SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SELADRENALİN 4 mg/4 mL IV Ampoule Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

One ampoule (4 ml) contains 8 mg norepinephrine bitartrate (equivalent to 4 mg norepinephrine base).

Excipients:

Sodium chloride	34,35 mg
Sodium metabisulphite	4 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated solution for infusion.
Sterile, clear, colorless-yellowish, aqueous solution with no visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for normalizing blood pressure in acute hypotension conditions.

4.2. Posology and method of administration

Posology /administrationfrequency and duration

SELADRENALİN must be administered only by experienced medical personnel.

SELADRENALİN contains 8 mg / 4 ml norepinephrine bitartrate. The dose is calculated on the basis of epinephrine. 2 mg of norepinephrine bitartrate is equivalent to 1 mg of norepinephrine base.

Therefore, each ampoule contains 4 mg of norepinephrine base.

Before administration of parenteral drug products, it must be visually controlled whether there is any particulate matter and if it discolorates. Parenteral norepinephrine is administered by I.V infusion.

Adults

Correction of blood pressure:

In acute hypotensive conditions: Blood volume depletion must be corrected as precisely as possible before using any vasopressor. Norepinephrine can be administered before or during blood volume replacement.

Usual dose:

Infusion is usually given at the beginning of 2-3 ml / minute (8-12 µg per minute) or 0.11-0.17 µg / kg / minute) and the amount is adjusted according to the state of blood pressure. The blood pressure value is recorded every two minutes initially and the infusion rate is constantly observed. After observing the patient's response to the initial dose, the flow rate is adjusted to create and maintain sufficient normal blood pressure (usually 80-100 mm Hg systolic) to maintain circulation in vital organs. It is recommended that blood pressure should not be increased to more than 400 mm Hg of pre-existing systolic pressure in patients who were previously hypertensive.

The average flow of the diluted solution 0.5-1 ml / min (or 0.03-0.06 µg / kg / min) is usually sufficient to achieve satisfactory blood pressure values.

The posology mentioned above is not certain. The dose is determined depending on the condition of the patient's heart and blood vessels. Sensitivity to the product may differ significantly from person to person.

If the patient remains hypotensive, it may be necessary to administer up to 17 ampoules of 4 ml in 24 hours (the amount corresponding to 0.67 micrograms / kg / min), but hidden blood volume depletion should always be suspected and corrected if necessary. Central venous pressure monitoring usually helps in the detection and treatment of this condition.

Treatment period:

The treatment period is different for each clinical case and can vary from 1-2 hours to 6 days.

Infusion should be continued until sufficient tissue infusion and sufficient blood pressure.

The infusion should be gradually reduced and stopped to prevent a serious drop in blood pressure.

Method of administration:

- Dilution:

SELADRENALİN is diluted in 1 liter of 5% glucose or in a mixture of 0.9% sodium chloride and 5% glucose (50/50) by diluting and administered as I.V. infusion. It is diluted only with 5% glucose solution in patients which are on salt-free diet. The glucose solution is used to prevent oxidation of norepinephrine to L-norepinephrine.

In calculating dilutions of ampoule contents to obtain the desired concentrations of norepinephrine, the following table can be used as a reference:

Norepinephrine base content desired to be obtained	Number of ampoules to be used	Dilution solution volume to be used
4 micrograms/ml	1	1 liter
8 micrograms /ml	2	1 liter
12 micrograms /ml	3	1 liter
16 micrograms /ml	4	1 liter
20 micrograms /ml	5	1 liter

SELADRENALİN is not mixed with plasma or whole blood, the application should be done separately (for example, if it is given at the same time, Y-tube or separate containers should be used).

- Fluid intake:

The degree of dilution depends on clinical volume requirements.

If a large volume of fluid (dextrose) is required for a flow rate containing an overdose of pressurizing agent per unit time, a solution less than 4 micrograms / ml should be used. On the other hand, when high volumes of fluid are undesirable, a concentration higher than 4 micrograms / ml may be required.

- Injection site:

Norepinephrine is administered only as an intravenous infusion. Norepinephrine infusions should be administered into large veins. Antecubital veins are especially preferred because in this case, the risk of necrosis of the tissue covering it due to prolonged vasoconstriction appears to be weak. Injection into the veins in the lower limb area should be avoided.

- Blood pressure control:

Blood pressure should be controlled every two minutes until the desired blood pressure is obtained from the beginning of the infusion. If administration is to be continued, it should be controlled every five minutes after reaching the desired blood pressure.

