SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FRINUTRI, amino acid solution with electrolytes, glucose solution and lipid emulsion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This medicinal product is presented in the form of a 3-compartment bag.

There are 3 presentations, which have the following different volumes:

Compartment	**1000 mL**	**1500 mL**	**2000 mL**
Lipid emulsion	200 mL	300 mL	400 mL
Amino acid solution	400 mL	600 mL	800 mL
Glucose solution	400 mL	600 mL	800 mL

Composition of a 1000 mL bag

Active Substances	**10% lipid emulsion compartment (corresponding to 10g/100ml)** **(200 ml)**	**5.5% amino acid solution compartment (corresponding to 5.5g/100ml)** **(400 ml)**	**20% glucose solution compartment (corresponding to 20g/100ml)** **(400 ml)**
Refined olive oil (80%) + refined soya oil (20%)	20 g	-	-
L-alanine	-	4,56 g	-
L-arginine	-	2,53 g	-
Glycine	-	2,27 g	-
L-histidine	-	1,06 g	-
L-isoleucine	-	1,32 g	-
L-leucine	-	1,61 g	-
L-lycine (As L-lycine HCl)	-	1,28 g (1,6 g)	-
L-methionine	-	0,88 g	-
L-phenylalanine	-	1,23 g	-
L-proline	-	1,5 g	-

L-serine	-	1,1 g	-
L-threonine	-	0,92 g	-
L-tryptophan	-	0,4 g	-
L-tyrosine	-	0,09 g	-
L-valine	-	1,28 g	-
Sodium acetate $3H_2O$	-	0,98 g	-
Sodium glycerophosphate $5H_2O$	-	2,14 g	-
Potassium chloride	-	1,19 g	-
Magnesium chloride $6H_2O$	-	0,45 g	-
Glucose	-	-	80 g
Calcium chloride $2H_2O$	-	-	0,3 g

Excipients:

FRINUTRI contains 21 mmol (481 mg) sodium in each liter.

For full list of the excipients, see section 6.1

After the contents of the three compartments have been mixed, the ternary mixture for each of the bag presentations provides the following:

Per bag	**1000 mL**	**1500 mL**	**2000 mL**
Nitrogen (g)	3,6	5,4	7,3
Amino acids (g)	22	33	44
Glucose (g)	80	120	160
Lipids (g)	20	30	40
Total calories (kcal)	610	910	1215
Non-protein calories (kcal)	520	780	1040
Glucose calories (kcal)	320	480	640
Lipid calories (kcal)	200	300	400
Non-protein calorie/nitrogen ratio (kcal/g N)	144	144	144
Sodium (mmol)	21	32	42
Potassium (mmol)	16	24	32

Magnesium (mmol)	2,2	3,3	4,4
Calcium (mmol)	2	3	4
Phosphate (mmol)**	8,5	13	17
Acetate (mmol)	30	46	61
Chloride (mmol)	33	50	66
pH	6	6	6
Osmolarity (mOsm/L)	750	750	750

** Including phosphates provided by the lipid emulsion

3. PHARMACEUTICAL FORM

After reconstitution:

Emulsion for infusion.

Appearance prior to reconstitution:

- The lipid emulsion is an homogeneous liquid with a milky appearance,
- The amino acid and glucose solutions are clear and colourless or slightly yellow.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Parenteral nutrition for adults and children greater than 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2. Posology and method of administration

Posology / frequency and duration of administration

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolize the constituents of FRINUTRI, as well as additional energy or proteins provided orally/enterally; therefore, the bag size should be chosen accordingly.

The administration may be continued for as long as is required by the patient's clinical conditions.

Maximum daily dose:

The maximum daily dose should not be exceeded in adult and paediatric patients. Due to the static composition of the multi-chamber bag, the ability to simultaneously meet all nutrient needs of the patient may not be possible. Clinical situations may exist where patients require amounts of nutrients varying from the composition of the static bag.

In adults

Requirements:

Average nitrogen requirements are 0.16 to 0.35 g/kg/day (approximately 1 to 2 g amino acids/kg/day).

Energy requirements vary depending on the patient's nutritional state and level of catabolism. On average these are 20 to 40 kcal/kg/day.

Maximum daily dose:

The maximum daily dose is 40 ml/kg body weight (equivalent to 0.88 g amino acids, 3.2 g glucose, 0.8 g lipids, 0.84 mmol of sodium and 0.64 mmol potassium / kg), i.e. 2800 ml of the emulsion for infusion for a patient weighing 70 kg.

In adolescents and children greater than two years of age

There have been no studies performed in the pediatric population.

Posology:

The dosage is based on fluid intake and daily nitrogen requirements.

These intakes should be adjusted to take account of the child's hydration status.

Daily fluid, nitrogen and energy requirements are constantly decreasing with age.

