PATIENT INFORMATION LEAFLET

EPHEDRINE HYDROCHLORIDE 0.05 g/1 mL I.M. /I.V./S.C. Solution for Injection

Sterile

Administered intravenously, intramuscularly or subcutaneously.

- ***Active substance:*** Each 1 mL ampoule contains 50 mg ephedrine hydrochloride.
- ***Excipients:*** Sodium chloride and water for injection.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use **high** or **low** doses other than the recommended dosage.*

What is in this Leaflet:

Headings are included.

1. What EPHEDRINE is and what it is used for?

• EPHEDRINE is presented as an ampoule containing solution for injection for intramuscular, intravenous or subcutaneous administration whose active ingredient is ephedrine hydrochloride.

• EPHEDRINE is included in the drug group called “adrenergic and dopaminergic drugs” used in the treatment of low blood pressure (hypotension).

• Each box contains 10 or 100 1 ml amber colored ampoules.

EPHEDRINE is used in the following situations:

Prevention and treatment of low blood pressure seen during general or local-regional anesthesia, with or without a decrease in heart rate;

- It is used in the symptomatic (symptomatic) treatment of severe acute bronchospasm (narrowing

of the bronchi) seen in respiratory tract diseases such as bronchial asthma.

- EPHEDRINE can also be used in the treatment of other diseases such as shock and arrhythmia (heartbeat irregularity).

If you have questions about how EPHEDRINE works or why it was given to you, please consult to your doctor.

2. What you need to know before you use EPHEDRINE

DO NOT USE EPHEDRINE;

If;

- You have hypersensitivity (allergy) to ephedrine hydrochloride or other sympathomimetic drugs (drug group including ephedrine) or any of the excipients in EPHEDRINE
- You have mental disorder (psychoneurosis), hyperexcitability, adrenal gland tumor (pheochromocytoma) that causes your blood pressure to rise, arteriosclerosis (atherosclerosis) or aneurysm (regional swelling in the vein, ballooning)
- You are taking other indirect sympathomimetic drugs such as phenylpropanolamine, phenylephrine, pseudoephedrine, methylphenidate
- You are taking medicines such as selegiline (used in the treatment of Parkinson's disease), moclobemide (used to treat depression) and linezolid (antibiotics), which are included in the group of MAO (monoamine oxidase) inhibitors, or have used them in the last 14 days
- You have a disease called "narrow angle glaucoma" that causes a sudden increase in the pressure in your eye.
- You have received cyclopropane or halogenated hydrocarbon derivative anesthetics in general anesthesia
- Generally, in cases where vasopressor (blood pressure increasing) drugs should not be used [eg; EPHEDRINE should not be used in patients with thyrotoxicosis (disease due to excessive increase of thyroid hormones in the blood), diabetes (diabetes), blood pressure greater than 130/80 mmHg in pregnant patients, hypertension (high blood pressure) or cardiovascular (cardiovascular) diseases.

USE EPHEDRINE CAREFULLY;

Caution should be exercised in the following situations:

- Hypovolemia (decrease in blood volume)
- Hypoxia (oxygen deficiency in tissues), hypercapnia (excessive carbon dioxide in the blood), acidosis (excessive acid accumulation in the blood)
- Prostate hypertrophy (prostate enlargement)
- You have a family history of known heart disease or long QT syndrome (a condition in the heart that can lead to serious arrhythmias and sudden death)

If these warnings are valid for you, even at any time in the past, please consult your doctor.
In addition, EPHEDRINE should not be used in children under 2 years of age unless it is absolutely necessary.
Warning for athletes:
This medicinal product contains an drug substance that causes a positive result in doping control tests.

Use of EPHEDRINE with food and drink

Not applicable.

Pregnancy

Consult your doctor or your pharmacist before using the drug.

It has been reported that EPHEDRINE administered during birth increases the heart rate of the unborn baby.
If the mother's blood pressure is over 130/80 mmHg during pregnancy, EPHEDRINE should not be used. It is not known whether EPHEDRINE is safe to use during pregnancy. For this reason, do not use EPHEDRINE during pregnancy unless your doctor recommends it.
If you notice you are pregnant during treatment, consult your doctor or pharmacist immediately.

Breast-feeding

Consult your doctor or pharmacist before using this medication.

It is known that EPHEDRINE passes into breast milk. For this reason, do not use EPHEDRINE during breastfeeding unless your doctor recommends it.

Driving and using machines

EPHEDRINE may have an effect on the use of vehicles and machines. Consult your doctor before using a vehicle or machine.

Important information about some excipients found in the composition of EPHEDRINE

If you do not have any hypersensitivity to the excipients in EPHEDRINE, no negative effects are expected due to these excipients.

Use with other medicines

Please inform your doctor if you plan to take, are taking or have recently taken any other medicines, including non-prescription medicines, vaccines and herbal medicines.

