SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NEFRASİN Amino Acid I.V. Solution for Infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEFRASİN 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
- L-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 HCI.H_20	< 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

NEFRASİN 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 NEFRASİN is given. This amount of NEFRASİN 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 NEFRASİN solution is mixed with 500 mL of 70% dextrose solution, a solution containing 1.8% NEFRASİN 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 NEFRASİN 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 NEFRASİN 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 NEFRASİN solution. During NEFRASİN 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 NEFRASİN / 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 NEFRASİN 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). NEFRASİN 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 osmolarity 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 osmolarity.

In children, especially the administration of high doses of NEFRASİN may cause hyperammonemia. Especially in newborns or infants with low birth weight, the administration of NEFRASİN 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 NEFRASİN 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 NEFRASİN 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.

NEFRASİN 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 NEFRASİN may cause hyperammonemia. Especially in newborns or infants with low birth weight, the administration of NEFRASİN 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 NEFRASİN 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 NEFRASİN 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, NEFRASİN 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 NEFRASİN 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 TROFSELAMİNE etc.) should be considered, especially in neonates or infants with low birth weight. If NEFRASİN 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 (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥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

NEFRASİN 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, NEFRASİN, 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.

NEFRASİN 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 NH4 + (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 NEFRASİN active ingredient.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients Sodium bisulfite(as antioxidant), Sodium hydroxide and 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 Months

6.4 Special precautions for storage

It should be protected from excessive heat and freezing.

Protect from light until before use.

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

19.08.2016