The following is the guideline information for the maximum recommended hourly infusion rate and daily volume for pediatric patients:

For FRINUTRI

Maximum daily dose

Component	Children 2-11 years of age		Children 12-18 years of age	
	Recommended Maximum Daily Dose[a]	FRINUTRI Maximum Daily Dose[b]	Recommended Maximum Daily Dose[a]	FRINUTRI Maximum Daily Dose[b]
Fluid (mL/kg/day)	60 - 120	50	50-80	50
Amino acids (g/kg/day)	1 - 2 (up to 2,5)	1,1	1 - 2	1,1
Glucose (g/kg/day)	1,4-8,6	4,0	0,7-5,8	4,0
Lipids (g/kg/day)	0,5-3	1,0	0,5 - 2 (up to 3)	1,0
Total energy (kcal/kg/day)	30-75	30,5	20-55	30,5
Sodium (mmol/kg/day)	1-3	1,1	1-3	1,1
Potassium (mmol/kg/day)	1-3	0,8	1-3	0,8

[a]: The recommended values at the 2018 ESPGHAN/ESPEN/ESPR guidelines.

[b]: The concentration of magnesium is the limiting factor for the maximum daily dose in both age groups.

Maximum infusion rate

Component	Children 2-11 years of age		Children 12-18 years of age	
	Recommended Maximum Infusion Rate[a]	FRINUTRI Maximum Infusion Rate[b]	Recommended Maximum Infusion Rate[a]	FRINUTRI Maximum Infusion Rate[b]
Fluid (mL/kg/hour)	N/A	4,5	N/A	3,0
Amino acids (g/kg/hour)	0,20	0,09	0,12	0,07
Glucose (g/kg/hour)	0,36	0,36	0,24	0,24
Lipids (g/kg/hour)	0,13	0,09	0,13	0,06

[a]: The recommended values at the 2018 ESPGHAN/ESPEN/ESPR guidelines.

[b]: The concentration of glucose is the limiting factor for the maximum infusion rate in both age groups.

Method of administration

For single use only.

It is recommended that after opening the bag, the contents should be used immediately and not stored for subsequent infusion.

Appearance after reconstitution: Homogeneous liquid with a milky appearance.

For instructions for preparation and handling of the emulsion for infusion see section 6.6.

BY INTRAVENOUS ADMINISTRATION THROUGH A CENTRAL OR PERIPHERAL VEIN (Due to low osmolarity of FRINUTRI).

The recommended duration of the parenteral nutrition infusion is between 12 and 24 hours.

The administration flow rate should be adjusted to take account of the dose being administered, the characteristics of the final mixture being infused, the daily volume intake and the duration of the infusion (see section 4.4).

Normally, the flow rate should be increased gradually during the first hour.

Maximal infusion rate

As a general rule, do not exceed 3.0 ml/kg/hour of the emulsion for infusion, i.e. 0.06 g amino acids, 0.24 g glucose and 0.06 g lipids / kg body weight / hour.

As a general rule, the infusion rates of 0.1 g/kg/h amino acid and/or 0.25 g/kg/h glucose and/or 0.15 g/kg/h lipid should not be exceeded, except in special cases.

Additional information on special populations

Renal Insufficiency:

Use with caution in patients with renal insufficiency, particularly if hyperkalaemia is present, because of the

risk of developing or worsening. (See Section 4.4)

Hepatic Insufficiency:

Use with caution in patients with hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia. (See Section 4.4)

Pediatric population

Not recommended in children less than 2 years of age.

Geriatric population:

No additional information on this population is available.

4.3. Contraindications

The use of FRINUTRI is contraindicated in the following situations:

- In premature neonates, infants and children less than 2 years old, as the calorie-nitrogen ratio and energy supply are inappropriate.
- Hypersensitivity to egg, soybean or peanut proteins, or to any other active substance or excipients (listed in section 6.1).
- Congenital abnormalities of amino acid metabolism.
- Severe hyperlipidaemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia.
- Severe hyperglycaemia
- Pathologically-elevated plasma concentration of sodium, potassium, magnesium, calcium, and/or phosphorus

4.4. Special warnings and precautions for use

An excessively fast administration of total parenteral nutrition (TPN) solutions, including FRINUTRI, may result in severe or fatal consequences.

The infusion must be stopped immediately if any signs or symptoms of an allergic reaction (such as sweating, fever, chills, headache, skin rashes, dyspnoeaor bronchospasm) develop. This medicinal product contains soybean oil and egg phosphatide. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean and peanut proteins have been observed.

FRINUTRI contains glucose derived from corn, which can cause hypersensitivity reactions in patients allergic to corn or corn products. (See 4.3 Section)

Specific clinical monitoring is required when an intravenous infusion is started.

Severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders must be corrected before starting the infusion.

Ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions even via different infusion lines or different infusion sites. Ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions (see sections 4.5 and 6.2).

Pulmonary vascular precipitates causing pulmonary vascular embolism and respiratory distress have been

reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of formation of calcium phosphate precipitates (see section 6.2).

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular, the stability of the lipid emulsion). Formation of precipitates or destabilization of the lipid emulsion could result in vascular occlusion (see section 6.2 and 6.6)

Vascular-access infection and sepsis are complications that may occur in patients receiving parenteral nutrition, particularly in case of poor maintenance of catheters, immunosuppressive effects of illness or drugs Careful monitoring of signs, symptoms, and laboratory tests results for fever/chills, leukocytosis, technical complications with the access device, and hyperglycemia can help recognize early infections. Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state. The occurrence of septic complications can be decreased with heightened emphasis on aseptic techniques in catheter placement and maintenance, as well as aseptic techniques in the preparation of the nutritional formula.

Monitor water and electrolyte balance, serum osmolarity, serum triglycerides, acid-base balance, blood glucose, liver and kidney function tests, coagulation tests and blood count, including platelets throughout treatment.

Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient's needs.

Serum triglyceride concentrations and the ability of the body to remove lipids must be checked regularly.

Serum triglyceride concentrations must not exceed 3 mmol/l during the infusion. These concentrations should not be determined before a minimum of a 3-hour period of continuous infusion.

If a lipid metabolism abnormality is suspected, it is recommended that tests be performed daily by measuring serum triglycerides after a period of 5 to 6 hours without administering lipids. In adults, the serum must be clear in less than 6 hours after stopping the infusion containing the lipid emulsion. The next infusion should only be administered when the serum triglyceride concentrations have returned to normal values.

Fat overload syndrome has been reported with similar products. The reduced or limited ability to metabolize the lipids contained in FRINUTRI may result in a "fat overload syndrome" which may be caused by overdose, however the signs and symptoms of this syndrome may also occur when the product is administered according to instructions (see also section 4.8).

In the event of hyperglycaemia, the infusion rate of FRINUTRI must be adjusted and/or insulin administered.

While FRINUTRI may be administered through a peripheral vein, thrombophlebitis may develop. The catheter insertion site must be monitored daily for local signs of thrombophlebitis.

When making additions, the final osmolarity of the mixture must be measured before administration. The mixture obtained should be administered through a central or peripheral venous line depending on its final osmolarity. If the final mixture administered is hypertonic, it may cause irritation of the vein when administered into a peripheral vein.

Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements and these should be added to prevent deficiencies from developing. See instructions for making additions to this product. (See section 6.6)

Caution should be exercised in administering FRINUTRI to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction.

Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes

while avoiding overfeeding can prevent these complications. This syndrome has been reported with similar products.

Do not connect bags in series in order to avoid the possibility of air embolism due to residual air contained in the primary bag.

Hepatic Insufficiency

Use with caution in patients with hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia. Regular clinical and laboratory tests are required particularly liver function parameters, blood glucose, electrolytes and triglycerides.

Renal Insufficiency

Use with caution in patients with renal insufficiency, particularly if hyperkalaemia is present, because of the risk of developing or worsening metabolic acidosis and hyperazotemia if extrarenal waste removal is not being performed. Fluid, triglycerides and electrolyte status should be closely monitored in these patients.

Hematologic

Use with caution in patients with coagulation disorders and anaemia. Blood count and coagulation parameters should be closely monitored.

Endocrine and Metabolism

- Use with caution in patients with:
- Metabolic acidosis. Administration of carbohydrates is not recommended in the presence of lactic acidosis. Regular clinical and laboratory tests are required.
- Diabetes mellitus. Monitor glucose concentrations, glucosuria, ketonuria and, where applicable adjust insulin dosages.
- Hyperlipidaemia due to the presence of lipids in the emulsion for infusion. Regular clinical and laboratory tests are required.
- Amino acid metabolism disorders

Extravasation

Catheter site should be monitored regularly to identify signs of extravasation. If extravasation occurs, the administration should be stopped immediately, keeping the inserted catheter or cannula in place for immediate management of the patient. If possible, aspiration should be performed through the inserted catheter/ cannula in order to reduce the amount of fluid present in the tissues before removing the catheter/ cannula. When involving an extremity, the concerned limb should be elevated.

Depending on the extravasated product (including the product(s) being mixed with FRINUTRI, if applicable) and the stage/extent of any injury, appropriate specific measures should be taken. Options for management may include non-pharmacologic, pharmacologic and/or surgical intervention. If there is any deterioration of the affected area (continued pain, necrosis, ulceration, suspected compartment syndrome), surgery should be consulted immediately.

The extravasation site should be monitored at least every 4 hours during the first 24 hours, then once daily

The infusion should not be and restarted in another the same peripheral or central vein.

