

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **DOPAMINE HYDROCHLORIDE S.A.L.F. 40 MG/1 ML**

#### **1. NAME OF THE DRUG**

Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml.

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each ampoule of 5ml contains:

*Active ingredient:* Dopamine hydrochloride 200 mg

Excipients with known effect:

Dopamine Hydrochloride S.A.L.F. 40 mg/1 ml contains 9 mg/ml of sodium chloride and 1 mg/ml of potassium metabisulfite.

For the full list of excipients, see section 6.1.

#### **3. PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

#### **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.

By diluting a 200 mg ampoule 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. The product is stable for 48 hours after dilution.

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 can not 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, 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).

The solution should be clear and slightly yellow (Y6, color scale of Eur. Ph. current edition) or slightly brown (B6, color scale of Eur. Ph. current edition).

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.

Not being known the effect of dopamine 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; in rare cases, it may cause allergic-type 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  $\beta$ -adrenergic blocking agents such as propranolol and metoprolol, while secondary peripheral vasoconstriction at high doses of dopamine is antagonized by  $\alpha$ -adrenergic blocking agents. The renal and mesenteric vasodilatation is not antagonized by either  $\alpha$ - or  $\beta$ -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 Side 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 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:* high level of 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<sub>50</sub> 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.

### **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 solution should be clear and slightly yellow (Y6, color scale of Eur. Ph. current edition) or slightly brown (B6, color scale of Eur. Ph. current edition).

The ampoules are intended for single use only: any unused solution should be discarded.

#### **6.5 Nature and contents of container**

Glass ampoule of 5 ml.

#### **6.6 Special precautions for disposal and other handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

#### **7. MANUFACTURER**

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

#### **8. MARKETING AUTHORISATION HOLDER**

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

#### **9. MARKETING AUTHORISATION NUMBER**

164-32-35059-00.

**Approved in: April 2020.**

RAZS3551-00