Infusion flow rate should be checked frequently and the patient should never be left alone during the infusion.

- Extravasation risk:

Infusion flow freeness should be controlled frequently.

Due to the increased permeability and vasoconstriction of the vein wall, drug leakage may occur in the tissues around the vein. This condition is not due to certain extravasation and causes the tissues to fade. Therefore, if fading occurs, the infusion site should be changed to reduce the effects of local vasoconstriction.

- Treatment of ischemia due to extravasation:

Tissue damage due to the vasoconstrictive effect of the drug may occur in the blood vessels during leakage of the drug out of the vein or injecting outside the vein.

The injection site should be washed as quickly as possible with a physiological salt solution containing 5-10 mg of phentolamine mesylate.

For this purpose, a fine syringe needle syringe should be used and injected locally.

Ampoules should be visually inspected before use, and should not be used if particle presence and color change are observed.

Additional information on special populations:

Renal / hepatic failure:

The pharmacokinetics of norepinephrine is not significantly affected by renal or hepatic diseases.

Care should be taken when using sympathomimetics in liver and kidney patients, as blood flow may decrease in organs such as liver and kidney.

Pediatric population:

Studies on norepinephrine effects in newborns are not sufficient. When giving norepinephrine to children, care should be taken similarly to that of adults. As an initial dose, norepinephrine can usually be infused to 0.05 µg / kg / minute norepinephrine base and increased to 0.5 µg / kg / minute base by blood pressure control.

Geriatric population:

It should be used with caution in the elderly, especially those who are sensitive to sympathomimetic agents and norepinephrine.

4.3. Contraindications

SELADRENALİN is contraindicated in the following cases:

- Hypersensitivity to norepinephrine or other excipients in the drug: SELADRENALİN contains sodium metabisulfite as an adjuvant. This rarely can cause serious hypersensitivity reactions and bronchospasm.
- Hypertension: Hypertensive patients may be more sensitive to the pressing effects of norepinephrine.
- Hypertroidism: Such patients are hypersensitive to the effects of norepinephrine, and low doses of toxicity may occur.
- Prinzmetal's Angini: In these patients, coronary blood flow may decrease in time and size that may cause myocardial infarction.
- Hypotension due to lack of blood volume
- Hypercapnia, hypoxia and obstructive vascular disease

- SELADRENALİN is contraindicated during chloroform, cyclopropane and halothane anesthesia, as norepinephrine can increase the excitability of the cardiac muscles and cause rapid and irregular contractions of the heart chamber.

4.4. Special warnings and special precautions for use

Cardiovascular system:

Due to its alpha-agonist properties, to avoid hypertension, when norepinephrine is to be infused, blood pressure and flow rate should be checked frequently until the desired blood pressure is achieved during administration. To avoid a drop in blood volume, norepinephrine should only be used with appropriate blood volume replacements. These may induce hypotension at the end of treatment and cause vasoconstriction or vascular obstruction.

Blood:

In the absence of oxygen or excessive concentrations of blood carbonic gases,

SELADRENALİN should not be used without a doctor's decision, as the use of SELADRENALİN may cause cardiac rhythm disturbances (acceleration of the pulse or uncoordinated and ineffective contact of the heart).

Extravasation:

Norepinephrine is a serious tissue irritant and only highly diluted solutions should be used. If possible, it should be centrally infused into a wide vein and care should be taken to avoid extravasation.

It should be used with caution in hypertroidism, diabetes, narrow-angle glaucoma and prostate hypertrophy.

Congenital prolonged QT syndrome diagnosed or suspected and its use in patients with Torsades de Pointes should be avoided.

SELADRENALİN contains sodium metabisulfite as an adjuvant, which can cause serious hypersensitivity reactions and bronchospasm.

SELADRENALİN contains less than 1 mmol (23 mg) sodium per ampoule; it is not expected to show any side effects at this dose.

4.5 Interaction with other medicinal products and other forms of interaction

SELADRENALİN should not be used together during chloroform, cyclopropane and halothane anesthesia (see 4.3 contraindications). Arrhythmias should be treated with the administration of β-adrenergic blocking drugs such as propranol.

