SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT
BİEMEFRİN 4 mg/4 ml I.V. Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active ingredient:
Each Vial contains 8 mg norepinephrine bitartrate (equivalent to 4 mg base norepinephrine).

Excipients:

Sodium metabisulphite (E223)	4 mg
Sodium chloride	34,35 mg
Sodium hydroxide	q.s.

For excipients, refer to 6.1.

3. PHARMACEUTICAL FORM
Concentrated solution for infusion.
Sterile, clear, colorless, aqueous solution with no apparent particulates.

4. CLINICAL PROPERTIES

4.1. Therapeutic indications

BİEMEFRİN is indicated for normalization of blood pressure in cases of acute hypotension.

4.2. Posology and administration route

Posology/ administration frequency and period

BİEMEFRİN must be administered only by expert medical professional.

BİEMEFRİN contains 8mg/4 ml norepinephrine bitartrate. Dosage is calculated according to base epinephrine. 2 mg of norepinephrine bitartrate equivalents to 1 mg base epinephrine. So, 4 mg base norepinephrine is available in each Vial.

Before administration of parenteral medicines, particulate matters and deterioration of color must be controlled visually. Parenteral norepinephrine is used for only by IV infusion.

In adults:

Correction of blood pressure:
In acute hypotensive conditions: Depletion of blood volume must be corrected before using any vasopressor. Norepinephrine can be administered during or before replacement of blood volume.

General dosage:
İnfusion is given generally at 2-3 ml/minute for initially (8-12 µg in minutes) or 0,11-0,17 microgram /kg/minutes) and quantity will adjust according to blood pressure. Values of blood pressure must be recorded at every two minutes initially and infusion rate is monitored continuously. After seeing the results for initial dosage, flow rate will be adjusted to obtain and maintain normal blood pressure (generally 80-100 mm Hg systolic) in order to maintain the circulations in important organs. In patients with hypertensive before, it is recommended that systolic pressure must not be increased to more than 400 mm Hg.
Average flow of 0,5-1ml/minutes diluted solution (or 0,03-0,06 microgram/kg/minute) is enough and generally it will provide enough values of blood pressure.
Posology mentioned above is not certain. Dosage must be determined according to conditions of heart and blood vessels of patient. Sensitivity to product can show important differences from patient to patient.
If patient remains hypotensive, administration of 17 Vials of 4 ml within 24 house can required (quantity equivalent to 0,67 microgram/kg/minutes) but always must be suspected about confident depletion of blood volume and if necessary it must be corrected. Monitoring central venous pressure generally helps the identification and treatment of this condition.
Treatment period:
Treatment period is different for each clinical case and can change 1-2 hours to 6 days. Infusion must continue until enough tissue infusion and enough blood pressure. In order to prevent the serious decreasing of blood pressure, infusion must be stopped slowly by decreasing step by step.
Method of administration:
Dilution:
BİEMEFRİN is administered by dilution of 1 liter of 5% glucose or mixture of 0.9% sodium chloride and 5% glucose (50/50) by IV infusion. For patients applied to non-salt diet, it is diluted only with 5% glucose solution. Glucose solution is used to prevent the oxidation of norepinephrine into L-norepinephrine.
To obtain the desired concentrations of norepinephrine, below table must be taken as reference to calculate the dilutions for Vial contents.

Desired norepinephrine base contents	**Used numbers of Vials**	**Used volume of dilution solutions**
4 microgram/ml	1	1 liter
8 microgram/ml	2	1 liter
12 microgram/ml	3	1 liter
16 microgram/ml	4	1 liter
20 microgram/ml	5	1 liter

BİEMEFRİN must not be mixed with plasma or complete blood. Applications must be done separately. (For example, if administration is at the same time, Y-tube or separate containers must be used).
Taking liquid:
Degree of dilution depends on clinical volume requirements.
If high volume is required for flow rate containing excess dosages of pressor agent per a unit of time (dextrose), a solution less rare than 4 microgram/ml must be used. Furthermore, if high volume of liquid is not desired, high concentrations more than 4 microgram/ml can be required.
Injection site:

Norepinephrine is administered as only intravenous infusion. Infusions of norepinephrine are administered into large veins. Especially antecubital veins must be preferred because risk of tissue necrosis seems weak caused by long vasoconstriction. Injections into veins at lower extremities are not recommended.
Control of blood pressure:
After the beginning of infusion, blood pressure must be controlled every two minutes until obtaining desired blood pressure. If administration will continue, controls must be done every 5 minutes after obtaining desired blood pressure.

