PATIENT INFORMATION LEAFLET

BİEMEFRİN 4 mg/4 ml I.V. ampoule of injectable solution for infusion

It is administered into veins.

•***Active ingredient:*** Each ampoule contains 8 mg norepinephrine bitartrate (equivalent to 4 mg base norepinephrine).

•***Excipients:*** Sodium metabisulphide, sodium chloride, sodium hydroxide, hydrochloric acid and water for injection.

Before use this medicine, please read this PATIENT INFORMATION LEAFLET carefully, because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, consult your doctor or your pharmacist.*
- *This medicine has been prescribed for you personally; you should not pass it on to others.*
- *During use of this medicine please tell to your doctor that you use this medicine when you go to the doctor or hospital.*
- *Follow the information in the leaflet exactly. Do not use lower or higher dosages rather than recommended dosages regarding the medicine.*

In this patient information leaflet:

1. What BİEMEFRİN is and what is used for?

BİEMEFRİN must be used by expert medical personnel in hospital.

BİEMEFRİN contains 10 of type 1 glass ampoules containing 4 ml solution. Each ampoule contains norepinephrine bitartrate as active ingredient.

BİEMEFRİN is presented as solution form and must only be used after dilution intravenously.

BİEMEFRİN is used for immediate medical conditions at below:

- Returning blood pressure to normal levels in acute hypotension conditions,

2. What you need to know before you use BİEMEFRİN?

Do not use BİEMEFRİN for following conditions:

If;

- You are allergic to Norepinephrine or other excipients of BİEMEFRİN
- You have hypertension (high blood pressure), because hypertensive patients can be more sensitive to effects of norepinephrine under increasing of blood pressure,
- Hypotension cases due to insufficient blood volume,
- Excess carbon dioxide in blood (hypercapnia), insufficiency of tissue oxygen (hypoxia) and obstructive vessel disease,
- You have a type of angina (chest pain) called Prinzmetal's angina. Because, coronary blood flow (blood vessel of heart) can decrease in time and quantity that can cause myocardial infarcts,
- Hyperthyroidism (excess working of thyroidal tissues). These patients are sensitive to effects of norepinephrine and toxicity can occur at low dosages,
- During anesthesia with chloroform, cyclopropan and halothane. Because, norepinephrine can increase stimulating of heart muscles and results rapid and not suitable contractions.

Use BİEMEFRİN carefully for following conditions:

- BİEMEFRİN must not be injected into lower extremity sites,
- Because of strong effects of BİEMEFRİN, risks for dangerous increases in blood pressure are possible. In case of excess increasing of blood pressure, treatment must be stopped.
- Longer use of a medicine which causes narrowing of blood vessels can cause decrease of plasma volume. This deficiency must be prevented by water and suitable salt.
- Use carefully in cases of diabetes, narrow angle glaucoma and growing of prostate.
- Norepinephrine is a strong irritant for tissues. Because of this, only very diluted solutions must be used. If you feel itching and pain at injection site, please inform your doctor immediately. Because solution can flow towards exterior of blood vessels.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Use of BİEMEFRİN with food and drinks

Not valid.

Pregnancy

Before use this medicine, consult your doctor or pharmacist.

BİEMEFRİN can decrease blood circulation of placenta and can accelerate heart rhythm of fetus. It can cause contraction effect on uterus and cause fetus death at the end of pregnancy. Because of this, if clinical benefits during the rescue of pregnant women are more than risk for babies it can be used.

If you notice that you are pregnant during treatment consult your doctor immediately.

Breast-feeding

Before use this medicine, please consult your doctor or pharmacist.

It is not known if norepinephrine is excreted with mother milk or not.

It was not researched on animals if norepinephrine excretes with milk or not. When deciding of stopping lactation or stopping treatment of BİEMEFRİN, your doctor will decide according to the benefits of lactation to baby and benefits of BİEMEFRİN treatment to lactating women.

Using machinery and vehicles

There are no effects of BİEMEFRİN for driving ability or using machinery or vehicles.

Important information about excipients in contents of BİEMEFRİN

Sodium metabisulphide rarely causes hyper-sensitivity reactions or bronchospasm.

This medicine contains less than 23 mg sodium in 4 ml in each ampoule. Sodium with this dosage level cannot cause side effects.

Use with other medicines

General anesthesia products like chloroform, cyclopropan or halothane (this substance can cause simulative effects on heart muscles and irregular contractions) must not be used with BİEMEFRİN.

Atropine sulphate which is used for slow heart rate, hypotension and disturbances for heart rhythm and antihistaminics which are used for allergy (diphenylhydramine, tripelennamine, dexchlorpheniramine) must be used carefully.

Some of the ergotamine derivate alkaloids (guanetidine or metildopa) can potantialize the vasopressor effects of norepinephrine and result in serious and persistent hypertension.

In patients taking high dosages of digitaline and quinidine heart rhythm disturbances can occur.

Rezepine, guanetidine and cocaine can increase the effects of BİEMEFRİN.

It must not be used with tricyclic antidepressants (exp; imipramine) and mono amine oxidase inhibitors which are used for treatment of depression.

It must be used carefully with Furosemide and other diuretics (medicines for increasing manufacturing of urine).

Norepinephrine increases levels of glycerol, acetoacetate, β-hydroxibutirate and glucose in circulation. Levels of plasma insulin, lactate, pyruvate and alanine decrease with norepinephrine.

If you are taking or have recently taken any other medicines, including medicines obtained without a prescription, please tell your doctor or your pharmacist.

3. How to use BİEMEFRİN

Instructions for suitable usage and dose/frequency:

BİEMEFRİN will be administered to you after being diluted with 5% glucose solution or mixture of 5% glucose and 0.9% NaCl.

Your doctor will decide the dosage according to your disease.

Information for medical experts is at the end of this leaflet.

Administration route and method:

BİEMEFRİN will preferably be injected to a large vessel of your arm by infusion.

If you think that the effect of BİEMEFRİN is too high or too low, please consult your doctor or your pharmacist.

If you receive more BİEMEFRİN than you should:

BİEMEFRİN will be administered by your doctor in hospital. Because of this, using a dosage more than required is not possible. But if you are suspicious about dosage, please speak to your doctor or your nurse.

In case of excess dosage or normal dosages in hyper-sensitivity cases of product, following effects are seen more frequently: hypertension, afraid of light, pain in chest, paleness, over-sweating and vomiting.

Treatment:

Administration must be stopped immediately until the patient stabilizes.

Antidote: Intravenous administration of alpha-blocker like phentolamine mesilate (5-10 mg). If necessary this dosage can be repeated.

If you think that more dosages of BİEMEFRİN have been administered to you than it should have, please speak to your doctor or pharmacist.

If you forgot to take BİEMEFRİN:

Not valid.

If you have further questions about the usage of this medicine, ask your doctor.

4. What are the possible side effects?

Like all medicines, side effects can be seen in patients who are hypersensitive to contents of substances for BİEMEFRİN.

Side effects are ordered according to below categorization:

Very common	: at least one in 10 patients.
Common	: less than one in 10 patients, but, more than one in 100 patients
Uncommon	: less than one in 100 patients, but, more than one in 1000 patients.
Rare	: less than one in 100 patients, more than one in 10000 patients.
Very rare	: less than one in 10.000 patients.
Not-known	: It is not estimated from available data.

Very common:

-Hypertension and oxygen insufficiency in tissue. Ischemic damage due to effect of strong contractions of vessels.

Common:

-Palpitations, low pulse, disturbances of heart rhythm, irregular heart rate, contraction of heart muscles sourced from β_1 adrenergic effects in heart, acute heart insufficiency

Not-common:

- Anxiety, insomnia, dizziness, headache, psychotic conditions, tiredness, palpitations, increasing of warnings, lack of appetite, vomiting, nausea.
- Sudden increasing of intraocular pressure, it is very frequent in patients with anatomically sensitivity for closing of iridocorn angle.
- Difficulties for inhalation, shortness of breath.
- Irritation and tissue death at injection site, coldness on face and extremities, paleness caused by contraction of blood vessels.

Long-term norepinephrine administration to patients without blood volume replacement in order to maintain blood pressure can cause following symptoms:

- Serious narrowing of vessels in internal and superficial organs
- Decrease in renal blood flow

- Decrease in manufacturing of urine
- Insufficient oxygen levels in tissues,
- Increase in levels of lactic acid in blood.

Life-threatening effects of norepinephrine are sourced from hypertensive effects related to dosage. Lung oedema and cerebral bleeding can cause acute hypertension.

During intravenous infusion, outflow of norepinephrine can cause tissue death and insensitivity in infusion area. Prolonged infusions can cause gangrene in extremities.

Circulation disturbances at injection site (filtrated or infiltrated) can be prevented with hot compress and phentolamine (diluted with 5mg/10ml serum physiologic).

Plasma insulin, lactate, pyruvate and alanine levels decrease with norepinephrine.

Long-term usage of any potent vasopressor can cause plasma volume depletions. It can be corrected with replacement treatment of proper liquid and electrolytes. If the plasma volumes are not corrected, hypotension can repeat when norepinephrine treatment ends or blood pressure can continue with peripheral and visceral vasoconstriction risks by decreasing of blood flow.

If you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

5. Storage of BİEMEFRİN

Keep BİEMEFRİN out of the reach end sight of children and store in the original pack.

Store ampoules of BİEMEFRİN below 25 ºC in outer pack and protect from light.

Diluted infusion solutions are stabile for 24 hour at room temperatures below 25ºC in 5% dextrose solutions containing of 0.9% sodium chloride (mixture 50/50 h/h) or non-containing 0.9% sodium chloride.

Please use BİEMEFRİN in accordance with expiry date.

Do not use BİEMEFRİN after expiry date on pack.

If you notice any deterioration on product and/or its packaging, do not use BİEMEFRİN.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicine no longer required.

Registration holder: Biem İlaç San. ve Tic. A.Ş.
Anıttepe Mah. Turgut Reis Cad. No: 21
Tandoğan / Çankaya – Ankara

Manufacturing site : Mefar İlaç Sanayii A.Ş.
Kurtköy-Pendik/İstanbul

This patient information leaflet is approved on 18.02.2015

FOLLOWING INFORMATION IS FOR MEDICAL PERSONEL WHICH WILL USE THIS PRODUCT:

Information on usage, packaging and destruction:

1) Concentrated solution must be diluted with below mentioned diluted solution. Aseptic technic must be used during norepinephrine dilution for intravenous infusion.

2) Products for injection must always be examined visually. Product must not be used in case of visible particulates or change of color.

3) Norepinephrine is only used as intravenous infusion. Infusion of Norepinephrine is administered into large veins. Especially antecubital veins are preferred. Because in this case risk of necrosis of tissue caused by extended vasoconstriction seems weak. Lower extremity veins must not be used.

4) In case of injections into exterior of veins, effected areas must be washed with phentolamine mesilate.

5) Please put intravenous catheter to a suitable center vein by injector needle and fix with sticking band.

6) Infusion site must be controlled frequently for free flow.

7) Blood pressure must be monitored regularly. 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.

8) Infusion flow rate must be monitored with infusion system and also patient must be watched during infusion.

9) Un-used product must be disposed of in accordance with local rules.

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 enough normal blood pressure (generally 80-100 mm Hg systolic) to keep the circulations in important organs. For patients hypertensive before, it is recommended that systolic pressure must not be increased to more than 400 mm Hg.

Average flow of 0,5-1 ml/minutes for diluted solution (or 0,03-0,06 microgram/kg/minute) is generally enough to 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 ampoules of 4 ml within 24 hours can be required (quantity equivalent to 0,67 microgram/kg/minutes) but always must be suspected about confidential depletion of blood volume and if necessary must be corrected. Monitoring of central venous pressure generally helps identifying and treating 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. Infusion must stop slowly by decreasing step by step to prevent serious decrease of blood pressure.

- Dilution

BİEMEFRİN is administered by dilution of 1 liter of 5% glucose or mixture of 0.9% sodium chloride and 5% glucose (50/50) as IV infusion. Patients applied to non-salt diet, it must be diluted only with 5% glucose solution. Glucose solution is used in order 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 ampoule contents.

Desired norepinephrine base contents	**Used numbers of ampoules**	**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. (If administration is at same time, it is recommended to use y-tubes or separate containers).

- Taking fluid:

Degree of dilution depends on clinical volume requirements.

If high volume of liquid is required for flow rate containing excess dosages of pressor agent (dextrose) solutions less rare than 4 microgram/ml must be used. Furthermore, if high volume of liquid is not desired, higher concentrations than 4 microgram/ml can be required.

- Injection site:

Norepinephrine is only used as intravenous infusion. Infusion of Norepinephrine is administered into large veins. Especially antecubital veins are preferred. Because in this case risk of necrosis of tissue caused by extended vasoconstriction seems weak. Lower extremity veins must not be used.

- 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. This condition is not because of extravasation certainly and results in weak tissues. Because of this, if weakness occurs, infusion site must be changed to decrease the effects of local vasoconstriction.

- Treatment of ischemia due to 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. Ampoule must be controlled visually and must not be used in case of seeing particulates and color changing.

Additional information for special populations:

Renal/liver insufficiencies:

Pharmacokinetic of norepinephrine is not affected by renal or hepatic diseases. Because of blood flow can decrease in liver or kidneys, please be careful when using sympathomimetic on patients with liver or renal diseases.

Pediatric populations:

Studies on newborns 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:

It must be administered carefully on geriatrics, especially on the ones who are sensitive to sympathomimetic agents and norepinephrine.

Warnings for use:

Norepinephrine is incompatible with alkaline solutions, oxidative substances, barbiturates, chlorpheniramines, chlorotiazide, nitrofurantoin, novobiosine, phenytoin, sodium bicarbonate, sodium iodide, streptomycin, insulin (one incompatibility were informed), complete blood and plasma.

Do not mix BİEMEFRİN with complete blood and plasma. If you want to increase blood volume, BİEMEFRİN must be used separately from plasma or complete blood, like using Y-system.

Infusion site must be controlled frequently. Please be careful for extravasations resulting in tissue necrosis around the vein used for infusion. During extravasation of norepinephrine or in case of injections into exterior of veins, tissue destructions can occur because of the vasoconstrictor effects of product in blood vessels.

Because of vasoconstrictions at vein walls caused by increased permeability, norepinephrine may flow into environmental tissues of infused vein. This situation is not certainly caused by extravasation and causes tissue deteriorations. If this situation occurs, infusion site must be changed to decrease the effects of local vasoconstrictions.

Treatment of ischemia because of extravasation:

In case of injection of medicine into exterior of vein or medicine flow into exterior veins, tissue destructions can occur due to 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, a good syringe with a proven good injector needle must be used and injected locally.

Treatment of other problems for circulations:

Deteriorated circulation at infusion site can be eased with infiltration of area with injection of solution for 10 ml sodium chloride containing 5 mg phentolamine mesilate and hot flaster (with extravasation or non-extravasation).

If you are given more BİEMEFRİN than you should:

Administration must be stopped immediately until the patient stabilizes.
Alpha-blocker like phentolamine mesilate (5-10 mg) can be administrated intravenous as antidote. If necessary, dosage can be repeated.

Interactions with laboratory tests:

Norepinephrine can increase levels of glycerol, acetoacetate, β-hydroxibutirate and glucose in circulation. Levels of plasma insulin, lactate, pyruvate and alanine decrease with effects of norepinephrine.