis and inhibition of aldosterone circulation.

5.2 Pharmacokinetic properties
The effect of dopamine administered intravenously occurs within 5 minutes.
Its half-life is about 2 minutes.
The drug is widely distributed in the body, but it does not significantly cross the brain blood barrier.
Dopamine is metabolized in the liver, kidney and plasma by MAO (monoamine oxidase) in 3,4-dihydroxyphenylacetic acid (DOPAC) and by COMT (catechol O methyltransferase) in homovanillic acid (HVA); in small amounts it is hydroxylated in adrenergic nerve endings, thus producing norepinephrine.
The drug is rapidly excreted in the urine (approximately 80% in 24 hours), mainly in the form of HVA, DOPAC and glucuronide conjugates.

5.3 Preclinical safety data
Acute toxicity studies conducted on various animal species have shown a LD_{50} of 225 mg/kg in mice, 80 mg/kg in rats and 302 mg/kg in guinea pigs, by intravenous route.
Chronic toxicity tests performed on Beagle dogs have shown no abnormalities in blood, blood chemistry and histological parameters.
Teratogenesis studies have shown no specific fetal toxicity.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients
Sodium chloride
Potassium metabisulfite
Water for injections

6.2 Incompatibilities
Dopamine is inactivated in alkaline solutions, such as 5% bicarbonate, and is incompatible with iron salts, oxidizing agents and alkaline drugs, such as furosemide and thiopental sodium.
Incompatibility with insulin, ampicillin, amphotericin B, gentamicin sulfate, cephalothin sodium, oxacillin sodium has been reported and, therefore, mixtures with such drugs should be avoided.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.
For shelf life after dilution see clause 6.6.

6.4 Special precautions for storage
Store in the original package to protect the product from light.
Do not store above 25°C. Do not freeze.
The ampoules are intended for single use only: any unused solution should be discarded.

6.5 Nature and contents of container
Yellow glass ampoule of 5 ml.

6.6 Special precautions for disposal and other handling
Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml must be diluted prior to use with one of the following:
1. Sodium chloride 0.9%
2. Glucose 5%
3. Ringer lactate

By diluting 200 mg of Dopamine HCl (ampoule of 5 ml) to 250 ml with Sodium chloride 0.9% (saline solution) or Glucose 5% or Ringer's lactate, you get a solution which contains 0.8 mg (800 micrograms)/ml of dopamine. And according to these volumes, in compliance with executed compatibility tests:
1. Dilute 5 ml of Dopamine HCl 200 mg/5ml in 250 ml of Sodium chloride 0.9%
2. Dilute 5 ml of Dopamine HCl 200 mg/5ml in 250 ml of Glucose 5%
3. Dilute 5 ml of Dopamine HCl 200 mg/5ml in 250 ml of Ringer lactate.

Shelf life and storage after dilution:
The product is stable for 48 hours after dilution at different temperatures: 2°C -8°C, 25°C ± 2°C and 40°C ± 2°C.
From a microbiological point of view, the product should be used immediately. If not used immediately,
in-use storage times and conditions prior to use are the responsibility of the user.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER and IMPORTER
RAZ PHARMACEUTICS LTD, ISRAEL
31 Gesher Haetz, Industrial Park, Emek Hefer, Israel

8. MARKETING AUTHORISATION NUMBER
164-32-35059-00

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