SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ephedrine Hydrochloride Osel 0.05 g/1 ml IM/IV/SC Solution for Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL ampoule:
Active substance:
Ephedrine hydrochloride 50 mg
Excipients:
Sodium Chloride 9 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colorless solution
pH=4.5-6.5

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Bronchospasm:
It is used as a bronchodilator in reversibl bronchospasm, which occurs in relation to mild bronchial asthma, chronic bronchitis, emphysema, and other obstructive pulmonary diseases. In severe cases and anaphylactic reactions, subcutaneous epinephrine should be preferred.

Hypotension and shock:
It is used to create cardiac stimulation and vasodilation, in order to correct hemodynamic imbalances in the treatment of shock that occurs after sufficient volume of fluid has formed.
Hypotension seen in anesthesia:
It is used in the prevention and treatment of hypotension seen during Spinal anesthesia.
Ephedrine may be used to treat hypotension in general anesthesia, but the possibility of cardiac arrhythmia should be considered.
Arrhythmias:
Ephedrine is used to provide transient ventricular velocity support in the treatment of syncopal episodes and bradycardia caused by atrioventricular node blockade. Ephedrine is also effective in AdamsStokes disease and carotid sinus syndrome; however, the effectiveness of isoproterenol is higher.

4.2. Posology and method of administration

Posology /administrationfrequency and duration
In Adults:

In the treatment of hypotension as a presor agent:

EPHEDRINE should be administered as soon as possible and at the lowest effective dose.

- Subcutaneous or intramuscular administration: 25-50 mg, if necessary up to maximum 150 mg in 24 hours can be repeated.
- Intravenous administration: 10 - 25 mg (as slow injection), repeated if necessary after 10 minutes, the maximum daily dose should not exceed 150 mg.

During treatment with a presor agent, blood pressure should be raised slightly below the patient's normal blood pressure. Systolic blood pressure should be maintained at 80-100 mmHg in patients who were previously normotensive. Systolic blood pressure should be maintained at 30-40 mmHg in patients who were previously hypertensive. In patients with severe hypotension, blood pressure may be lower if blood or fluid replacement treatments are not completed.

Treatment of severe acute bronchospasms:

-The lowest effective dose should be administered intravenously (slowly): 12.5 - 25 mg, additional doses should be decided according to the patient's response.

Method of administration:

EPHEDRINE can be administered subcutaneously, intramuscularly and intravenously. Method of administration is determined by individual need.

IV administration should be preferred in emergency situations where immediate response is required. IV administration is preferred to bypass the absorption stage in patients undergoing shock. In IV administrations, the injection should be administered slowly.

Care must be taken to avoid extravasation otherwise tissue necrosis and skin shedding may occur.

EPHEDRINE must be administered at the lowest effective dose.

Daily maximum dose= Must not be exceeded 150 mg.

Additional information for special populations:

Renal / Hepatic failure:

No data available.

Pediatric population:

In children, daily doses of 3 mg/kg or 100 mg/m^2 can be administered subcutaneously or IV by dividing 4-6 equal doses.

Should not be used in children under the age of 2 unless it is very necessary.

Geriatric population:

Because ephedrine causes acute urinary retention, it should be administered with caution in elderly patients, especially those with prostatic hypertrophy.

4.3. Contraindications

Ephedrine should not be used in the following cases:

- Known hypersensitivity to ephedrine or other sympathomimetic drugs or any of the excipients of drug.
- Psychoneurosis, hyperexcitability, pheochromocytoma, atherosclerosis and aneurysm
- Combined with other indirect sympathomimetics such as phenylpropanolamine, phenylephrine, pseudoephedrine, methylphenidate
- Along with alpha sympathomimetic drugs
- In patients that have monoamine oxidase (MAO) inhibitor treatment or had in the

last two weeks
- Acute glaucoma
- Patients rhaving anesthesia with cyclopropane or halothane treatment
- In general, vasopressor drugs are contraindicated (e.g. in patients with thyrotoxicosis or diabetes mellitus, in obstetric cases where maternal blood pressure is > 130/80 mmHg, in patients with hypertension or other cardiovascular disorders)
- Diseases associated with tachycardia.
- Coronary artery disease

4.4. Special warnings and special precautions for use

The use of ephedrine as a pressing agent does not replace blood, plasma, fluid and / or electrolyte replacement. The decrease in blood volume should be corrected as much as possible before starting ephedrine therapy. Although ephedrine may be used in emergency situations as an adjunct to fluid volume replacement or as a temporary support measure to maintain coronary and cerebral artery perfusion until volume replacement therapy is complete, it should not be used as the only treatment in hypovolemic patients. Additional volume replacement may be necessary during or after administration of the drug, especially if hypotension is repeated.

Monitoring of central venous pressure or left ventricular filling pressure may be helpful in the detection and treatment of hypovolemia. Monitoring of central venous or pulmonary artery diastole pressure is also necessary to prevent overloading of the cardiovascular system and ambient preparation for congestive heart failure.

Conditions that reduce the effectiveness of ephedrine and/or increase the incidence of adverse effects, such as hypoxia, hypercapnia, and acidosis, should be identified and corrected before or during administration of ephedrine.

The fact that ephedrine depletes norepinephrine storage from sympathetic nerve endings can result in a reduction in the cardiac and presor effects of the drug. For this reason, noradrenaline may be used to replace tissue storeage in order to improve the pressing effect of ephedrine.

Long-term use of presor agents has been associated with edema, hemorrhage, focal myocardial infarction, subpericardial hemorrhage, and intestinal, kidney and liver necrosis. Since these effects are usually observed in the case of severe shock, it is not known exactly whether these effects are caused by drug or shock. This should therefore be considered before using ephedrine.

It should be used with caution in patients who may be susceptible to ephedrine effects, especially in patients with hyperthyroidism.

Ephedrine can cause a state of shock by reducing the circulating plasma volume, or restore hypotension when the drug is discontinued.
Ephedrine can cause hypertension, which can result in intracranial bleeding.

In patients with hypertension and hyperthyroidism, there is a high probability of adverse reactions to ephedrine and this drug should be administered with caution in these patients.

Older men (especially those with prostatic hypertrophy), diabetics, cardiovascular disease (coronary insufficiency, angina pectoris, cardiac arrhythmias, hypertension, and organic heart disease) should be avoided in those with.
Psychological and psychic dependence may occur due to ephedrine use.
Use in patients with diagnosed or suspected congenital elongated QT syndrome or *Torsades de Pointes* should be avoided.
Must not be used in children under the 2 ages unless it is very necessary.

The use of ephedrine in combination with other sympathomimetic agents, halogenated inhalation anesthetics, α and β - adrenergic blockers, MAO inhibitors is not recommended. (See Section 4.5).

Monitoring:
During ephedrine treatment, cardiovascular parameters such as blood pressure, ECG, cardiac flow, central venous pressure and pulmonary artery pressure should be monitored. Urination output should also be monitored.

Drug abuse and misuse:
Due to the stimulating effects of ephedrine, misuse and abuse have been reported by young adults, bodybuilders and other athletes.
Food supplements containing ephedrine alkaloids have been associated with severe cardiac adverse effects (e.g., MI, hypertension resulting in stroke or death), CNS effects, and death. These issues should be considered when prescribing and storing the drug.

Athletes:
Athletes should be warned that this medicinal product contains an active substance that causes a positive reaction to doping control tests.
This medicinal product contains less than 1 mmol (23 mg) of sodium per 50 mg/mL dose, meaning it can be considered essentially sodium-free.

4.5. Interaction with other medicinal products and other forms of interaction

Ephedrine must not be used in combination with sympathomimetic agents, α and β-adrenergic blockers, general anesthetics, MAO inhibitors.

Sympathomimetic agents:
Ephedrine, when used in combination with other sympathomimetic agents (eg, phenylpropanolamine, phenylephrine, pseudoephedrine, methylphenidate), has an additive

effect and increases toxicity.

α and β-adrenergic blockers:
α adrenergic blockers reduce the vasopressor response to ephedrine. Phentolamine blocks the β - adrenergic action of ephedrine, causing vasodilation. Due to the cardiac stimulator effect of ephedrine, presor response can only be taken when adequate doses are administered.
Administration of β-adrenergic blockers (propranolol), as with other sympathomimetic drugs with a cardiostimulation effect, may inhibit the cardiac and bronchodilator effects of ephedrine.

General anesthetics:
Drugs that increase cardiac irritability, such as cyclopropane or halogenated hydrocarbon general anesthetics, may occur when ephedrine is administered to patients with arrhythmia. If a pressuor drug is required when such anesthetics are used, products with minimal cardiac stimulation effect such as methoxamine or phenylephrine should be preferred. When arrhythmia occurs, β-adrenergic blockers such as propranolol may be used.

MAO inhibitors:
MAO inhibitors increase norepinephrine amounts in adrenergic nerve tissues, increasing the presor effects of indirect-acting sympathomimetics such as ephedrine. Therefore, ephedrine should not be used in patients receiving MAO inhibitor therapy or who have taken it within the last 14 days.

Hypotensive agents:
Agents that reduce the amount of norepinephrine in sympathetic nerve endings, such as reserpine and methyldopa, can reduce the presor response to ephedrine.
It reduces the action of neuron-blocking substances such as ephedrine, guanetidine. As a result, antihypertensive effects are lost. In patients receiving ephedrine with guanetidine, antihypertensive effects should be carefully monitored and if necessary, the dose of guanetidine should be increased or another antihypertensive drug should be added to the treatment.

Atropine:
Atropine sulfate blocks reflex bradycardia and increases the resulting presor response to ephedrine.

Derivatives of theophylline:
The use of theophylline derivatives such as aminophylline in combination with ephedrine has been associated with greater incidence of adverse effects than in situations where these drugs are used alone.

Corticosteroids:
Ephedrine has been shown to increase dexamethasone clearance.

Sibutramine:
Paroxysmal hypertension may occur in conjunction with possible arrhythmias (due to inhibition of adrenaline or noradrenaline entry into sympathetic fibers)

Linezolid:
Risk of vasoconstriction and / or episodes of hypertension.

Cardiac glycosides:
Cardiac glycosides make the myocardium more sensitive to the effects of sympathomimetic agents. Ephedrine should be used with caution in patients using cardiac glycosides.

Ergotamine, ergometrin, methylergometrin, oxytocin:
The use of these drugs in combination with ephedrine may lead to an increase in the pressor effects of ephedrine. When ergotamine and ephedrine are used together, peripheral vascular ischemia and gangrene may occur.

Diuretics:
Furosemide and other diuretics reduce the arterial effects of ephedrine-type pressing agents.

Tricyclic antidepressants (ex. imipramine):
Paroxysmal hypertension may occur in conjunction with possible arrhythmias (due to inhibition of adrenaline or noradrenaline entry into sympathetic fibers).

Noradrenergic-serotonergic antidepressants (minalsipran, venlafaxine):
Paroxysmal hypertension may occur in conjunction with possible arrhythmias (due to inhibition of adrenaline or noradrenaline entry into sympathetic fibers).

Antiepileptics:
Ephedrine increases plasma concentrations of phenytoine; it can also increase plasma concentrations of phenobarbitone and pyrimidine.

Doxapram:
There is a risk of hypertension when ephedrine and doxapram are used together.

Oxytocin:
Hypertension may occur with vasoconstrictor sympathomimetics.

Clonidine:
Previous treatment with clonidine may increase the pressor effect of ephedrine.

Drugs that alkalize urine, such as acetazolamide, dichlorphenamide, sodium bicarbonate, and sodium citrate:

These drugs can increase the half life of ephedrine and reduce its elimination. This can result in increased therapeutic or toxic effects of ephedrine.

4.6. Pregnancy and lactation

General advice

Pregnancy category is C.

Women with child-bearing potential / Contraception

It is not known whether ephedrine affects fetal damage or reproductive capacity. Therefore, women with childbearing potential should not be used unless it is very necessary.

Pregnancy

Teratogenic effects have been observed in studies in animals. Clinically, epidemiological studies involving a limited number of women do not show that ephedrine has particular malformation effects.

Maternal hypertension has been reported in isolated cases where vasoconstrictor amines have been chronically or misused.

It was observed that fetal heart rate increased during ephedrine injection during delivery under epidural anesthesia. This medicine should not be administered when the patient's blood pressure is above 130/80 mmHg.

In addition, there is insufficient evidence to confirm that the administration of ephedrine during pregnancy causes fetal toxicity.

Ephedrine should not be used during pregnancy unless it is very necessary.

Lactation

Ephedrine passes into breast milk. Irritability and impaired sleep patterns have been reported in breastfed newborn infants. There is evidence that ephedrine is eluted 21-42 hours after administration; therefore, a decision should be made by considering the benefit of breastmilk to the baby and the possible benefit of the drug to the mother between not using during lactation or interrupting breastfeeding for two days after administration of ephedrine.

Fertility

The effect of EPHEDRINE on reproductive ability is unknown.

4.7. Effects on ability to drive and use machines

Side effects of central nervous system such as dizziness, fatigue, fear, anxiety patients who drive and use machines that require attention should be warned about this as it may show.

4.8. Undesirable effects

Undesirable reactions are listed below by body systems. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (>1 / 1,000 to <1/100); rare (>

1 / 10,000 to <1 / 1,000); very rare (<1 / 10,000), unknown (cannot be estimated from the available data).