SELADRENALİN should be used with extreme caution in patients taking the following medicines due to potentially dangerous interactions:

- Atropine sulfate,
- Tricyclic antidepressants (eg imipramine),
- Antihistamines (diphenhydramine, tripelennamine, dexchlorpheniramine),
- Certain algaloids, guanethidine or methyldopa,which are derivatives of ergotamine, can potentiate the vasopressor effect of norepinephrine and cause severe and persistent hypertension.
- Serious and prolonged hypertension can occur with MAOI (monoamine oxidase) inhibitors.
- High amounts of digitalin and quinidine can cause arrhythmias.
- Furosemide and other diuretics may reduce the arterial response to norepinephrine.

Thevasopressoreffectresulting from theαadrenergiceffect in the vesselscan bereducedby the simultaneous administration of the α-blocking agent such as phentolamine mesylate. The administration of a blok-blocking agent (propranolol) causes the stimulating effect of the drug ontheheart(fromβ_1 adrenergic effect) to decrease, while the hypertensive effect following the decreasein arteriolar dilatation (fom the β adrenergic effect) also increases.

4.6 Pregnancy and lactation

General advice

Pregnancy category: C

Women with childbearing potential / Contraception

There is no data on whether SELADRENALİN has an effect on birth control methods.

Pregnancy

Studies on animals are insufficient in terms of effects on pregnancy and / or embryonal / fetal development and / or birth, postpartum development.

Safety for use in pregnant women has not been proven. Therefore, it should be used in pregnancy, if it is very necessary. Since norepinephrine will reduce blood circulation in the placenta, it may cause slowing of the fetus in the heart rhythm. It can also increase the rate of uterine contraction and cause the fetus to suffocate in the final period of pregnancy. For this reason, it should be used in emergency situations where the clinical advantages of SELADRENALİN are more than the possible risks that it will cause in the fetus.

Lactation

It is unknown whether norepinephrine is excreted in human breast milk. The excretion of norepinephrine in milk has not been studied in animals. A decision on whether to continue/ discontinue breast-feeding or to continue/discontinue therapy with SELADRENALİN

should be made taking into account the benefit of breast-feeding to the child and the benefit of SELADRENALİN therapy to the woman.

Fertility

Animal reproduction studies have not been performed with norepinephrine.

4.7 Effects on ability to drive and use machines

SELADRENALİN has no effect on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are listed as: Very common (≥ 1/10); common (≥ 1/100 - <1/10); uncommon (≥ 1 / 1,000 - <1/100); infrequently (≥1 / 10,000 - <1 / 1,000); very rare (<1 / 10,000), unknown (cannot be estimated from the available data).

Nervous system disorders

Uncommon : Anxiety, insomnia, confusion, cephagia, headache, psychotic state, weakness, tremor, hypervigilance, anorexia, nausea and vomiting.

Eye diseases

Uncommon :Acute glaucoma: It is very common in those with anatomically predisposed closure of the iridochond angle.

Cardiac diseases

Common : Tachycardia, bradycardia, arrhythmias, palpitation, increased contractility of the cardiac muscle resulting from β_1 adrenergic effect in the heart, acute cardiac failure.

Vascular diseases

Very common : Arterial hypertension and tissue hypoxia: Ischemic damage due to potent vasoconstrictor effect.

Respiratory, thoracic and mediastinal diseases

Uncommon : Respiratory failure and difficulty, dyspnea.

General disorders and diseases related to the administration site

Uncommon : Irritation and necrosis at the injection site, limbs and contraction of blood vessels that may result in cold and pallor face.

If blood volume replacement is not performed, continuous administration of norepinephrine to maintain blood pressure can cause the following symptoms:

-Severe peripheral and visceral vasoconstriction

-Decreased renal blood output

-Decrease in urine production

-Insufficient oxygen level in tissues

-An increase in the level of lactic acid in the blood.

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:

Overdose causes headaches, severe hypertension, pallor, abnormally slow pulse, increased peripheral resistance and low cardiac output.

In cases of overdose or at usual doses in hypersensitive people, the following effects may appear more frequently: Hypertension, photophobia, retrosternal pain, pallor, sweating and vomiting.

The potential life-threatening effects of norepinephrine are due to its dose-related hypertensive effect. With pulmonary edema and cerebral hemorrhage, acute hypertension can occur.

The extravasation of norepinephrine during intravenous infusion can cause drowsiness and necrosis around the infusion site. Prolonged infusions can follow gangrene of the extremities. Impaired circulation in the infusion site (with or without extravasation) can be alleviated by infiltration of a solution of phentolamine in warm dressing and 5mg / ml saline.