EPHEDRINE should not be used with the following drugs:

- Drugs such as phenelzine or moclobemide used to treat severe depression [These drugs are known

as MAO (monoamine oxidase) inhibitors]. Do not use EPHEDRINE if you are using these medicines or if two weeks have not yet passed although you have stopped.

- Medicines to treat high blood pressure (eg, reserpine, methyldopa, guanetidine, clonidine)
- Theophylline and its derivatives used in the treatment of respiratory tract diseases
- Some medicines with vascular constricting effects, used in migraine headaches or during childbirth (e.g. ergotamine, ergometrine, methylergometrine, oxytocin)
- Medicines effective against depression/mental breakdown such as tricyclic antidepressants (eg imipramine) and serotonergic-noradrenergic antidepressants (eg minalsipram, venlafaxine)

Other drugs that may interact with EPHEDRINE are listed below:

- Atropine sulfate used in slow heartbeat, hypotension and heart rhythm disorder
- Medicines that strengthen the heart muscle (eg digoxin) known as cardiac glycosides
- Diuretic drugs (eg furosemide)
- Medicines that make urine more basic (eg acetazolamide, dichlorphenamide, sodium bicarbonate and sodium citrate)
- Methylphenidate [Used in the treatment of "Attention Deficit Hyperactivity Disorder (ADHD)"]
- Indirect sympathetic nervous system inhibitors such as phenylpropyl amine or pseudoephedrine drugs used to treat nasal congestion)
- Phenylephrine (a drug used to treat low blood pressure)
- Drugs that act by directly stimulating alpha receptors in the sympathetic nervous system (used in the treatment of low blood pressure and nasal congestion in the mouth and/or nose)
- Anesthetic drugs used by inhalation, such as halothane
- Sibutramine (a drug used as an appetite suppressant)
- Linezolid (a drug used to treat infections)
- Corticosteroids (It is a type of drug used in the treatment of inflammation (inflammation or inflammation) in many diseases and allergic conditions)
- Medicines used in the treatment of epilepsy
- Doxapram (It is a drug used in respiratory problems)
- Oxytocin (a drug used during childbirth)

Special precautions should be taken if these drugs that may interact with EPHEDRINE are to be used together.

If you are using or have recently used any type of prescription or non-prescription drugs, please

inform your physician or your pharmacist.

3. How to use EPHEDRINE

EPHEDRINE will be administered to you by your doctor or a nurse.

Instructions for appropriate use and dose/administration frequency:

Your doctor will determine the dose of your medicine depending on your illness and will administer it to you.

Method of administration:

EPHEDRINE is administered intravenously, intramuscularly or subcutaneously.

Various age groups

Use in Children:

Your doctor will determine the dose of the drug based on your child's weight or height and administer it to your child.

Use in Elderly:

EPHEDRINE should be administered with caution in elderly patients, especially men with prostate disease.

Kidney/Liver failure:

If you have liver or kidney problems, use this drug product carefully.

Talk to your doctor or pharmacist if you have the impression that the effect of EPHEDRINE is too strong or weak.

If you have used more EPHEDRINE than you should

Since this medicine is administered to you by your doctor or nurse, it is unlikely that you will use too much EPHEDRINE. However, in excessive doses, migraine, nausea, vomiting, high blood pressure, accelerated heartbeat, fever, mental disorders, imagination, heart rhythm disorders, respiratory difficulties, convulsion and coma can be observed. If you think you have any of these symptoms, tell your doctor immediately.

If you have used more than you should use from EPHEDRINE, talk to a doctor or pharmacist.

If you forget to use EPHEDRINE

Do not administer a double dose to make up for forgotten doses.

Effects that may occur when treatment with EPHEDRINE is concluded

Low blood pressure (hypotension) may recur when the medication is stopped. Carefully follow the instructions your doctor recommends to you.

4. What are the possible side effects?

Like all medicines, there may be side effects in people who are sensitive to the substances contained in EPHEDRINE.

If you experience any of the following side effects, stop using the drug immediately and contact your doctor for immediate assistance:

- Difficulty in breathing
- Abnormal heart rhythm
- Palpitations in the heart, working faster than normal, increased blood pressure or pain in the heart area, decreased heart rate, low blood pressure
- Heart failure (cardiac arrest)
- Celebral hemorrhage
- Fluid accumulation in the lungs (pulmonary edema)
- Increase in intraocular pressure (glaucoma)
- Difficulty urinating

Side effects are listed as shown in the categories below.

Very common	: It can be seen in at least 1 of 10 patients.
Common	: Less than one in 10 patients, but more than one in 100 patients.
Not Common	: Less than one in 100 patients, but more than one in 1000 patients.
Rare	: Less than one in 1000 patients but more than one in 10,000 patients.
Very rare	: Less than one in 10,000 patients can be seen.
Unknown	: Cannot be estimated from the available data.

