1. NAME OF THE MEDICINAL PRODUCT

EPHEDRINE HCl STEROP 50MG/1ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule of 1 ml solution contains 50mg ephedrine hydrochloride.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, administered subcutaneously, intravenously, intramuscularly.
Aqueous, clear, uncolored solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and treatment of hypotension from spinal or epidural anesthesia and during general anesthesia, with or without a reduction in the heart rate, administered for a surgical or obstetric procedure.

4.2 Posology and method of administration

Posology

Adults and adolescents

Ephedrine must be administered at the lowest effective dose over the shortest possible period of time. Adjust the dosage of Ephedrine HCl Sterop 50mg/1ml on case-by-case basis depending on the cardiovascular and hemodynamic parameters. The following dosage is provided for guidance purposes only.

Adults:

5-25mg I.V., administered slowly.
It is recommended that Ephedrine HCl Sterop 50mg/1ml be administered in divided doses of 5-10mg until the blood pressure normalizes.
Maximum daily dose - 150 mg/24h.

Ephedrine HCl Sterop 50mg/1ml can also be administered S.C. or I.M. The dose is 25-50mg (range 10-50mg). If necessary, a second of 50mg may be administered I.M., or 10-25mg administered I.V.

Children:

The recommended pediatric dose is 3mg/kg per day (750 microgram/kg per dose) or 100mg/m² per day (25mg/m^2 per dose) in 4-6 doses per day, administered S.C. or I.V.
The bolus I.V. dose for hypotension is 0.1-0.3 mg/kg.
When administered intravenously, the injection should be given slowly.

Elderly patients

As for adults, starting from 5mg boluses.

Method of administration
Ephedrine must be used solely by or under the supervision of the anesthetist.

4.3 Contraindications
Ephedrine should not be used in case of:
* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
* Hyperexcitability, pheochromocytoma, arteriosclerosis and aneurism.
* Combination with phenylpropanolamine, phenylephrine, pseudoephedrine, methylphenidate (other indirect sympathomimetics).

The administration of ephedrine to patients who are undergoing or have undergone treatment with MAO inhibitors within the last 2 weeks is contraindicated as the combination may cause severe, possibly fatal, hypertension.

4.4. Special warnings and precautions for use
Special warnings
Ephedrine should be used with caution in case of:
* Diabetes mellitus
* Hypertension
* Prostatic hypertrophy
* Uncontrolled hyperthyroidism
* Coronary heart disease and chronic heart diseases
* Angle-closure glaucoma
* Chronic anxiety/psychiatric disorders.

Patients with renal impairment may be at risk for toxicity and should be treated with caution at the minimum effective dose.

Patients with impaired circulation of the cerebrum and autonomic dysfunction should be treated with special caution.

Precautions for use
Ephedrine should be used with caution in patients with cardiac history.

Interference with serological testing
Athletes: warning, this medicinal product contains an active substance that may cause a positive reaction in anti-doping tests.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations
- Indirect sympathomimetic agents (phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate): risk of vasoconstriction and/or of acute episodes of hypertension.
- Alpha- and beta-adrenergic blocking agents (phentolamine): reduce the vasopressor effect of ephedrine.
- The administration of ephedrine to patients who are undergoing or have undergone treatment with MAO inhibitors within the last 2 weeks is contraindicated as the combination may cause severe, possibly fatal, hypertension.

Combinations not recommended

- Volatile halogen anesthetics: Serious ventricular arrhythmias (increase in cardiac excitability). Nonetheless, the new volatile drugs, such as sevoflurane and desflurane, show less cardiac side effect allowing a possible co-administration of ephedrine.
- Tricyclic antidepressants (e.g. imipramine): Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibers).
- Noradrenergic-serotoninergic antidepressants (minalcipran, venlafaxine): Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibers).
- Guanethidine and related products: Substantial increase in blood pressure (hyperreactivity linked to the reduction in sympathetic tone and/or to the inhibition of adrenaline or noradrenaline entry in sympathetic fibers). If the combination cannot be avoided, use with caution lower doses of sympathomimetic agents.
- Sibutramine: Paroxysmal hypertension with possibility of arrhythmias (inhibition of adrenaline or noradrenaline entry in sympathetic fibers).

Combinations requiring precautions for use

- Reserpine and methyldopa reduce the vasopressor action of ephedrine.
- Theophylline and derivatives (aminophylline). Concomitant administration of ephedrine and theophylline may result in insomnia, nervousness and gastrointestinal complaints.
- Agents that alter urine pH (alkalization, e.g. from Acetazolamide or Sodium Bicarbonate, inhibits renal excretion of ephedrine).
- Corticosteroids.
- Alcohol.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Ephedrine in pregnant women. Teratogenicity studies in animals demonstrated that ephedrine could cause cardiovascular defects, reduction in fertility, foetal loss and midline wall defects.
The use of ephedrine in pregnancy should be avoided as ephedrine crossed the placenta and this has been associated with an increase in fetal heart rate and beat-to-beat variability.

Breast-feeding

Although specific data are lacking in this regard, it is assumed that ephedrine crosses the placenta and passes into breast milk. Breastfeeding should be suspended for two days after the administration. Irritability and disturbed sleep patterns have been reported in breast-fed infants.

Fertility

Animal studies are insufficient with respect to effects on fertility (see section 5.3).