Prolonged administration of any potent vasopressor can cause plasma volume depletion, this can be corrected by appropriate fluid and electrolyte replacement therapy. If plasma volumes do not improve, hypotension may recur when norepinephrine treatment is discontinued or blood pressure may continue with a reduced risk of peripheral and visceral vasoconstriction with a decrease in blood flow.

Treatment:

The administration should be stopped until the patient's condition stabilizes.

Antidote: Intravenous administration of an alpha-blocker (5-10 mg), such as phentolamine mesylate. If necessary, this dose may be repeated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adrenergic drugs

ATC code: C01CA03

Norepinephrine is an endogenous catecholamine synthesized in the adrenal medulla and is the biochemical precursor of epinephrine. Norepinephrine has a predominantly direct effect on α-adrenergic receptors. Norepinephrine also directly stimulates the heart β-adrenergic receptors (β_1-adrenergic receptors) but does not affect those that are not found in the bronchi or peripheral blood vessels (β_2-adrenergic receptors). However, norepinephrine is less effective on β_1 receptors than epinephrine and isoproterenol. While beta adrenergic effects consist of adenyl cyclase activity stimulation; It consists of inhibition of the production of α-adrenergic effects by the inhibition of adenyl cyclase enzyme and cyclic adenosine-3 ',5'-monophosphate (AMP).

The main effects of therapeutic doses of norepinephrine are vasoconstriction and cardiac stimulation.

Cardiovascular effects: Norepinephrine, with its effects on α-adrenergic receptors, narrows both the resistance and capacitance of blood vessels. Increased total peripheral resistance results in increased systolic and diastolic blood pressure.

Norepinephrine acts on β_1-adrenergic receptors in the heart, creating a positive inotropic effect on the myocardium. In addition, although it shows a positive chronotropic effect through the sinoatrial node, this effect is overcome by increased vagal activity that occurs as a response to increased arterial blood pressure and often results in bradycardia. Bradycardia is inhibited by atropine.

In hypotensive patients, with the positive inotropic effect of norepinephrine, cardiac output may increase and may contribute to the presertive effects of the drug. However, cardiac output may change or decrease due to reflex bradycardia. If venous return to the heart decreases as a result of increased peripheral vascular resistance, a decrease in cardiac output may occur following prolonged use of the drug or administration at high doses.

5.2 Pharmacokinetic properties

General properties:

Absorption:

After pressing intravenously, a pressing response occurs quickly. The drug has a short-term effect, and the pressor effect stops within 1-2 minutes after the infusion is stopped.

Distribution:

Norepinephrine is mainly localized to sympathetic nerve tissues. The drug crosses the placenta but does not cross the blood-brain barrier. It binds to about 50% plasma proteins. The volume of distribution is 0.09-0.4 L / kg.

Biotransformation:

Pharmacological effects of norepinephrine primarily end with involvement and metabolism in the sympathetic nerve endings. Norepinephrine is metabolized in the liver and other tissues by a combination of reactions involving catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) enzymes. Major metabolites are normetanephrine and 3-methoxy-4-hydroxy mandelic acid (vanilylmandelic acid, VMA), both of which are inactive. Other inactive metabolites include 3-methoxy-4-hydroxyphenylglycol, 3,4 dihydroxyphenylglycol.

Elimination:

Norepinephrine metabolites are primarily excreted in the urine as sulfate conjugates and to a lesser extent as glucuronide conjugates. Only a very small amount of norepinephrine is excreted unchanged.

5.3 Preclinical safety data

No data are available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium metabisulphite

Water for injection

6.2 Incompatibilities

Norepinephrine; It is incompatible with alkaline solutions or oxidative substances, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiosin, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, insulin (reported incompatibility).

Norepinefirine has been shown to increase circulating levels of glycerol, acetoacetate, β-hydroxybutyrate and glucose. Plasma insulin, lactate, pyruvate and alanine levels decrease with

norepinephrine.

SELADRENALİN should not be mixed with plasma or whole blood, it should be applied separately.

6.3 Shelf life

24 months

After opening the ampoule, it must be diluted immediately.

6.4 Special precautions for storage

Store in the refrigerator at temperatures between 2-8°C, protected from light until the expiration date indicated on the box.

6.5 Nature and contents of container

10 pieces type I glass ampoule, containing 4 ml solutions in a carton box (10 x 4 ml).

6.6 Special precautions for 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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8. MARKETING AUTHORISATION NUMBER

2015/332

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation date: 04.05.2015

Renewal date of authorisation:-

10. DATE OF REVISION OF THE TEXT

15.04.2020