Common:

- Unconsciousness, feeling anxious (anxiety), depression
- Nervousness, easy excitability, restlessness, weakness, sleep problems, headache, sweating
- Shortness of breath
- Nausea, vomiting

Unknown:

- Problems associated with blood clotting
- Allergy (hypersensitivity)
- Changes in personality or how you feel or think about yourself, fears, dizziness
- Shivering, excessive salivation

- Decreased appetite
- Low levels of potassium in the blood or changes in your blood sugar levels

All these are serious side effects. Emergency medical attention may be required. If you notice any of these symptoms, tell your doctor immediately.

If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.

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.

5. How to store EPHEDRINE

Keep EPHEDRINE out of the sight and reach of children, and in its packaging.

Store at room temperature between 15-30 °C, protect from light.

Use in compliance with the expiry date.

Do not use EPHEDRINE after the expiration date stated on the packaging.

Do not throw away expired or unused medicines! Give to the collection system determined by the Ministry of Environment and Urbanization.

Marketing Authorization Holder and Manufacturing Site:

OSEL İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Caddesi No:52
34820 Beykoz/İSTANBUL

This patient information leaflet was approved on 05/10/2017.

FOLLOWING INFORMATION IS FOR HEALTH PROFESSIONAL TO ADMINISTER THIS MEDICINAL PRODUCT

Posology/administration frequency and duration:

In adults:

As a pressor agent in the treatment of hypotension:

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 a maximum of 150 mg in 24 hours.

Intravenous administration: 10 - 25 mg (as slow injection), if necessary, can be repeated after 10 minutes, the maximum daily dose should not exceed 150 mg.

During treatment with a pressor agent, blood pressure should be raised slightly below the patient's normal blood pressure. In patients who were previously normotensive, systolic blood pressure should be kept at the level of 80-100 mmHg. The systolic blood pressure of patients who were previously hypertensive should be kept 30-40 mmHg below the patient's normal blood pressure. In patients with severe hypotension, even lower blood pressure may be desirable if blood or fluid replacement therapies are not completed.

In the 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. The route of administration is determined according to individual needs.

IV administration should be preferred in emergency situations that require immediate response. IV administration is preferred to overcome the absorption phase in patients with shock. In IV administrations, the injection should be given slowly.

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

EPHEDRINE should be administered at the lowest effective dose.

The maximum daily dose = 150 mg should not be exceeded.

Additional information on special populations:

- **Pediatric population:**

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

- **Geriatric population:**

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

- **Monitoring:**

Cardiovascular parameters such as blood pressure, ECG, cardiac output, central venous pressure and pulmonary artery pressure should be monitored during EPHEDRINE treatment. Urine output should be monitored separately.

Drug abuse and misuse:

Due to the stimulating effects of ephedrine, misuse and abuse by young adults, bodybuilders and other athletes have been reported.

Food supplements containing ephedrine alkaloids have been associated with serious cardiac adverse effects (eg hypertension possibly resulting in MI, stroke or death), CNS effects, and death. These aspects should be taken into account in the prescription and storage of the drug.

Psychological and psychic dependence may occur due to the use of ephedrine.

Athletes:

Athletes should be warned that this medicinal product contains a drug substance that causes a positive reaction in doping control tests.

Overdose and treatment

Symptoms:

In excessive doses, migraine, nausea, vomiting, hypertension, tachycardia, fever, paranoid psychosis, hallucinations, ventricular and supraventricular rhythm disturbances, respiratory depression, convulsion and coma may be seen.

The lethal dose in humans is about 2 g and corresponds to blood concentrations of 3.5 - 20 mg/l.

Treatment:

Intensive supportive therapy may be required in case of drug-induced ephedrine overdose. For the treatment of supraventricular tachycardia, 50-200 mg labetalol can be administered by slow intravenous injection under electrocardiographic monitoring.

The development of marked hypokalemia (< 2.8 $mmol.l^{-1}$) due to potassium displacement between body compartments increases susceptibility to cardiac arrhythmias and can be treated by infusion of potassium chloride in addition to propranolol and correction of respiratory alkalosis, if present.

A benzodiazepine and/or neuroleptic agent may be required for stimulating effects in the central nervous system. Treatment options for severe hypertension include intravenously administered nitrates, calcium channel blockers, sodium nitroprusside, labetalol, or phentolamine. The choice of antihypertensive drug depends on the accompanying conditions in the patient, the clinical condition of the patient and which drug is available in the clinic.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

EPHEDRINE HYDROCHLORIDE 0.05 g/1 mL I.M. /I.V./S.C. Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL ampoule:

Drug 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

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 30-140 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 age of two 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 (toclitic 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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10. DATE OF REVISION OF THE TEXT