Flow of infusion must be controlled frequently and patient must not be left alone during infusion.
Risk of extravasation:
Freeness of flowing of infusion must be controlled frequently.
Because of increasing permeability and vasoconstriction of vein walls, flowing of medicine can occur at environmental tissues of vein. Because of this, if weakness occurs, infusion site must be changed to decrease the effects of local vasoconstriction.
Treatment of ischemia because of extravasation.
In case of injection of medicine into exterior of vein or flowing medicine into exterior veins, tissue destructions can occur sourced from vasoconstrictor effects of medicine at blood vessels.
Injection site must be washed rapidly with physiological salt solution containing 5-10 mg phentolamine mesilate.
For this purpose, an injector with thin needle must be used and injected locally. Vial must be controlled visually and must not be used in case of seeing particulates and color changing.
Additional information for special populations:
Renal/liver disorders:
Pharmacokinetic of norepinephrine is not effected by renal or hepatic diseases. Because of the fact that blood flow can decrease in liver or renally, please be careful when using symphatomimetics on patients with liver or renal diseases.
Pediatric populations:
Studies on new-borns for effects of norepinephrine are not enough. While using norepinephrine for children, please be careful like adults. As initial dosage for children, infuse 0,05 µg/kg/minute base norepinephrine with controlling blood pressure and increase to 0,5 µg/kg/minute base.
Geriatric population:
Must be administered carefully on geriatrics, especially on the ones who are sensitive to sympathomimetic agents and norepinephrine.
4.3. Contraindications
BİEMEFRİN is contraindicated in following conditions:

- Hypersensitivity to norepinephrine or excipients in contents of medicine: BİEMEFRİN contains sodium metabisulphite as excipient. It rarely causes serious hyper-sensitivity reactions and bronchospasm.
- Hypertension: Hypertensive patients can be more sensitive to pressor effects of norepinephrine.
- Hyperthyroidism: These patients are sensitive to norepinephrine effects and toxicity can occur at low dosages.
- Prinzmetal’s Angina: In these patients, coronary blood flow can decrease in times and quantities that can cause myocardial infarcts.
- Hypotension because of blood volume deficiencies,
- Hypercapnia, hipoxia and obstructive vascular disease,

- Norepinephrine can increase excitability of heart muscles and causes rapid and irregular contractions of cardiac rooms. Because of this, BİEMEFRİN is contrendicated during anesthesias with chloroform, siklopropane and halothane.

4.4. Special warnings and precautions for use

Cardio-vascular system:

Because of alpha-agonist properties, while infusing norepinephrine, blood pressure and flow rate must be controlled frequently until obtaining desired blood pressure to prevent hypertension. To prevent decreasing effects of blood volume, norepinephrine must be used with only suitable blood volume replacement. These are induced hypotension at the end of treatment and cause vasoconstrictions and vascular obstructions.

Blood:

In case of oxygen deficiency and excessive concentrations of blood carbonic gases, BİEMEFRİN must not be used without doctor desicion due to risks of causing cardiac rthym disturbances (rapid pulse or non-effective and non-coordinated contractions of hearth).

Extravasations:

Norepinephrine is serious tissue irritant and must be used only with very diluted solutions. If possible, it must infused into large vens into central position and must carefull for extravasations.

It must be used carefully in diabet, narrow angle gloko and prostat hypertrophias.

BİEMEFRİN contains sodium metabisulphite as excipient and it can cause hyper-sensivity reactions and broncospasms.

BİEMEFRİN contains less than 1 mmol (23 mg) sodium. In this dosage, any side effects caused by sodium are not expected.

4.5. Interactions with other medicines and other interaction types

BİEMEFRİN must not be used with chloroform, cyclopropane and during halothan anestesias (refer to contrendications). Aritmias must be treated with β-adrenergic blocer like propranole.

BİEMEFRİN must use carefully in patients using following medicines because of potential dangerous interactions:

- Atrophine sulphate,
- Tricyclic antidepressants (exp; imipramine),
- Antihistaminics (diphenhydramine, tripelennamine, dexchlorpheniramine),
- Vasopressor effects of norepinephrine can potantialized by alcoholoids derivated ergotamine, guanethidine or methyl dopa and cause serious hypertension.
- Serious and longer hypertension can occur with MAOI (monoamine oxidase) inhibitors.
- Digitaline and quinidine can cause arytmias.
- Arterial response of norepinephrine can decrease by furosemide and other diuretics.

Vasopressor effect sourced from α adrenergic effect of vessels can decrease with same-time application of α-blocker agent like phentolamine mesilate. Administration of β-blocker agent (propranolol) can decrease stimulane effects of medicine on heart (coming from β1 adrenergic effects) and increase hypertansor effects following arteriol dilatations (from β2 adrenergic effects).

4.6. Pregnancy and lactations

General recommendations:

Pregnancy category: C

Womens with bearing children/ birth control (contraception)
There is no data about effects of BİEMEFRİN on methods for contraception.

Pregnancy period:
Studies on animals are deficient with regard to pregnancy and/or embrional/fetal development and/or birth and developments after births.
Safety usage in pregnants is not demonstrated. Because of this, it should be used during pregnancy if absolutely necessary. It can cause decreasing of heart rthym for fetus because of decreasing effect of blood circulations in placenta. Furthermore it can increase ratio of uterus contractions and it can cause fetus die at the last stage of pregnancy. Because of this, it must be used in case of clinical advantages of BİEMEFRİN is more than possible risks to fetus in emergency cases.

Lactation period:
It is not-known if norepinephrine excretes with human milk or not. Excretion of norepinephrine with milk was not researched on animals. When deciding about stopping of lactation or stopping of BİEMEFRİN treatment, benefits of lactation to baby and benefits of BİEMEFRİN treatment to lactating women must carefully evaluated.

Reproductive capability/Fertility
Animal reproductive studies with norepinephrine are not conducted.

4.7. Effects on driving and usage of machinery
There are no effects of BİEMEFRİN on driving and usage of machinery capabilities.

4.8. Side effects
These are classified as very common (≥1/10); common (≥1/100 between <1/10); non-common (≥1/1.000 between <1/100); rarely (≥1/10.000 between <1/1.000); very rare (<1/10.000), not-known (it is not estimated from available data).

Disease of nerve system:
Not-common: Anxiety, insomnia, confusion, sefalgia, headache, psicotic condition, tremor, tiredness, hypervigilance, anorexia, vomiting and nausea.

Eye disorders:
Not-common: Acute glokom: it is very frequent in anatomically sensitive to closing angle of iridokorn.

Cardiac diseases:
Common: Tachicardia, bradycardia, aritmias, palpitations, contractility increasing of cardiac muscles sourced from $ß_1$ adrenergic effects, acute cardiac insufficiencies.
Vascular disease:
Very-common: arterial hypertension and tissue hipoxias: because of potent vasoconstructor effects, ischemical defaults.

Breathing, chest disturbances and mediastinal disease:
Not-common: diffuculties in breathing, dispnea

General disturbances and disease related to injection site:
Not-common: irritation at injection site and necrosis, coldness at extremities and face, contraction of blood vessels resulting faintness.
If blood volume replacement treatment is not performed, continuous norepinephrine administration can cause following symptoms for continuing of blood pressure:
- Serious peripheral and visseral vasoconstructions,

- Decrase in out-put of renal blood,
- Decrese in manufacturing of urine,
- Insufficient oxygen level in tissues,
- Increase of levels for lactic acide in blood.

4.9. Overdose and treatment
Symptoms:

Overdose can cause headache, serious hypertension, faintness, abnormal slow pulse, increasing of peripheral resistance and low heart ratio.
Following effects can be seen in overdose cases or usual dosage on hypersensitive patients: hypertension, photofobia, retrosternal pain, faintness, vomiting, excessive secretion.

Possible life-threatening effects of norepinephrine are sourced from its hypotensive effects which are related to dosage. Pulmonary oedema and cerebral hemorrhage can occur in acute hypertension.
Extravasation of norepinephrine during intravenous infusion can result in insensivity at injection site and necrosis in enviromental of injection site. Prolonged infusions can result in gangrene at extremities. Deterioted circulation at injection site (with extravasation or without extravasation) can be eased with hot flaster and infiltration of phentolamine solution in 5 mg/ml serum physiologic.
Prolonged administration of any potent vasopressor can cause plasma volume depletion and this can be corrected by replacement treatment of liquid and electrolites. If plasma volumes were not corrected, hypotension can repeate after stopping of norepinephrine treatment or blood pressure can continue with serious peripheric and visseral vasoconstructions by decreasing of blood flow.

