1. NAME OF THE MEDICINAL PRODUCT

Nephrotect®

2. PRESCRIPTION STATUS/RESTRICTION OF SALES TO PHARMACIES ONLY

For sale in pharmacies only

3. COMPOSITION OF THE MEDICINAL PRODUCT

3.1 Substance or indication group

Special amino acid solutions for parenteral nutrition in renal diseases

3.2 Active ingredients

1000 ml of the solution for infusion contain:

L-isoleucine	5.80 g
L-leucine	12.80 g
L-lysine monoacetate = 12 g L-lysine	16.925 g
L-methionine	2.00 g
L-phenylalanine	3.50 g
L-threonine	8.20 g
L-tryptophane	3.00 g
L-valine	8.70 g
L-arginine	8.20 g
L-histidine	9.80 g
L-alanine	6.20 g
N-acetyl-L-cysteine = 0.40 g L-cysteine	0.54 g
glycine	5.305 g
L-proline	3.00 g
L-serine	7.60 g
L-tyrosine	0.60 g
N-glycyl-L-tyrosine = 0.994 g glycine = 2.40 g tyrosine	3.155 g

acetate	124 mmol/l
malate	15 mmol/l

3.3 Other ingredients

Acetic acid
L-Malic acid
Water for injections

Total amino acids	100 g/l
Total nitrogen	16.3 g/l
Total energy	1600 kJ/l = 400 kcal/l
pH	5.5 – 7.0
Titration acidity	approx. 40 mmol NaOH/l
Theoretical osmolarity	935 mosm/l

4. THERAPEUTIC INDICATIONS

Building blocks for protein synthesis in the parenteral nutrition of patients with acute or chronic renal insufficiency with or without dialysis treatment including intradialytic nutrition.
Amino acid solutions used for parenteral nutrition should be generally administered in combination with energy supplying solutions for infusion.
If electrolytes, and if necessary, vitamins, and trace elements are administered additionally, Nephrotect® can be used for total parenteral nutrition.

5. CONTRAINDICATIONS

Disturbances in the metabolism of amino acids, acidosis, life-threatening unstable cardiovascular system (shock), advanced liver insufficiency, hypokalaemia, decompensated cardiac insufficiency, pulmonary and cerebral oedema, hyperhydration.
Must not be used on newborns, infants and children.
Caution should be observed in patients with hyponatraemia or elevated serum osmolarity.
Because of the lack of experiences during pregnancy and lactation Nephrotect® should be used only after a careful benefit risk evaluation.

6. UNDESIRABLE EFFECTS

None known.

7. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS

None known

8. WARNINGS

None

9. MOST IMPORTANT INCOMPATIBILITIES

Amino acid containing solutions should not be mixed with other medicinal products, except for parenteral nutrition products, due to the increased risk of microbiological contamination and incompatibilities.
When mixing with other nutrients such as electrolytes, vitamins or trace elements to Nephrotect® for complete parenteral nutrition, care should be given to aseptic techniques, thorough mixing and, in particular, to compatibility. Under no circumstances Nephrotect® should be stored after addition of other components.

10. POSOLOGY WITH SINGLE AND DAILY ADMINISTRATIONS

Dosage is according to individual need.

Unless otherwise prescribed,

in acute and chronic renal insufficiency
- for patients not requiring dialysis:
  0.6 - 0.8 g AAs/kg bodyweight/day
  = 6 - 8 ml/kg bodyweight/day

- for patients requiring dialysis
  0.8 - 1.2 g AAs/kg bodyweight/day
  = 8 - 12 ml/kg bodyweight/day

- in case of intradialytic nutrition with chronic haemodialysis
  0.5 - 0.8 g AAs/kg bodyweight/dialysis
  = 5 - 8 ml/kg bodyweight/dialysis

Maximum daily dose:
0.8 - 1.2 g AAs/kg bodyweight
= 8 - 12 ml/kg bodyweight
= 560 - 840 ml in a patient weighing 70 kg

Maximum infusion rates:

Parenteral nutrition:
Max. 0.1 g AAs/kg bodyweight/hour

Intradialytic nutrition:
Max. 0.2 g AAs/kg bodyweight/hour

11. METHOD AND DURATION OF ADMINISTRATION

For intravenous infusion via central veins.

Nephrotect® can be used either via separate infusion lines with other nutritional substrates (multiple bottle system) or to prepare a solution for total parenteral nutrition, which contains all components (amino acids, carbohydrates, fat, electrolytes, vitamins, trace elements) mixed in a single container.

Nephrotect® is administered via a central venous catheter.

For intradialytic nutrition Nephrotect® can be infused directly into the venous drip chamber of the dialysis apparatus.

Amino acid solutions, and thus Nephrotect® as well, are in general administered together with caloric nutrients (carbohydrates and fat) in order to guarantee an anabolic utilisation of the amino acids. An exception is intradialytic supplementary nutrition, when a dialysate containing glucose is used.

The duration of use depends on the clinical status of the patient. There is at present no clinical experiences over an application period of more than 6 weeks (parenteral nutrition) or 14 weeks (intradialytic supplementary nutrition).

A change may be made to a conventional amino acid solution where there has been a decrease in the serum creatinine value of below 3 mg/dl.

12. EMERGENCY MEASURES, SYMPTOMS AND ANTIDOTES

In principle nausea, fever, shivering, flush, vomiting, hyperammonaemia and acidosis can occur as symptoms of an overdosage or increased infusion rate. In this case the infusion is to be discontinued immediately.

No signs of overdosages or toxication due to the administration of N-glycyl-L-tyrosine are known so far. Even under a highly dosed bolus injection of the pure substance, no side effects of any kind have been observed (see pharmacokinetics).

13. PHARMACOLOGICAL AND TOXICOLOGICAL PROPERTIES, PHARMACOKINETICS AND BIOAVAILABILITY IN SO FAR AS THESE DETAILS ARE REQUIRED FOR THERAPEUTIC USE

Nephrotect is an amino acid solution, which can be used to supply the building blocks for protein synthesis during parenteral nutrition of patients with renal insufficiency.
A largely complete profile of L-amino acids is present in the solution, in relative quantities which are appropriate to the metabolic status of patients with renal

insufficiency. As tyrosine is not readily soluble in water, but represents an essential amino acid in kidney disorders, the dipeptide glycyl-L-tyrosine has been added to provide an additional source of tyrosine. This dipeptide is rapidly cleaved to release its constituent components after administration (half-life approximately 5 minutes), even in patients with renal insufficiency. The released amino acids accumulate, together with the other administered amino acids, as nutrients in the appropriate endogenous pools, and are metabolised as required by the body for protein synthesis.

Acute toxicity:
An LD_{50} for the dipeptid N-Glycyl-l-tyrosin could not be determined since at the highest dosage possible by solution (2.7 g/kg body weight x 6 hours) no animal died. In a four week toxicity study on rats Nephrotect® proved to be systemically well tolerated. It was only in the highest dosage group (9 g AA/kg body weight x 6 hours) where local incompatibility reactions appeared due to the daily peripheral venous application into the vein in the tail which were probably attributable to the higher osmolarity compared to blood. Haematologic changes which occurred in this group (fall in haematocrit and the haemoglobin of the erythrocytes and as a result an increase in reticulocytes) are to be attributed to the 4 week long daily large volume loading (180 ml/kg body weight x 6 hours) with the hyperosmolaritic solution. After a 4 week follow-up period all changes had disappeared.

14. OTHER POINTS TO CONSIDER

It is necessary to monitor fluid balance, serum electrolyte levels, acid-base balance, serum urea and blood ammonia levels during therapy.

Suitable for total parenteral nutrition with additional administration of energy carriers, electrolytes, vitamins and trace elements.

Too rapid infusion may cause nausea, vomiting, shivering, hyperammonaemia, acidosis, hyperamino-acidaemia can occur.

15. SHELF-LIFE

2 years.
Any unused solution should be discarded.

16. SPECIAL PRECAUTIONS FOR STORAGE

Protect from light, do not store above 25°C.

17. PHARMACEUTICAL FORM AND PACK SIZES

Infusion for solution

Glass bottles containing:	250 ml 500 ml
Packs of:	10 x 250 ml 10 x 500 ml

18. DATE OF INFORMATION

May 2000

19. MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
61346 Bad Homburg v.d.H.
Germany

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