For the use of a registered medical practitioner or a Hospital or a Laboratory only

Amino Acids (7% w/v) Injection

NIRMIN NEPHRO 7%™*

Description:

NIRMIN NEPHRO®* is a clear, sterile, Non-pyrogenic injection containing well-balanced mixture of pure crystalline, essential and non-essential amino acids.

The infusion could be given either by peripheral or central route by suitable adjusting the flow rate.

Composition:

Composition	NIRMIN NEPHRO®* (7% w/v)
Each 100 ml contains:	
L-Isoleucine USP	0.510 g
L- Leucine USP	1.030 g
L-Lysine Monoacetate USP equivalent to L-Lysine	0.710 g
L-Methionine USP	0.280 g
L-Phenylalanine USP	0.380 g
L-Threonine USP	0.480 g
L-Teyptophan USP	0.190 g
L-Valine USP	0.620 g
L-Arginine IP	0.490 g
L-Histidine USP	0.430 g
Glycine IP	0.320 g
L-Alanine USP	0.630 g
L-Proline USP	0.430 g
L-Serine USP	0.450 g
Acetyl Cysteine USP equivalent to L-Cysteine	0.037 g
L-Malic acid USP	0.150 g
Glacial Acetic Acid IP	0.138 g
Water For Injection IP	q. s.
Total Amino Acids	70.00g/L
Total Nitrogen content	10.80g/L
Energy content	287kcal/L
Osmolarity	635 mOsmol/L

Clinical Pharmacology:

Pharmacodynamic

Infusion of Amino acid 7% provides essential amino acids and calories for protein synthesis to promote improved cellular metabolic balance. Infusion of these components can decrease the rate of rise of blood urea nitrogen and minimize deterioration of serum potassium, magnesium, and phosphorus balance in patients with impaired renal function. The extent to which essential amino acids and calories promote incorporation of waste urea nitrogen into newly synthesized amino acids in man is not so far established as it does in experimental animals.

The accelerated decrease in serum creatinine levels seen in patients with limited extra-renal complications suggests that treatment with Amino acid 7% leads to earlier return of renal function in patients with potentially reversible acute renal failure. By providing nutritional support and promoting biochemical improvement as well as earlier return of renal function,

Amino acid 7% decrease morbidity associated with acute renal failure.

Pharmacokinetic

Protein and amino acid metabolism in ARF(Acute Renal Failure) are affected by impairment of the metabolic functions of the kidney itself. Various amino acids are synthesized or converted by the kidneys and released into the circulation: cysteine, methionine (from homocysteine), tyrosine, arginine, and serine. Thus, loss of renal function can contribute to the altered amino acid pools in ARF and to the fact that several amino acids, such as arginine or tyrosine, which conventionally are termed nonessential, might become conditionally indispensable in ARF. In addition, the kidney is an important organ of protein degradation. Multiple peptides are filtered and catabolized at the tubular brush border, with the constituent amino acids being reabsorbed and recycled into the metabolic pool. In renal failure, catabolism of peptides such as peptide hormones is retarded. With the increased use of dipeptides in artificial nutrition as a source of amino acids (such as tyrosine and glutamine) which are not soluble or stable in aqueous solutions, this metabolic function of the kidney may also gain importance for utilization of these novel nutritional substrates. In the case of glycyl-tyrosine, metabolic clearance progressively decreases with falling creatinine clearance but extrarenal clearance in the absence of renal function is sufficient for rapid utilization of the dipeptide and release of tyrosine. [(1)]

Indications:

NIRMIN NEPHRO 7%™* is highly appreciated as a parenteral nutrition supplement in the following conditions.

Acute and chronic renal insufficiency in haemofilteration, peritoneal and haemodialysis.

For the compensation of amino acid losses during and after dialysis or haemofilteration.

Renal failure following polytrauma, extensive surgery and sepsis. Supplementing a low protein diet in chronic renal failure patients.

Dosage and Administration:

For intravenous infusion.

If not otherwise prescribed, the recommended dosage is:

<u>Recommended Dosage for NIRMIN NEPHRO®*</u>

- Up to 0.5 gm amino acids/kg BW and day = 500ml/day at 70 kg body weight in acute and chronic renal insufficiency without dialysis treatment.
- Up to 1 gm amino acid/kg BW and day = 1000ml/day at 70 kg body weight in acute and chronic renal insufficiency under hemodialysis, hemofiltretion or peritoneal dialysis treatment.
- Maximum dosage: Up to 1.5 g amino acids/kg BW and day = 1500 ml/day at 70 kg BW.
- The drop rate should not exceed 20 drops/minute.
- Administer calorie carriers either before or simultaneously by mouth or parenterally.

Duration of application:

In acute renal insufficiency duration of application is from some days up to maximum of two weeks.