4.7 Effects on the ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Frequency	Very common (≥1/10)	Common (≥1/100 to	Uncommon (≥1/1,000 to	Rare (≥1/10,000 to	Very rare (<1/10,000)	Not known

Organ system		<1/10)	<1/100)	<1/1,000)		
Blood and lymphatic system disorders		changes in primary hemostasis				
Immune system disorders		hypersensitivity reactions				
Psychiatric disorders				anxiety		confusion, depression
Nervous system disorders		Insomnia nervousness	Trembling, sweating, migraine			irritability
Eye disorders	episodes of angle-closure glaucoma in patients who are anatomically predisposed					
Cardiac disorders			tachycardia, palpitations	cardiac arrhythmias, hypertension, precordial pain		
Gastrointestinal disorders			nausea, vomiting			
Musculoskeletal and connective tissue disorders						Muscle weakness
Renal and urinary disorders			acute urinary retention			

Reporting Side Effects
Side effects can be reported to the Ministry of Health (MoH) by clicking on the "Report on side effects due to medication therapy" link on the MoH home page (www.health.gov.il) which refers to the online form for side effects reporting, or by entering the link: https://sideeffects.health.gov.il

4.9 Overdose Symptoms

In the event of an overdose, the following are seen to occur: migraines, nausea, vomiting, hypertension, tachycardia, fever, paranoid psychosis, hallucinations, ventricular and supraventricular heart rhythm disorders, respiratory depression, convulsions and coma. The lethal dose in humans is about 2 g, equivalent to blood concentrations of about 3.5 to 20 mg/l.

Management
To treat the overdose and control stimulation of the central nervous system and convulsions, diazepam can be administered at doses ranging from 0.1 to 0.2 mg/kg per injection. The dose of 10 to 20 mg can be administered at once via slow intravenous route.
To treat excitation, hallucinations and hypertension, chlorpromazine should be administered. To treat severe hypertension, phentolamine or another alpha-adrenergic receptor blocker can be administered.

To treat hypertension or severe tachyarrhythmia, a beta-blocker such as propranolol may prove beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic and Dopaminergic Agent.
ATC Code: R03CA02.
Ephedrine is a sympathomimetic amine acting directly on the alpha and beta receptors and indirectly by increasing the release of noradrenaline by the sympathetic nerve endings. As with any sympathomimetic agent, ephedrine stimulates the central nervous system, the cardiovascular system, the respiratory system, and the sphincters of the digestive and urinary systems. Ephedrine is also a monoamine oxidase (MAO) inhibitor and can provoke an increase of glycemia.

5.2 Pharmacokinetic properties

Absorption
Ephedrine is rapidly and completed absorbed after oral, intramuscular or subcutaneous administration.
Ephedrine hydrochloride circulates freely in the plasma.
The pressure and cardiac effects persist for approximately one hour after the intravenous and intramuscular administration of 10 to 25 mg and 25 to 50 mg of ephedrine, respectively.

Distribution
Although specific information is lacking, ephedrine is presumed to cross the placenta and to distribute into milk.
After injection, it is rapidly distributed in the body and accumulates in the liver, kidneys, lungs, spleen and brain. This accumulation results in high distribution volumes ranging between 122 and 320 liters.

Biotransformation
A small fraction of ephedrine is slowly metabolized in the liver by oxidative deamination, demethylation, aromatic hydroxylation, and conjugation. The metabolites are identified as p-hydroxyephedrine , p-hydroxynorephedrine, norephedrine, and conjugates of these compounds.

Elimination
Excretion depends on urine pH:
From 73 to 99% (mean: 88%) in acidic urine,
From 22 to 35% (mean: 27%) in alkaline urine.
After oral or parenteral administration, 77% of ephedrine is excreted in unchanged form in the urine.
The half life depends on urine pH. In acidic urine at pH = 5, the half life is 3 hours; in alkaline urine at pH = 6.3, the half life is approximately 6 hours.

5.3 Preclinical safety data

No studies to current standards on fertility have been conducted. However, anti-estrogenic effects of ephedrine have been found in immature rats given ephedrine at a dose of 5 mg/kg orally, indicating the potential for effects on female fertility.
Teratogenicity studies in animals demonstrated that ephedrine could cause cardiovascular defects, reduction in fertility, foetal loss and midline wall defects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Water for injections.

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life
The expiry date of the product is indicated on the packaging material.
After opening: the product must be used immediately.

6.4 Special precautions for storage
Do not store above 25˚C. Store in the original package in order to protect from light.

6.5 Nature and contents of container
Type I uncolored glass.
Boxes of 5, 10 or 100 ampoules containing 1ml of solution.

6.6 Special precautions for disposal and other handling
Instructions for use:
The ampoule is for single use only. The solution should be used immediately after the opening of the container. Any unused product or waste material should be disposed of in accordance with local requirements.
Discard ampoule after use. DO NOT REUSE.
The content of un-opened and un-damaged ampoule is sterile, and must not be opened until use. The product should be inspected visually for particles and discoloration prior to administration. Only clear colorless solution free from particles or precipitates should be used.

7. MANUFACTURER
Laboratoires sterop
Avenue de Scheut 46-50, 1070 Brussels, Belgium

8. LICENSE HOLDER
RAZ PHARMACEUTICS LTD., 6 Hamatechet st., Kadima, Israel.

9. MARKETING AUTHORISATION NUMBER
163-13-35347-00

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