Blood and the lymphatic system disorders
Unknown: Primary hemostasis changes

Immune system disorders
Unknown: Hypersensitivity

Psychiatric disorders
Common: Confusion, anxiety, depression
Unknown: Psychotic states, fear, dizziness

Nervous system disorders
Common: Nervousness, irritability, restlessness, weakness, insomnia, headache, sweating.
Unknown: Shivering, excessive salivation

Eye disorders
Unknown: Acute glaucoma crises

Cardiac disorders
Common: Palpitations, hypertension,
Rare: Cardiac arrhythmias
Unknown: Anginal pain, reflex bradycardia, cardiac arrest, hypotension

Vascular disorders
Unknown: Cerebral hemorrhage

Respiratory, chest and mediastinal disorders
Common: Dyspnea
Unknown: Pulmonary edema

Gastrointestinal disorders
Common: Nausea, vomiting
Unknown: Loss of appetite

Kidney and urinary tract disorders
Rare: Acute urinary retention

Researches
Unknown: Hypokalemia, changes in blood glucose level

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You

can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Symptoms:
In excessive doses, migraine, nausea, vomiting, hypertension, tachycardia, fever, paranoid psychosis, hallucinations, ventricular and supraventricular arrhythmias, respiratory depression, convulsions, and coma can be seen.
The letal dose in humans is about 2 g, corresponding to blood concentrations of 3.5 - 20 mg/L.

Treatment:
In case of an overdose of ephedrine, intensive supportive therapy may be required. 50-200 mg labetalol can be given by slow intravenous injection under electrocardiographic monitorization for the treatment of supraventricular tachycardia.

Significant hypokalemia due to the displacement of potassium between the body compartments (<2.8 $mmol.L^{-1}$) development increases susceptibility to cardiac arrhythmias and can be treated by infusing potassium chloride in addition to propranolol and correcting respiratory alkolosis, if any.
A benzodiazepine and/or neuroleptic agent may be required for stimulant effects in the central nervous system. Treatment options for severe hypertension include intravenous route applied nitrates include calcium channel blockers, sodium nitroprussid, labetolol, or phentolamine. The choice of antihypertensive medication depends on the accompanying conditions in the patient, the clinical condition of the patient and which drug is available in the clinic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Adrenergic and dopaminergic drugs
ATC code : C01CA26

Ephedrine is a sympathomimetic amine that acts directly on α and β-adrenergic receptors and indirectly acts by increasing neurotransmitter (noradrenaline) release from sympathetic nerve endings.
Other sympathomimetic agents such as ephedrine stimulate also the central nervous system, the cardiovascular system (increases blood pressure, stimulates cardiac activity), respiratory system (bronchial smooth muscle relaxes and increases the flow of air, reduces the volume of secretion in the nasal mucosa) and the sphincter digestive (stimulates the gastrointestinal system: reduces intestinal tone) and the urinary sphincter (detrusor muscle relaxation with sphincter contraction and bladder wall relaxation).
Ephedrine is also an MAO inhibitor.

It relaxes the uterine muscles and prevents contractions (tocolytic effect).
It causes blood glucose levels to rise.

5.2 Pharmacokinetic properties

General properties

Absorption:
Ephedrine is absorbed very quickly after intramuscularly and subcutaneous administration. The duration of presor and cardiac responses to ephedrine is 1 hour after 10-25 mg of IV and 25-50 mg of IM or subcutaneous administration. Plasma concentrations of ephedrine vary greatly in connection with bronchodilation. In one study, therapeutic plasma concentrations were reported to be between 20 ng/mL and 80 ng/mL.

Distribution:
After injection, it quickly dissipates in the body and accumulates in the liver, kidney, lung, spleen and brain. The distribution volume is approximately 122-320 litres.

Although certain information is not available, ephedrine passes into the placenta and is thought to be distributed in milk.

Biotransformation:
Low amounts of ephedrine metabolize very slowly in the liver by oxidative deamination, demethylation, aromatic hydroxylation, and conjugation. These metabolites have been identified as β-hydroxy ephedrine, β-hydroxynorephedrine, norephedrine, and conjugates of these compounds.

Elimination:
Ephedrine and its metabolites are excreted by urine.
Excretion depends on urine pH:

- 73-99% in acidic urine (avg. 88 %)
- 22-35% in alkaline urine (avg. 27 %)

77% of ephedrine administered orally or parenterally is excreted in urine unchanged. Half-life depends on urine pH. Ephedrine elimination half-life was found to be about 3 hours when the pH value of urine was set to 5, and about 6 hours when the pH value was set to 6.3.

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities
It should not be mixed with drugs of unknown compatibility.

6.3 Shelf life
36 months.
This drug does not contain any preservatives, should be used immediately after the ampoule is opened.

6.4 Special precautions for storage
Store at room temperature 15-30 ° C in its original packaging, protected from light.

6.5 Nature and contents of container
1 mL amber colored ampoules are packaged in cardboard boxes containing 10 or 100 ampoules.

6.6 Instructions for use and handling and disposal
Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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