In chronic renal insufficiency without dialysis treatment as well as in acute and chronic renal insufficiency under hemodialysis, hemofiltration, or peritoneal dialysis treatment Nirmin Nephro* can be used until a sufficient oral supply of protein can be again given.

Contraindication:

NIRMIN NEPHRO®*is contraindicated in patients with severe, uncorrected electrolyte and acid-base imbalance, hyperammonemia, decreased (subcritical) circulating blood volume, inborn errors of amino acid metabolism, or hypersensitivity to one or more amino acids present in the solution.

Disturbances of amino acid metabolism, metabolic acidosis, renal insufficiency without haemodialysis or haemofiltration treatment, advanced liver insufficiency, fluid overload, shock, hypoxia, decompensated heart failure.

The administration of NIRMIN NEPHRO®* is contra-indicated in neonates.

For parenteral nutrition of infants and children pediatric amino acid preparations should be used, which are formulated to meet the different metabolic needs of children.

Warning and Precaution:

Safe and effective use of central venous nutrition requires a knowledge of nutrition as well as clinical expertise in recognition and treatment of the complications which can occur. **Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of central venous nutrition.** Laboratory tests should include measurement of blood sugar, electrolyte, and serum protein concentrations; kidney and liver function tests; and evaluation of acid-base balance and fluid balance. Other laboratory tests may be suggested as per the patient's condition.

NIRMIN NEPHRO®* does not replace dialysis and conventional supportive therapy in patients with renal failure.

Clinically significant hypokalemia, hypophosphatemia, or hypomagnesemia may occur as a result of therapy with NIRMIN NEPHRO®* and replacement therapy may become necessary.

Administration of nitrogen in any form to patients with marked hepatic insufficiency or hepatic coma may result in plasma amino acid imbalances, hyperammonemia, or central nervous system deterioration therefore NIRMIN NEPHRO®* should be used with caution in such patients.

The intravenous administration of these solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The

risk of dilutional states is inversely proportional to the solute concentration of the solution infused. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the concentration of the solution.
Conservative doses of amino acids should be given, dictated by the nutritional status of the patient.

PRECAUTIONS:
Serum electrolytes, fluid balance and renal function should be monitored.
In cases of hypokalemia and/or hyponatremia adequate amounts of potassium and/or sodium should be supplied simultaneously.
Amino acid solutions may precipitate acute folate deficiency, folic acid should therefore be given daily.
The choice of a peripheral or central vein depends on the final osmolarity of the mixture. The general accepted limit for peripheral infusion is about 800 mosm/l, but it varies considerably with the age and the general condition of the patient and the characteristics of the peripheral veins.
Strict asepsis should be maintained, particularly when inserting a central vein catheter.
NIRMIN NEPHRO®* is applicable as part of a total parenteral nutrition regimen in combination with adequate amounts of energy supplements. (Carbohydrate solutions, fat emulsions), electrolytes, vitamins and trace elements.
Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.
In order to promote urea nitrogen reutilization in patients with renal failure, it is essential to provide adequate calories with minimal amounts of the essential amino acids, and to severely restrict the intake of nonessential nitrogen. Hypertonic dextrose solutions are a convenient and metabolically effective source of concentrated calories.
Fluid balance must be carefully monitored in patients with renal failure and care should be taken to avoid circulatory overload, particularly in association with cardiac insufficiency.
In patients with myocardial infarct, infusion of amino acids should always be accompanied by dextrose, since in anoxia, free fatty acids cannot be utilized by the myocardium, and energy must be produced anaerobically from glycogen or glucose.
Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.
Administration of glucose at a rate exceeding the patient’s utilization may lead to hyperglycemia, coma, and death.
Administration of amino acids without carbohydrates may result in the accumulation of ketone bodies in the blood. Correction of this ketonemia may be achieved by the administration of carbohydrates. Abrupt cessation of hypertonic dextrose infusion may result in rebound hypoglycemia.
In subjected to changes in storage temperature, there is a chance that some transient crystallization of amino acids may occur. Thorough shaking of the bottle for about one minute should redissolve the amino acids. If the amino acids do not completely redissolve, the bottle must be rejected.

To minimize the risk of possible incompatibilities arising from mixing this solution with other additives that may be prescribed, the final infusate should be inspected for cloudiness or precipitation immediately after mixing, prior to administration, and periodically during administration.
Use only if solution is clear and vacuum is present.

Laboratory Tests:
Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring during administration.
Laboratory tests should include measurement of blood sugar, electrolyte, and serum protein concentrations; kidney and liver function tests; and evaluation of acid-base balance and fluid balance. Other laboratory tests may be suggested by the patient's condition.

Drug Interaction:
No interactions are known to date.
Due to the increased risk of microbiological contamination and incompatibilities, amino acid solutions should not be mixed with other medicinal products.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No in vitro or in vivo carcinogenesis, mutagenesis, or fertility studies have been conducted with NIRMIN NEPHRO®*.

