

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

BIEMEFRİN 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

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

4.2. Posology and administration route

Posology/ administration frequency and period

BIEMEFRİN must be administered only by expert medical professional.

BIEMEFRİN 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:

Infusion 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:

BIEMEFRİN 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

BIEMEFRİN 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:

Freedom 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 sympathomimetics 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

BIEMEFRIN is contraindicated in following conditions:

- Hypersensitivity to norepinephrine or excipients in contents of medicine: BIEMEFRIN 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, hypoxia and obstructive vascular disease,

- Norepinephrine can increase excitability of heart muscles and causes rapid and irregular contractions of cardiac rooms. Because of this, BIEMEFRIN is contraindicated during anesthetics 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, BIEMEFRIN must not be used without doctor decision due to risks of causing cardiac rhythm 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 be infused into large veins into central position and must be careful for extravasations.

It must be used carefully in diabetes, narrow angle glaucoma and prostatic hypertrophias.

BIEMEFRIN contains sodium metabisulphite as excipient and it can cause hyper-sensitivity reactions and bronchospasms.

BIEMEFRIN 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

BIEMEFRIN must not be used with chloroform, cyclopropane and during halothane anesthetics (refer to contraindications). Arrhythmias must be treated with β -adrenergic blocker like propranolol.

BIEMEFRIN must be used carefully in patients using following medicines because of potential dangerous interactions:

- Atropine sulphate,
- Tricyclic antidepressants (e.g. imipramine),
- Antihistaminics (diphenhydramine, triprolidine, dexchlorpheniramine),
- Vasopressor effects of norepinephrine can be potentiated by alcoholoids derived ergotamine, guanethidine or methyl dopa and cause serious hypertension.
- Serious and longer hypertension can occur with MAOI (monoamine oxidase) inhibitors.
- Digitalin and quinidine can cause arrhythmias.
- 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 stimulant effects of medicine on heart (coming from β 1 adrenergic effects) and increase hypertensive effects following arteriolar dilatations (from β 2 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 BIEMEFRIN 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 pregnant 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 BIEMEFRIN 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 BIEMEFRIN treatment, benefits of lactation to baby and benefits of BIEMEFRIN 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 BIEMEFRIN on driving and usage of machinery capabilities.

4.8. Side effects

These are classified as very common ($\geq 1/10$); common ($\geq 1/100$ between $< 1/10$); non-common ($\geq 1/1.000$ between $< 1/100$); rarely ($\geq 1/10.000$ 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 β_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,

- Decrease in out-put of renal blood,
- Decrease in manufacturing of urine,
- Insufficient oxygen level in tissues,
- Increase of levels for lactic acid 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, photophobia, 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 insensitivity at injection site and necrosis in environment of injection site. Prolonged infusions can result in gangrene at extremities. Deteriorated 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 electrolytes. If plasma volumes were not corrected, hypotension can repeat after stopping of norepinephrine treatment or blood pressure can continue with serious peripheral and visceral vasoconstrictions by decreasing of blood flow.

Treatment

Administration must not be stopped until stabilization of patient.

Antidote: Administration of alpha-blocker like phentolamine mesilate (5-10 mg) by intravenously. If necessary this dosage can repeat.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutical group: Adrenergic medicines

ATC code: C01CA03

Norepinephrine is an endogenous catecholamine which is synthesized 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 (β_1 -adrenergic receptors), but, it is not effective on not-available receptors on bronchi and peripheral blood vessels (β_2 -adrenergic receptors). Furthermore, norepinephrine effects β_1 receptors less than epinephrine and isoproterenol. Beta adrenergic effects is occurred by stimulation of adenylate cyclase activity. α -adrenergic effects can occur by inhibition of adenylate cyclase enzyme and inhibition of manufacturing of cyclic adenosine-3',5'-monophosphate (AMP).

Main effects of norepinephrine at therapeutical dosages are vasoconstriction 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 systolic and diastolic blood pressures.

Norepinephrine effect on β_1 - 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 bradycardia. Bradycardia prevents with atropine. Heart ratio can increase in hypotensive patients because of positive inotropic effects of norepinephrine and cause additional effects on pressor effects of medicine. Furthermore, because of reflex bradycardia, 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 symptactical 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 symptactical 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 major metabolites are normetanephrine and 3- metoxi-4-hydroxi mandelic acid (vanililmandelic acid, VMA). Other inactive metabolites are 3-metoxi-4-hydroxi phenilglycole, 3,4-dihydroxi phenilglycole.

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 incompatible with alkaline solutions, oxidative substances, barbiturates, chlorpheniramine, chlorothiazide, nitrofurantoin, novobiosine, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, insulin (one incompatibility is informed).

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

BIEMEFRİN must not be mixed with plasma and complete blood they must be administered separately.

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% dextrose 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 cardboard boxes.

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

9. FIRST REGISTRATION DATE/ RENEWAL DATE:

First registration date: 11.03.2014

Renewal date:

10. REVISION DATE OF SMPC: