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

Amino Acids (8% w/v) Injection
NIRMIN HEPA 8%™*

Description

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

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

Composition

Each 100 ml contains:	
L-Isoleucine USP	1.040 g
L-Leucine USP	1.309 g
L-Lysine Monoacetate USP equivalent to L-Lysine	0.688 g
L-Methionine USP	0.110 g
L-Phenylalanine USP	0.088 g
L-Threonine USP	0.440 g
L-Tryptophan USP	0.070 g
L-valine USP	1.008 g
L-Arginine IP	1.072 g
L-Histidine USP	0.280 g
Glycine IP	0.582 g
L-Alanine USP	0.464 g
L-Proline USP	0.573 g
L-Serine USP	0.224 g
Acetylcysteine USP equivalent to L-Cysteine	0.052 g
Glacial Acetic Acid IP	0.442 g
Water for injections IP	q. s.
Total Amino Acids	80.00 g/L
Total Nitrogen content	12.90 g/L
% of Branched Chain Amino Acids	41.96
Osmolarity (mOsmol/L)	770

Pharmacological Properties

Pharmacodynamic

The amino acids contained in NIRMIN HEPA®* are all naturally occurring physiological compounds. As with the amino acids derived from the ingestion and assimilation of food proteins, parenterally administered amino acids enter the body pool of free amino acids and all subsequent metabolic pathways.

NIRMIN HEPA®* provides a mixture of essential and nonessential amino acids with high concentrations of the branched chain amino acids isoleucine, leucine, and valine.

The precise mechanisms which produce the therapeutic effects of NIRMIN HEPA®* are not known. The etiopathology of hepatic encephalopathy is also unknown and is thought to be of multifactorial origin.

The rationale for NIRMIN HEPA®* is based on observations of plasma amino acid imbalances in patients with liver disease and on theories which postulate that these abnormal patterns are causally related to the development of hepatic encephalopathy.
As per published literature, The BCAA may ameliorate hepatic encephalopathy by promoting ammonia detoxification, correction of the plasma amino acid imbalance, and by reduced brain influx of aromatic amino acids. The influence of BCAA supplementation on hepatic encephalopathy could be more effective in chronic hepatic injury with hyperammonemia and low concentrations of BCAA in blood than in acute hepatic illness, where hyperaminoacidemia frequently develops. The favorable effect of BCAA on liver regeneration and nutritional state of the body is related to their stimulatory effect on protein synthesis, secretion of hepatocyte growth factor, glutamine production and inhibitory effect on proteolysis. Presumably the beneficial effect of BCAA on hepatic cachexia is significant in compensated liver disease with decreased plasma BCAA concentrations, whereas it is less pronounced in hepatic diseases with inflammatory complications and enhanced protein turnover.
Several studies have demonstrated the stimulatory effect of BCAAs or their metabolites on protein synthesis and/or inhibitory effect on proteolysis[(1)]

Pharmacokinetic
As per literature review, BCAA levels are unreliable because fasting causes increased levels of BCAAs, and poor nutritional status can lead to increased catabolism of BCAAs. BCAAs favor the protein anabolic pathway. BCAAs are not a significant energy source during exercise when compared to carbohydrate or fat. They participate in interorgan nitrogen transfer. They are important nitrogen donors to glutamine and alanine, which are important glucose precursors and fuel for the gut. They have a complex interaction with hormones, with glucagon being a key regulator of leucine oxidation. Leucine and isoleucine can stimulate insulin release, especially in children in which they may inhibit glucagon. With age, there is some evidence that there is decreased potency of AAs. BCAA metabolism may be affected by renal or liver dysfunction. [(2)]

Indications
NIRMIN HEPA®* is indicated for the treatment of hepatic encephalopathy in patients with cirrhosis or hepatitis. NIRMIN HEPA®* provides nutritional support for patients with these diseases of the liver who require parenteral nutrition and are intolerant of general purpose amino acid injections, which are contraindicated in patients with hepatic coma.

Dosage and Administration
Dosage depends on the severity of the catabolic state and on the amino acid requirement.
For intravenous use.
Unless otherwise prescribed, the recommended dosage is:
Recommended Dosage for NIRMIN HEPA®*

- 1.0 to 1.25 ml / kg body weight and hour = 0.08 to 0.1 g amino acids / kg body weight and hour.
- Maximum daily dose: 1.5 g amino acids / kg body weight according to 18.75 ml / kg body weight corresponding to about 1300 ml at 70 kg body weight.
- Maximum Infusion rate: 1.25 ml / kg body weight and hour corresponding to 0.1 g amino acids / kg body weight and hour
- For the administration via a peripheral or central vein as a continuous infusion.
  Children and adolescents:
- The safety and effectiveness of use in children and adolescents are no data.

Fat emulsion coadministration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (E.F.A.D.). Serum lipids should be monitored for evidence of E.F.A.D. in patients maintained on fat free TPN.
The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is required for optimum utilization of amino acids. Approximately 60-180 mEq of potassium, 10-30 mEq of magnesium, and 10-40 mmole of phosphate per day appear necessary to achieve optimum metabolic response. In addition, sufficient quantities of the major extracellular electrolytes sodium, calcium, and chloride, must be given. In patients with hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate salts to provide bicarbonate precursor. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

Contraindication
NIRMIN HEPA®* is contraindicated in patients with anuria, inborn errors of amino acid metabolism, especially those involving branched chain amino acid metabolism such as Maple Syrup Urine Disease and Isovaleric Acidemia, 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 HEPA®* is contra-indicated in neonates.
For parenteral nutrition of infants and children paediatric amino acid preparations should be used, which are formulated to meet the different metabolic needs of children.

Warning and Precaution
WARNING
Safe, effective use of parenteral nutrition requires 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 parenteral nutrition. Studies should include blood sugar, serum proteins, kidney and liver function tests, electrolytes, hemogram, carbon dioxide content, serum osmolarities, blood cultures, and blood ammonia levels.
Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.
Administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, over-hydration, congested states, or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the solutions.

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.
Care should be exercised in the administration of large volume infusion fluids to patients with cardiac insufficiency.
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 HEPA®* is applicable as part of a total parenteral nutrition regimen in combination with adequateamounts 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.
Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

Peripheral intravenous administration of NIRMIN HEPA®* (8% Amino Acid Injection) requires appropriate dilution and provision of adequate calories. Care should be taken to assure proper placement of the needle within the lumen of the vein. The venipuncture site should be inspected frequently for signs of infiltration. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.
Infusion of NIRMIN HEPA®* may not affect the clinical course of patients with fulminant hepatitis who have a poor prognosis and are generally unresponsive to treatment. It has been shown that the abnormal plasma amino acid pattern in fulminant hepatitis differs from that in chronic liver disease.
Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea, or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.
Administration of glucose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma, and death.

Metabolic acidosis can be prevented or readily controlled by adding a portion of the cations in the electrolyte mixture as acetate salts
Some patients, especially those with hypophosphatemia, may require additional phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. To assure adequate intake, serum levels should be monitored frequently.
NIRMIN HEPA®* has not been adequately studied in pregnant women and pediatric patients; therefore, its safe use in such patients has not been demonstrated.
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 NIRMIN HEPA®* only if solution is clear, the seal unbroken 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 HEPA®* (8% Amino Acid Injection).

Pregnancy - Teratogenic Effects - Pregnancy Category C.
Pregnancy Category C. Animal reproduction studies have not been conducted with NIRMIN HEPA®* (8% Amino Acid Injection). It is also not known whether NIRMIN HEPA®* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NIRMIN HEPA®* should be given to a pregnant woman only if clearly needed.

Labor and Delivery
Information is unknown.

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 HEPA®* 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
Due to insufficient data availability, it is not clear whether geriatric patient respond similarly to younger patient. Some clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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 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 transaction, injury to the brachialplexus, malposition of the catheter, formation of arterio-venous fistula, phlebitis, thrombosis, pericardial tamponade, and air and catheter embolus.

Septic - The constant risk of sepsis is present during total parenteral nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of 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 culturing the contents 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. Non-specific, 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 - The following metabolic complications have been reported during the use of central venous nutrition; metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo- and hyper-vitaminosis, electrolyte imbalances and hyperammonemia in pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of therapy to prevent or minimize these complications.

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 or phlebitis extending from the site of injection, extravasation and hypervolemia.
Symptoms may result from an excess or deficit of one or more of the ions present in the solution; therefore, frequent monitoring of electrolyte levels is essential.
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.
Those that occur during overdose (see below) are usually reversible and regress when therapy is discontinued. Infusion via peripheral veins in general can cause irritation of the vein wall and thrombophlebitis.

Overdose
As with other amino acid solutions shivering, vomiting, nausea, and increased renal amino acid losses can occur when NIRMIN HEPA®* is 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.
A too rapid infusion can cause fluid overload and electrolyte disturbances.

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 HEPA 8%™* 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 HEPA®* – In 200 mL, 250 mL, 500 mL and 1000 mL Glass Bottle.

References:

(1) Three targets of branched-chain amino acid supplementation in the treatment of liver disease, Milan Holecek, Nutrition 26 (2010) 482-490.
(2) Branched-Chain Amino Acids: Metabolism, Physiological Function, and Application, John T. Brosnan4 and Margaret E. Brosnan, J. Nutr. 136: 207S–211S, 2006.

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