Pregnancy - Teratogenic Effects - Pregnancy Category C.
Animal reproduction studies have not been conducted with NIRMIN NEPHRO®*. It is also not known whether NIRMIN NEPHRO®* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NIRMIN NEPHRO®* should be given to a pregnant woman only if clearly needed.

Labor and Delivery
Data not available

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NIRMIN NEPHRO®* is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of amino acid injections in pediatric patients have not been established by adequate and well-controlled studies. However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is well established in the medical literature.

Geriatric Use

Elderly patients are known to be more prone to fluid overload and electrolyte imbalance than younger patients. This may be related to impairment of renal function which is more frequent in an elderly population. As a result the need for careful monitoring of fluid and electrolyte therapy is greater in the elderly. All patients, including the elderly, require an individual dose of all parenteral nutrition products to be determined by the physician on an individual case-by-case basis, which will be based on body weight, clinical condition and the results of laboratory monitoring tests. There is no specific geriatric dose.

Special Precautions for Central Venous Nutrition

Administration by central venous catheter should be used only by those familiar with this technique and its complications.

Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure including solution preparation, administration, and patient monitoring. **It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.**

Although a detailed discussion of the complications of central venous nutrition is beyond the scope of this insert, the following summary lists those based on current literature:

Technical. The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arterio-venous fistula, phlebitis, thrombosis, and air and catheter embolus.

Septic. The constant risk of sepsis is present during central venous nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of parenteral nutrition solutions and the placement and care of catheters be accomplished under controlled aseptic conditions.

Administration time for a single bottle and set should never exceed 24 hours.

Typical management includes replacing the solution being administered with a fresh container and set, and the remaining contents are cultured for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip cultured, and a new catheter reinserted when the fever has subsided. Nonspecific, prophylactic antibiotic treatment is not recommended. Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

Metabolic. As per literature reviewed, the following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo- and hypervitaminosis, electrolyte imbalances, and elevated plasma amino acid levels and hyperammonemia in infants and pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of central venous nutrition, to prevent or minimize these complications.

Special Precautions in Patients with Renal Insufficiency

Frequent laboratory studies are necessary in patients with renal insufficiency due to underlying metabolic abnormalities. Hyperglycemia, a frequent complication, may not be reflected by glycosuria in renal failure. Therefore, Blood glucose must be determined frequently, often every six hours to guide dosage of dextrose and insulin if required.

Serum concentrations of potassium, phosphorus, and magnesium may dramatically decline with successful treatment, individually or together; these substances should be supplemented as required. Special care must be taken to avoid hypokalemia in digitalized patients, or those with cardiac arrhythmias.

Undesirable effect:

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis, and hypervolemia.

Symptoms may result from an excess or deficit of one or more of the ions present in the solution infused, therefore, frequent monitoring of electrolyte levels is essential.

As per literature reviewed, Infrequent instances of hyperammonemia have been reported following administration of essential amino acid solutions to patients with massive gastrointestinal hemorrhage, nonuremic infants and pediatric patients or following administration of higher than recommended doses to adult or pediatric patients. Elevated plasma amino acid levels (hypermethionemia) have also been reported in infants especially in higher dosage ranges. Elevated serum ammonia levels, plasma amino acid levels, and clinical symptoms may subside when the infusions are discontinued.

Phosphorus deficiency may lead to impaired tissue oxygenation and acute hemolytic anemia. Relative to calcium, excessive phosphorus intake can precipitate hypocalcemia with cramps, tetany, and muscular hyperexcitability.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

Overdose:

A too rapid infusion can cause fluid overload and electrolyte disturbances.

As with other amino acid solutions shivering, vomiting, nausea, and increased renal amino acid losses can occur when given in overdose or the infusion rate is exceeded. Infusion should be stopped immediately in this case. It may be possible to continue with a reduced dosage.

There is no specific antidote for overdose. Emergency procedures should be general supportive measures, with particular attention to respiratory and cardiovascular systems. Close biochemical monitoring would be essential and specific abnormalities treated appropriately

Administration:

NIRMIN NEPHRO 7%™* are available as a sterile, non-pyrogenic single dose container that can be administration through peripheral veins or by central venous route using non-pyrogenic I.V. administration set with aseptic technique.

Storage:

Store below 25° C, Do not Freeze, Protect from Light.

Presentation:

NIRMIN NEPHRO 7%™* is available in 200 mL, 250 mL, 500 mL and 1000 mL Glass Bottle.

References:

1) Nutrition and Metabolism in Acute Renal Failure, Wilfred Druml, chapter-18, 18.1-18.22

aculife®

Manufactured in India by:
Aculife Healthcare Pvt. Ltd.
Sachana, Gujarat 382150,
India.

* TM owners-Nirma Ltd.