Treatment
Administration must not be stopped until stabilization of patient.
Antidote: Administration of alpha-blocer like phentolamine mesilate (5-10 mg) by intravenously. If necessary this dosage can repeate.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Pharmaco-therapeutical group: Adrenergic medicines
ATC code: C01CA03

Norepinephrine is an endogen catecolamine which is synthesed by adrenal medulla and precursor of epinephrine. Norepinephrine effects on α-adrenergic receptors directly. Also, norepinephrine is stimulated directly to β- adrenergic receptors in heart (β1-adrenergic receptors), but, it is not effective on not-availible receptors on bronciols and peripheral blood vessels (β2-adrenergic receptors). Furthermore, norepinephrine effects β1 receptors less than epinephrine and isoproterenole. Beta adrenergic effects is occured by stimulation of adenile cyclase activity. α-adrenergic effects can occur by inhibition of adenile cyclase enzym and inhibition of manufacturing of cyclic adenosine-3',5'-monophosphate (AMP).

Main effects of norepinephrine at therapeutical dosages are vasoconstruction and cardiac stimulation.

Cardiovascular effects: Norepinephrine is contracted capacity and resistance of blood vessels by its effects on α-adrenergic receptors. Total increasing of peripheral resistance results in increase in sistolic and diastolic blood pressures.

Norepinephrine effect on β1- adrenergic receptors in heart by positive inotropic effects on myocardium. Furthermore, it shows positive inotropic effects by sinoatrial points and this effect can be prevented by increasing vagal activity which is answer for increased arterial blood pressure and generally results in bardicardy. Bradicardy prevents with atrophine. Heart ratio can increase in hypotensive patients because of positive inotropic effects of norepinephrine and cause additional effects on presor effects of medicine. Furthermore, because of reflex bradycardy, heart ratio can change or decrease. If venous circulation to heart decreases by increasing peripheral vascular resistance, heart ratio can decrease after prolonged usage of medicine or usage at high dosages of medicine.

5.2. Pharmacokinetic properties

General properties

Absorption:

After intravenous administration, a pressor answer can obtain rapidly. Medicine has got short effects and its pressor effects stop after stopping of infusion within 1-2 minutes.

Distribution:

Norepinephrine is essentially localized in tissues of sympatical nerve. Medicine passes to placenta but, it does not across brain-blood barrier. It binds to plasma protein in ratio of 50%. Distribution volume is 0.09-0.4 L/kg

Biotransformation:

Pharmacological effects of norepinephrine are ended by firstly holding on end of sympatical nerves and metabolization. Norepinephrine is metabolized by combination reactions of catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO) enzymes in liver and other tissues. Inactive majör metabolites are normetanephrine and 3- metoxi-4-hydroxi mandelic acid (vanililmandelic acid, VMA). Other inactive metabolites are 3-metoxi-4-hydoxiphenilglycole, 3,4-dihydroxiphenilglycole.

Elimination:

Metabolites of norepinephrine are excreted by urine as more sulphate conjugates and less glucuronide conjugates. Only small quantity of norepinephrine is excreted as un-changed.

5.3. Pre-clinical safety data

Any data are not available.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Sodium metabisulphite (E223)
Sodium chloride
Sodium hydroxide
Hydrochloric acide
Water for injections

6.2. Incompatibilities
Norepinephrine is incompable with alkaline solutions, oxidative substances, barbiturates, chlorpheniramine, chlorotiazide, nitrofurantoine, novobiosine, phenytoin, sodium bicarbonate, sodium iodide, streptomicine, insulin (one incompatibility is informed).

It is showed that norepinephrine can increase levels of glycerole, acetoacetate, β-hydoxibutirate and glucose in circulation. Levels of plasma insulin, lactate, pyruvate and alanine decrease with norepinephrine.

BİEMEFRİN must not be mixed with plasma and complete blood they must be administered seperately.

6.3. Shelf-life
24 months (un-opened vial)
After opening, vial must dilute immediately. In view of microbiologically, product must use immediately after dilution. It must be used within 24 hours when it is diluted (5% dekstrose or mixture of 5% dextrose and 0.9% sodium chloride) and when it is stored at below 25°C room temperature.

6.4. Storage instructions
It must be stored in a refrigerator (2-8°C), protected from light until expiry date of written on the box.

Storage conditions for diluted products refer to section 6.3.

6.5. Nature of packaging and contents

Type 1 glass of 10 Vials containing 4 ml solution in cardboxes.

6.6. Destructions of excessive substances from product and other special precautions
Un-used products and waste materials must destroy suitable according to guideline on waste materials and controls of packaging and packaging waste.

7. REGISTRATION HOLDER
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8. REGISTRATION NUMBER
2014/217

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First registration date: 11.03.2014
Renewal date:

10. REVISION DATE OF SMPC: