

## PATIENT INFORMATION LEAFLET

### NEFRASIN IV Amino Acid Solution for Infusion

#### Sterile

#### Administered intravenously.

• **Active substance:** Each 100 mL solution contains 0.25 g L-Histidine, 0.56 g L-Isoleucine, 0.88 g L-Leucine, 0.64 g Lysine (0.90 g L-Lysine Acetate), 0.88 g L-Methionine, 0.88 g L-Phenylalanine, 0.40 g L-Threonine, 0.20 g L-Tryptophan, 0.64 g L-Valine and less than 0.02 g L-Cysteine hydrochloride monohydrate.

• **Excipients:** Sodium bisulfite and water for injection

**Before using this medicine, read all of this PATIENT INFORMATION LEAFLET carefully. Because, this leaflet includes important information for you.**

- *Keep this patient information 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. Do not pass it on to others.*
- *During the use of this medicine, tell that you are using this medicine when you go to a doctor or hospital.*
- *Follow these instructions exactly as written. Do not use **higher or lower** dose other than your recommended dose.*

#### What is in this Leaflet:

1. *What NEFRASIN is and what it is used for?*
2. *What you need to know before you use NEFRASIN*
3. *How to use NEFRASIN?*
4. *What are the possible side effects?*
5. *How to store NEFRASIN*

#### Headings are included.

#### 1. What NEFRASIN is and what it is used for?

- NEFRASIN is a solution that contains amino acids, which are the building blocks of proteins, which are nourishing substances for the body. It is available in 500 mL bottles.

NEFRASIN is used to provide the necessary nutritional support in renal patients who cannot tolerate the administration of general purpose amino acids.

## **2. What you need to know before you use NEFRASIN**

### **DO NOT USE NEFRASIN in the following cases;**

If,

- If you have previously had an allergic reaction when you took NEFRASIN or one of its ingredients, that is, if you suddenly developed symptoms such as shortness of breath, wheezing, skin rash, itching or swelling in your body (if you are not sure whether you have allergies, consult your doctor);
- If the salt and acid-base balance in your body is seriously disturbed;
- - If you have higher than normal levels of ammonia, which is a very harmful substance for the nervous system, which is formed in the blood as a result of the breakdown of amino acids (hyperammonemia);
- If the volume of blood circulating in your veins has dropped below critical levels;
- If the production and destruction of amino acids (amino acid metabolism) is congenitally damaged, DO NOT use this medicine.

### **USE NEFRASIN CAREFULLY for the following cases;**

- If you have severe hepatic impairment or liver coma;
- If you have been receiving intravenous nutrition or fluid administration for a long time and you have excessive fluid accumulation in your body (edema) or fluid accumulation in your lungs;
- If you have asthma;
- If you have heart failure;
- If you are using this medicine with other nutrients and you have diabetes or a predisposition to this disease;
- If this product is given to you through the veins in your arms or legs (In this case, NEFRASIN will be diluted in the appropriate proportion and will be given with sufficient calories).

Your doctor will perform blood tests or clinical evaluations at regular intervals in cases where you have been fed intravenously for a long time and will use additional drugs in case of deviation from normal values.

In addition, if NEFRASIN is used in pre-term (premature) infants or children with low birth weight; your doctor will pay special attention when using this medication and perform tests at certain intervals during treatment more often.

If these warnings are valid for you, even at any time in the past, please consult your doctor.

### **Use of NEFRASIN with food and drink**

During intravenous nutrition, you can consume your normal food and drinks.

### **Pregnancy**

*Consult your doctor or your pharmacist before using the drug.*

Your doctor will decide whether you can use NEFRASIN during pregnancy or not, after comparing the benefits of this treatment with the possible harms.

*If you notice you are pregnant during treatment, consult your doctor or pharmacist immediately.*

### **Breast-feeding**

When you are breastfeeding your baby, if your doctor thinks that the benefits of this drug are more than the possible harms, you can use the drug with the decision of your doctor.

*Consult your doctor or pharmacist before using this medication.*

### **Driving and using machines**

It is not possible to drive and use machines during intravenous feeding. It has no effect on the ability to drive and use machines after your treatment is terminated.

### **Important information about some excipients found in the composition of NEFRASIN**

If you do not have a hypersensitivity to the substances contained in NEFRASIN, a negative effect is not expected against these excipients.

This product contains sodium bisulfite as an excipient. Sulfide can lead to allergic reactions, anaphylaxis, or a severe and life-threatening asthma attack in some sensitive people. Although the general prevalence of sensitivity to sulfite in society is unknown, it is estimated to be very low. Sulfide sensitivity is more common in people with asthma than in those who do not.

### **Use with other medicines**

Please tell your doctor if you are planning, taking, or have recently taken any other medications, including non-prescription drugs, vaccines, and herbal medications.

Your physician will check whether any medication he / she adds is compatible with the solution. In cases where any drug is added to NEFRASIN or the drug is mixed with other nutrients, the mixture should be administered immediately.

*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 NEFRASIN**

#### **Instructions for appropriate use and dose/administration frequency:**

The frequency of administration of your medication, the amount to be administered each time, and how long you will continue intravenous administration will be determined by your doctor.

In general, 250-500 mL of NEFRASIN per day is sufficient. You should also get enough calories.

#### **Method of administration:**

NEFRASIN is used intravenously with the help of a plastic tube (catheter) placed in your veins. Intravenous administration can be done from the veins in your arms or legs or from large veins in your neck area.

#### **Various age groups**

##### **Pediatric Use:**

Your doctor will calculate the total volume and rate of administration of the feeding fluid individually based on the child's age, body weight and renal function. If the patient is a newborn and a small baby, your doctor will closely monitor many blood values, including blood sugar levels.

##### **Geriatric Use:**

Older patients are known to be more prone to fluid loading and salt imbalances than younger ones. This condition may be associated with impaired renal function, which is more common in the elderly. As a result, careful monitoring is more necessary during liquid-salt treatments in the elderly.

Although there is no specific dose set for the elderly, during all parenteral nutrition practices, your doctor will individually determine the dose of your drug from case to case in all patients, including the elderly, based on your body weight, clinical status, and the results of laboratory tests performed during monitoring.

It will also start your treatment with the lowest effective dose, taking into account that liver and heart function are lower in older patients than in younger ones; other diseases and drug use are more frequent together.

#### **Special use cases:**

##### **Renal/ Hepatic impairment:**

Administration of amino acid in cases of renal dysfunction can further increase the elevated blood

urea nitrogen.

NEFRASIN can be used safely in these patients, as it is specifically formulated to provide the necessary nutritional support for kidney diseases that cannot tolerate general-purpose amino acid infusions.

Administration of amino acid solutions for general use in patients with hepatic insufficiency can lead to an imbalance of amino acids in the blood, an increase in ammonia, loss of consciousness and coma. For this reason, solutions specifically formulated (such as HEPASELAMIN, etc.) should be used to provide the necessary nutritional support for liver diseases that need to be fed through the vascular way and do not tolerate general-purpose amino acids.

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

#### **If you have used more NEFRASIN than you should**

*If you have used NEFRASIN more than you should, talk to a doctor or pharmacist.*

#### **If you forget to use NEFRASIN**

Do not forget to take your medication on time.

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

#### **Effects that may occur when treatment with NEFRASIN is concluded**

Your doctor will tell you how long your treatment with NEFRASIN will last. Do not stop treatment early because you will not get the desired result.

If you are using high-density dextrose (glucose) solutions with NEFRASIN, your treatment will be continued for some time with less dextrose-containing solutions (for example, 5% dextrose solution) so that you do not experience a blood sugar drop (rebound hypoglycemia) that may occur when your treatment is terminated.

#### **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 NEFRASIN.

Side effects are listed as shown in the following categories:

Very common : It can be seen in at least one of 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 1,000 patients can be seen.

Very rare : less than one in 10,000 patients.

Unknown : Cannot be estimated from the available data.

Unknown:

- Hypersensitivity reactions (itching, redness, swelling, burning sensation in some or all parts of the body; respiratory distress, wheezing, chest pain; excessive heat or cold feeling in the body; swelling of hands, feet, lips, face or whole body; dizziness fainting feeling).

These are all very serious side effects.

If you have one of these, it means you have a serious allergy to NEFRASIN. You may need urgent medical attention or hospitalization.

All of these very serious side effects are very rare.

Apart from hypersensitivity reactions, the following side effects may also occur:

Unknown:

- A type of anemia (Acute hemolytic anemia)
- Spasms, cramps in your muscles
- Increase or decrease in salt levels in your body
- Increased levels of ammonia in the blood (hyperammonemia)
- Increased levels of amino acids in the blood (hyperketonemia)

Redness, swelling or pain around the applied vein (phlebitis, thrombosis); All these are serious side effects. It may depend on your medication or intravenous administration. Emergency medical attention may be required.

*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 will contribute to obtaining more information about the safety of the drug that you are using.

#### **5. How to store NEFRASIN**

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

**Use in compliance with the expiry date.**

The shelf life of NEFRASİN is two years. An expiration date is written on the label on each bottle. If this date has passed, you will not be given this medicine.

*Do not use NEFRASİN after the expiration date stated on the packaging/ Use before the expiry date.*

Do not store at temperatures above 25°C. Protect from extreme heat and freezing. Protect from light until use. Do not use solutions that are not clear and leaky. Dispose of incomplete solutions; do not re-use the unused part.

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 19/08/2016.*

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

NEFRASIN I.V. Amino Acid Solution for Infusion

Sterile

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEFRASIN is a sterile, hypertonic solution containing crystalline amino acids.

#### Drug substance(s):

Each 100 mL solution contains;

- L-Histidine	0.25 g
- L-Isoleucine	0.56 g
- L-Leucine	0.88 g
- Lysine	0.64 g (as 0.90 g L-Lysine Acetate)
- L-Methionine	0.88 g
- L-Phenylalanine	0.88 g
- L-Threonine	0.40 g
- L-Tryptophan	0.20 g
- L-Valine	0.64 g
- L-Cysteine HCl.H <sub>2</sub> O	< 0.020 g
- Sodium bi sulfite (as antioxidant)	< 0.05 g

pH 6,5 (adjusted by sodium hydroxide) Osmolarity 435 mOsm/L

Electrolyte Concentrations (mEq/litre): Sodium 5; Chloride < 3; Acetate: approximately 44 (from acetic acid and lysine acetate)

#### Excipients:

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Solution for intravenous infusion.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

NEFRASIN is used to provide the necessary nutritional support in adult and pediatric uremic patients, together with other precautions, especially when oral nutrition is not possible or insufficient.

## **4.2 Posology and method of administration Posology /administration frequency and duration**

The purpose of nutritional therapy in renal impairment is to provide sufficient amino acids and calories to ensure protein synthesis in the body without exceeding the capacity of the kidneys to expel metabolic products.

Nitrogen balance can be achieved in most patients with chronic uremia in a stable condition by supplying 3 grams of nitrogen and sufficient calories per day with essential amino acids. Although nitrogen requirement is higher in patients undergoing dialysis in patients with severe or acute uremia, additional nitrogen cannot be provided due to the limited fluid intake in such patients and glucose intolerance.

Conventional methods such as nitrogen balance and daily body weight, which are used to determine the individual amino acid requirement of the patient, are difficult to administer and interpret in the uremic patient. Therefore, the metabolic and clinical response of the patient to the treatment with the amount of fluid, dextrose and nitrogen that can be tolerated by the patient becomes guiding in determining the dosage. Often with essential amino acid infusions, the rate of increase of urea nitrogen in the blood decreases. However, excessive protein intake with diet or increase in protein catabolism can change this response.

### Dosage for adults:

Usually; daily 250-500 mL NEFRASIN is given. This amount of NEFRASIN provides the patient with 1.6 -

3.2 grams of nitrogen in 13.4 - 26.8 grams of essential amino acid.

The patient should also be given sufficient calories. For example, when 250 mL of NEFRASIN solution is mixed with 500 mL of 70% dextrose solution, a solution containing 1.8% NEFRASIN and 47% dextrose is obtained. The calorie: nitrogen ratio of this solution is 744: 1.

The osmolarity of the solutions to be administered from peripheral veins should not be more than 718 mOsmol / L, which is twice the normal serum osmolarity.

### Dosage for children:

Initially, the total daily dose should be low and slowly increased. In order to avoid clinically significant increases in serum ammonia and plasma amino acid levels, frequent laboratory measurements and clinical monitoring are recommended when increasing the dose, especially in very young children. The maximum dose of NEFRASIN should not exceed 1 gram of essential amino acids per kilogram per day. The osmolarity of the solutions to be administered through peripheral veins in pediatric patients should not exceed 718 mOsmol / L, which is twice the normal serum osmolarity.

The use of NEFRASIN in children should be done by paying attention to the issues that need to be considered in the use of any amino acid solution in the pediatric age group. The amount to be

administered should be determined according to body weight.

In cases where parenteral nutrition is prolonged (longer than 5 days), the use of amino acid solutions and oil emulsions together should be considered in order to avoid essential fatty acid deficiency. In the case of prolongation of fat-free total parenteral nutrition, serum lipid levels should be closely monitored to detect a possible essential fatty acid deficiency early.

Some patients may need additional electrolyte administration. There is 5 mEq sodium per liter of undiluted NEFRASIN solution. During NEFRASIN treatment, the increased levels of potassium, phosphorus and magnesium in the serum of the patients decrease. Although the decrease in elevated electrolyte levels is beneficial in many patients and especially in acute renal failure, excessive reduction of electrolytes can be seen with treatment in some cases.

These decreased blood electrolytes may need to be replaced, especially in patients with cardiac arrhythmia and digitalis toxicity. During anuria and oliguria, patients should be careful when administering electrolytes, even if the serum values of electrolytes are at the lower limit of normal.

During the electrolyte addition, the compatibility of electrolytes with NEFRASIN / hypertonic dextrose mixture should be considered; Electrolytes that may be incompatible, such as calcium and phosphate, can be given in other bottles to avoid precipitation. In hyperchloremic acidosis and other metabolic acidosis, acetate salts of sodium and potassium should be used as bicarbonate precursors. While calculating the patient's daily electrolyte intake, the electrolyte content of NEFRASIN should be taken into account. Serum electrolytes, including magnesium and phosphate, should be checked frequently. If the patient's diet is mainly through parenteral nutrition, additional vitamins, especially water-soluble, should be given.

Initially, the infusion rate should be slow, usually 20-30 mL per hour. The dose can then be increased by 10 mL / hour every 24 hours to a maximum dose of 60-100 mL per hour. If the administered dose lags behind the daily planned amount, it should not be tried to keep up.

The administration rate is adjusted according to the patient's nitrogen, fluid and glucose tolerance. Glucose tolerance is common in uremic patients, especially if they are under peritoneal dialysis treatment, and additional insulin may be required. Blood glucose level should be measured frequently. To prevent rebound hypoglycemia, a 5% dextrose solution should be continued after discontinuation of hypertonic dextrose.

**Route of administration:**

Hypertonic mixtures of essential amino acids and dextrose can be safely infused continuously through a central vein catheter with the tip located in the vena cava superior. Parenteral drugs should be examined for the presence of foreign bodies or

discoloration before administration.

Incompatible additions should be avoided. Consult your pharmacist.

**Additional information on special populations Renal impairment:**

Administration of amino acids in cases of renal dysfunction may further increase the increased blood urea nitrogen. In such patients, essential amino acids should be given minimal amounts of essential amino acids, with adequate calories, and non-essential nitrogen intake should be severely restricted in order to re-utilize the accumulated urea in the body (See Section 4.4: Special warnings and precautions for use). NEFRASIN contains crystalline essential amino acids and histidine and provides essential amino acids recommended for uremic patients, including histidine, which is considered the essential amino acid (see Chapter 5: Pharmacological properties).

**Hepatic impairment:**

Administration of general-purpose amino acid solutions in patients with hepatic insufficiency may cause plasma amino acid imbalance, hyperammonemia, pre-renal azotemia, stupor and coma.

Therefore, solutions specially formulated (such as HEPASELAMIN etc.) should be used to provide the necessary nutritional support in liver diseases that require parenteral nutrition and cannot tolerate general purpose amino acid infusions.

**Pediatric population:**

Initially, the total daily dose should be low and gradually increased. In order to avoid clinically significant increases in serum ammonia and plasma amino acid levels, more frequent laboratory and clinical monitoring is recommended as the dose is increased, especially in very young children. It is not recommended to administer more than 1 gram of essential amino acids per kilogram per day. The osmolality of the solutions to be administered through peripheral veins in children should not be more than 718 mOsmol / L, which is twice the normal serum osmolality.

In children, especially the administration of high doses of NEFRASIN may cause hyperammonemia. Especially in newborns or infants with low birth weight, the administration of NEFRASIN may cause increased plasma amino acid levels (e.g., hyperketonemia) and hyperammonemia. In this very young age group, the use of amino acid solutions (such as TROFSELAMIN) specially formulated for infants and children should be considered.

The use of NEFRASIN in children should be done by paying attention to the issues that need to be considered in the use of any amino acid solution in the pediatric age group. The amount to be administered should be determined according to body weight.

It should be administered with blood glucose monitoring due to the risk of hyperglycemia in the newborn.

**Geriatric population:**

No studies have been conducted for active ingredient of NEFRASIN regarding its use in the elderly. Elderly patients are known to be more prone to fluid overload and electrolyte imbalances than younger ones. This may be associated with impaired kidney function, which is more common in the elderly population. As a result, the need for careful monitoring during fluid-electrolyte treatments in the elderly is more. During all parenteral nutrition administrations, the dose should be determined by the physician individually from case to case, based on body weight, clinical condition and the results of laboratory tests performed during follow-up. There is no specific geriatric dose determined.

**4.3 Contraindications**

- Patients with severe, uncorrected electrolyte and acid-base imbalances.
- Hyperammonemia states.
- Circulating blood volume falls below the critical level.
- Inborn disorders of amino acid metabolism.
- Hypersensitive to one or more of the amino acids in solution.

**4.4 Special warnings and precautions for use**

**CAUTION:** This product contains aluminum, which can be toxic. In cases with impaired renal function, aluminum can reach toxic levels with long-term parenteral administration. Premature newborns are particularly at risk as their kidneys are not fully developed and require large amounts of calcium and phosphate, which hold aluminum.

Studies have shown that in patients with impaired renal function, including premature newborns, parenteral aluminum administered at doses above 4-5 micrograms per kilogram per day causes aluminum accumulation at levels leading to central nervous system and bone toxicity. Tissue accumulation can be seen even at lower administration rates.

This product contains sodium bisulfite as an antioxidant. Sulfite can cause allergic-type reactions, anaphylaxis or severe and life-threatening asthma attack in some sensitive individuals. Sulfite sensitivity is more common in people with asthma than those without. Sulfite sensitivity is more common in people with asthma than those without.

Adequate knowledge and experience is required in terms of nutrition, as well as in recognizing and treating complications that may develop during treatment, in order to administer central venous nutrition

effectively and safely.

**Laboratory examinations and clinical evaluations should be performed frequently during the monitoring of central venous nutrition therapy.** Laboratory tests should include evaluations regarding blood sugar level, serum proteins, kidney and liver function tests, and acid-base and fluid balance. Other tests can be done depending on the patient's condition.

NEFRASIN cannot replace dialysis and generally accepted therapies in kidney patients.

The efficacy and safety of injectable amino acid solutions in pediatric patients has not been demonstrated by proper studies, which are the control group. However, it has been shown in the medical literature that injectable amino acid solutions are successfully used as an adjunct in the treatment of pediatric patients with nitrogen loss or negative nitrogen balance. The osmolarity of the solutions to be administered in children should not be more than 718 mOsmol / L, which is twice the normal serum osmolarity. In children, especially the administration of high doses of NEFRASIN may cause hyperammonemia. Especially in newborns or infants with low birth weight, the administration of NEFRASIN may cause increased plasma amino acid levels (e.g., hyperketonemia) and hyperammonemia. In this very young age group, the use of amino acid solutions (such as TROFSELAMIN) specially formulated for infants and children should be considered.

Clinically significant hypokalemia, hypophosphatemia or hypomagnesemia may occur in the blood during treatment with NEFRASIN and hypertonic dextrose, and replacement therapy may be required.

Administration of nitrogen in any form to patients with severe hepatic failure and hepatic coma may cause imbalance in plasma amino acid values, hyperammonemia or central nervous system disorders. Therefore NEFRASIN should be used with caution in such patients.

During intravenous administration of these solutions, the patient may develop fluid and / or solute loading, resulting in dilution in serum electrolyte concentrations, excessive fluid accumulation in the body, congestion or edema in the lung. Dilution risk is inversely proportional to the electrolyte content of the solutions. Solute loading, which causes congestion together with peripheral and pulmonary edema, is directly proportional to the electrolyte content of the solutions.

Amino acids to be administered should be in conservative doses appropriate for the nutritional status of the patient. Clinical evaluations and laboratory tests should be performed at regular intervals to detect changes in fluid balance, electrolyte density and acid-base balance during long-term parenteral nutrition or when the general condition of the patient requires. Excessive deviations from normal values require the use of additional electrolyte supplements.

In patients with renal impairment, essential amino acids should be given minimal amounts of essential amino acids with sufficient calories, and non-essential nitrogen intake should be severely restricted in order to allow the accumulated urea to be re-used in the body. It is appropriate to use hypertonic dextrose solutions as a metabolically effective, concentrated calorie source.

In patients with renal impairment, fluid balance should be closely monitored and care should be taken not to overload the circulation, especially in patients with heart failure.

In anoxic conditions, since the myocardial tissue cannot utilize free fatty acids, it provides its energy requirement anaerobically, from glycogen or glucose. Therefore, amino acid solutions should always be given with dextrose in patients with myocardial infarction.

Highly hypertonic solutions should be administered through an intravenous catheter with the tip inserted into a central vein and preferably in the superior vena cava.

Special care is needed when administering hypertonic dextrose to glucose intolerant diabetic or pre-diabetic patients and uremic patients, especially if these patients are receiving peritoneal dialysis treatment. In such patients, insulin may be required to prevent severe hyperglycemia.

Glucose delivery faster than the patient can use can lead to hyperglycemia, coma, and death.

Carbohydrate-free amino acid administration can lead to an increase in ketone bodies in the blood. Ketonemia can be corrected by giving carbohydrates.

Abrupt cessation of hypertonic dextrose infusion can lead to rebound hypoglycemia.

Transient crystallization of amino acids may occur if NEFRASIN is exposed to sudden temperature changes. By shaking the bottle for about a minute, these crystals dissolve again. Solutions in which crystals do not dissolve should not be used.

The final mixture should be checked for turbidity and sediments immediately after mixing, before and during administration, in order to detect an incompatibility due to the presence of additives mixed into the solution.

Only solutions in clear and intact bottles should be used. The drug contains less than 25 µg / L aluminum per liter.

**Issues to be paid attention in central venous nutrition:**

**Central venous catheter administration should be done by people who know its technique and complications.**

Central venous nutrition have complications that can be prevented or reduced when solution preparation, administration and patient follow-up procedures administered carefully. All procedures should be done by experienced people in accordance with current medical knowledge.

Although the complications of this treatment method are beyond the scope of the summary of product characteristics, a summary from current medical literature is provided below.

**Technique:** Insertion of a central venous catheter is a surgical procedure. Various techniques and complications of catheter insertion into the central vein should be known. Details of catheter insertion techniques can be found in the medical literature. The location of the catheter is best determined by radiological control. Complications related to the insertion technique of central vein catheters include pneumothorax, hemothorax, hydrothorax, arterial puncture and rupture, brachial plexus injury, catheter misplacement, arterio-venous fistula, phlebitis, thrombosis, air and catheter embolism.

**Septic:** There is a risk of sepsis during central venous nutrition therapy. Since contaminated solutions and infusion catheters can be sources of infection, the preparation of solutions, placement and maintenance of catheters should be done under aseptic conditions.

Solutions should be prepared in the hospital pharmacy in a laminar flow cabinet. The most important factor in preparation is the administration of an aseptic technique in order to prevent contamination. Parenteral nutrition solutions should be administered as soon as they are prepared. The holding should be when necessary, only for a very short time and under refrigerator conditions. A single bottle and set should not remain attached for more than 24 hours.

Medical literature should be reviewed for the treatment of sepsis that may develop during central venous feeding. As a summary of treatment, it is recommended to replace the applied solution and set with new ones, and to make bacteriological culture from the old solution and set. If sepsis continues and another source of infection cannot be detected, the venous catheter should be removed, a culture should be made from the tip, and a new one should be inserted after the fever subsides. Nonspecific, prophylactic antibiotic treatment is not recommended. According to clinical experience, catheters are often the primary source of infection.

**Metabolic:** Metabolic complications reported in the literature are: Metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glucosuria, osmotic diuresis and dehydration, elevated liver enzymes, hypo and hypervitaminosis, electrolyte imbalances, and hyperammonemia in children. Frequent clinical and laboratory evaluations should be made especially in the first days of venous nutrition in order to prevent or minimize these complications.

**Special precautions to be taken in patients with renal impairment:**

Because of metabolic disorders in patients with renal failure, frequent laboratory checks are required in these patients. Hyperglycemia, one of the common complications, is not seen as glucosuria in renal impairment. Blood glucose should be checked frequently, sometimes every 6 hours, in order to determine the required dextrose and insulin to the patient.

During successful treatment, serum potassium, phosphorus and magnesium levels drop rapidly. When necessary, it should replace the missing ions. Particular care should be taken to avoid hypopotassemia in digitized patients or those with cardiac arrhythmias.

**Special precautions to be taken in pediatric patients:**

Due to the limited clinical trials, NEFRASIN should be administered with great caution in pediatric patients and especially in children with low birth weight.

Pediatric patients and especially those with severe malnutrition should be monitored frequently by clinical and laboratory controls, the initial daily dose of the solution should be kept low, and the dose should be increased slowly. Doses of NEFRASIN higher than 1 gram of essential amino acid per kilogram per day should not be used.

The use of amino acid solutions specially formulated for children (such as TROFSELAMINE etc.) should be considered, especially in neonates or infants with low birth weight. If NEFRASIN will be used in this very young age group, the patient should be monitored closely by measuring plasma amino acid levels and serum ammonia levels frequently.

Since hypertonic dextrose carries a higher risk of hyperglycemia in newborns and infants with low birth weight or sepsis, blood glucose measurements should be performed more frequently in these children.

The absence of arginine in NEFRASIN may increase the risk of hyperammonemia in babies. The osmolarity of the solutions for children should not be more than 718 mOsmol / L, which is twice the normal serum osmolarity.

**4.5 Interaction with other medicinal products and other forms of interaction**

No interactions reported. However, it should be reviewed whether there is any incompatibility of the drug to be used together.

Aseptic technique should be used when adding additional medication. It should be ensured that the solution formed after the addition is mixed thoroughly. The added solutions should not be stored and used as soon as possible.

**4.6 Pregnancy and lactation General advice:**

Pregnancy category: C

### **Women of childbearing potential / contraception**

There is no known negative effect.

### **Pregnancy period**

For the active ingredient of NEFRASİN, there is not enough data on the use of it in pregnant women.

Animal studies are insufficient for effects on pregnancy / and / or / embryonal / fetal development / or / birth / and / or / postnatal development. (See Section 5.3). The potential risk for humans is unknown.

NEFRASİN should not be used in pregnant women unless considered necessary by the doctor. The solution should be applied to pregnant women only when absolutely necessary and there is no other option.

### **Lactation period**

It is not known whether the drug is excreted in breast milk. Since many drugs are excreted in breast milk, care should be taken when administering NEFRASİN to a nursing mother.

### **Reproductive ability / Fertility**

There is no known negative effect.

### **4.7 Effects on ability to drive and use machines**

It has no known effect.

### **4.8. Undesirable effects**

The frequency classification of adverse drug reactions seen is as follows: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10.000$  and  $< 1/1000$ ), very rare ( $< 1/10.000$ ) and unknown (estimation based on the existing data is impossible).

### **Blood and lymphatic system disorders**

Unknown: Acute hemolytic anemia

Phosphorus deficiency can lead to impaired tissue oxygenation and hemolytic anemia.

### **Metabolism and nutrition disorders**

Unknown: Hyperammonemia, increased plasma amino acid levels (hyperketonemia)

It has been reported that in patients with severe gastrointestinal bleeding, the administration of essential amino acid solutions to non-uremic infants and young children or the use of higher doses than recommended may cause hyperammonemia.

It has been reported that there may be an increase in plasma amino acid hyperketonemia in babies, especially in high doses. In such cases, after the infusion is discontinued, elevated ammonia and amino acid levels in serum and clinical findings related to these elevations disappear.

## **Musculoskeletal, connective tissue and bone disorders**

Unknown: Tetany, cramps

Giving more phosphorus than calcium may lead to increased tetany, cramping and muscle excitability due to hypocalcemia.

## **General disorders and administration site conditions:**

Unknown: Fever, injection site infection, venous thrombosis and hypervolemia \*.

\* Side effects depending on the application technique of the solution

There may be various symptoms in the excess or lack of one of the ions added to the solution.

Therefore, blood electrolytes should be checked frequently.

When side effects develop, the infusion should be discontinued immediately, the patient should be re-evaluated, appropriate therapeutic measures should be taken, and the remaining solution should be stored so that it can be examined when necessary.

### 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 and treatment**

If fluid or solute overload occurs in the patient during parenteral fluid therapy, the patient should be re-evaluated and appropriate treatment should be performed.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

**Pharmacotherapeutic Group:** Parenteral Nutrition Solutions

**ATC Code:** B05BA01

NEFRASIN is a sterile, non-pyrogenic solution containing crystallized essential amino acids and histidine. When 250 mL of the solution is administered to the organism, it provides the daily essential

amino acids recommended by Rose and 625 mg of histidine, which is considered the essential amino acid in uremic patients. 250 mL of the solution contains 14 grams of amino acids and 1.6 grams of nitrogen equivalent to 10 grams of protein.

In addition to hypertonic dextrose solutions to be used as an energy source, NEFRASIN, which is applied with electrolytes, vitamins and minerals, meets all the needs of total parenteral nutrition in kidney patients, except essential fatty acids, in a small liquid volume.

NEFRASIN and hypertonic dextrose infusion provides essential amino acids and calories required for protein synthesis, aimed at restoring the metabolic balance of cells. In patients with impaired renal function, the rate of increase of urea nitrogen in the blood decreases with the administration of these nutrients, and the impairment of potassium, magnesium and phosphorus balance in these patients is minimized.

According to the results obtained in experimental studies on animals, essential amino acids, which are given to the organism together with caloric substances, facilitate the incorporation of urea nitrogen, which consists of breakdown products, into the body of newly synthesized amino acids.

In patients with reversible acute renal failure with limited extrarenal complications, the rapid decrease in serum creatinine levels after the administration of NEFRASIN and hypertonic dextrose indicates that renal functions may start at an earlier period in these patients, depending on the treatment. NEFRASIN and hypertonic dextrose solution, in addition to providing the necessary nutritional support to the patients, facilitates the biochemical recovery and earlier onset of kidney functions and reduces the morbidity in acute renal failure.

During parenteral nutrition, it is believed that acetate ions from lysine acetate will not disturb the net acid-base balance as long as kidney and respiratory functions are normal. Clinical observations support this view.

The sodium and chloride ions contained in NEFRASIN are not in clinical significance.

## **5.2 Pharmacokinetic properties General characteristics:**

The pharmacokinetics of amino acids administered intravenously are essentially the same as for oral amino acids. However, amino acids from the proteins in foods pass through the portal vein before reaching the systemic circulation.

### Absorption:

Active substances in drugs administered intravenously reach their maximum plasma concentrations immediately after administration.

### Distribution:

Intravenously administered amino acids are rapidly removed from the blood by tissue absorption and are rapidly metabolized here (protein synthesis, oxidation).

### Biotransformation:

Intravenously administered amino acids are metabolized in a similar manner and rate to amino acids absorbed from the intestine. In addition to their use in protein synthesis, amino acids are now used as metabolic fuel. Amino acids are deaminated and enter the ammonium urea cycle. The carbon atoms of the amino acid are immediately converted into the pyruvate, acetyl CoA, acetoacetate or citric acid cycle.

### Elimination:

As amino acids are used in protein synthesis, they are not eliminated as they are taken. Amino acid residues are deaminated and enter the  $\text{NH}_4^+$  (ammonium) - urea cycle and are mainly excreted in urine.

## **5.3 Pre-clinical safety data**

There are no in vitro or in vivo carcinogenesis, mutagenesis or fertility studies performed with NEFRASIN active ingredient.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients Sodium bisulfite (as antioxidant) Water for injection**

### **6.2 Incompatibilities**

There is no known incompatibility. However, the fluids and drugs to be used together should be evaluated in terms of incompatibility. Care should be taken to ensure that the mixture is clear in order to understand incompatibility with the substances to be mixed into the solution.

### **6.3 Shelf Life**

24 24 Months

### **6.4 Special precautions for storage**

It should be protected from excessive heat and freezing.

Protect from light until before use.

25 It should be stored at room temperature below 25° C.

#### **6.5 Nature and contents of container**

500 mL glass bottle

#### **6.6 Special precautions for disposal and other handling**

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

### **7. MARKETING AUTHORIZATION HOLDER**

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### **8. MARKETING AUTHORIZATION NUMBER**

203/49

### **9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**

03.12.2003

### **10. DATE OF REVISION OF THE TEXT**