Special precautions in paediatrics

When administered to children greater than 2 years old, it is essential to use a bag which has a volume corresponding to the daily dosage.

Vitamin and trace element supplementation is always required. Paediatric formulations should be used.

This medical product contains 21 mmol (approximately 481 mg) of sodium per 1000 mL. This represents approximately 24% of the maximum daily sodium intake of 2 g recommended by the WHO for adults and is considered to be a “high” level of sodium. This also applies to children, for whom the maximum daily intake is considered proportional to adults and based on energy requirements.

FRINUTRI contains soybean oil. Do not use this medicinal product if you are allergic to peanuts or soy.

It contains 80 g of glucose in each 1000 ml of it. This should be taken into account in patients with sugar (diabetes mellitus).

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

No interaction studies have been performed.

Precipitation of ceftriaxone-calcium can occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing intravenous solutions, including FRINUTRI, through the same infusion line (e.g., via Y-site). However, ceftriaxone and calcium containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see sections 4.4 and 6.2).

FRINUTRI contains vitamin K, naturally present in lipid emulsions. The amount of Vitamin K in recommended doses of FRINUTRI are not expected to influence effects of coumarin derivatives.

This emulsion for infusion must not be administered simultaneously with blood through the same infusion tubing because of the possibility of pseudoagglutination.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, blood haemoglobin) if the blood sample is taken before the lipids have been eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

Due to the potassium content of FRINUTRI, special care should be taken in patients treated with potassium sparing diuretics (e.g, amiloride, spironolactone, triamterene) angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists or the immunosuppressants tacrolimus and cyclosporine in view of the risk of hyperkalemia.

Additional information about special populations

No clinical interaction studies have been conducted on the special population.

Pediatric population

No clinical interaction studies have been conducted on the pediatric population.

4.6. Pregnancy and Lactation

General recommendation

Pregnancy category: C

Women with childbearing potential / Contraception

No known effect.

Pregnancy

There are not at present sufficient relevant clinical findings to assess the tolerability of the ingredients in FRINUTRI in women who are pregnant.

In the absence of data, the prescriber must assess the risks/benefits before deciding to administer this emulsion during pregnancy.

Lactation

There are not at present sufficient relevant clinical findings to assess the tolerability of the ingredients in FRINUTRI in women who are breast-feeding.

In the absence of data, the prescriber must assess the risks/benefits before deciding to administer this emulsion to women who are breast-feeding.

Fertility

There is no known effect.

4.7. Effects on ability to drive and use machines

There are no data on the effects of the ability to operate and automobile or other heavy machinery

4.8. Undesirable effects

Potential undesirable effects may occur as a result of inappropriate use (for example: overdose, excessively fast infusion rate) (see sections 4.4 and 4.9).

At the beginning of the infusion, any abnormal signs or symptoms of an allergic reaction (e.g. sweating, fever, shivering, headache, skin rashes, dyspnoea, bronchospasm) should be cause for immediate discontinuation of the infusion.

The reference product (550 and 1000 forms) (and another electrolyte-free form that is not in medical use in Turkey) were used in 286 patients in four (4) clinical studies.

Three (3) studies evaluated the ease of use, safety and nutritional effectiveness of the product.

Two of the three studies were open-label, non-comparative studies conducted in patients undergoing gastrointestinal surgery for stomach cancer. In these studies, a total of 36 patients were given the reference product (form 550) (N=20) at a dose of up to 40 mL/kg/day, and the reference product (form 1000) (N=16) at a dose of 36 mL/kg/day for 5 days.

The third study is a randomized, double-blind, actively controlled efficacy and safety study conducted with a reference product (electrolyte-free form that is not used in medicine in Turkey). In this study, cardiac, respiratory, gastrointestinal, metabolic, nervous system, infectious, and neoplastic renal diseases that require parenteral nutrition is associated with several medical conditions (e.g., starvation after surgery, severe malnutrition, lack of enteral intake or restriction) of 28 patients were included, and these patients the medication for 5 days, up to 40 ml/kg/day to be taken.

The latest study is a randomized, open-label, actively controlled trial evaluating the safety and effectiveness of the reference product (form 550) in 226 patients presented to the surgical service. In this study, 86.3% of the patients underwent surgery (most of them were abdominal surgery due to gastrointestinal disease). The study treatments were intended to provide 25 kcal/kg/day for 5 to 14 days.

Data collected from clinical trials and post-marketing experience indicate the following adverse drug reactions (ADRs) related to the reference product.

Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 with< 1/10); uncommon (≥ 1/1000 with< 1/100); rare (≥ 1/10000 to< 1/1000); very rare (< 1/10000); not known (cannot be estimated from the available data)

Immune system disorders

Uncommon: Hypersensitivity*

Not known: Bronchospasm** (as part of allergic reaction)

Nervous system disorders

Not known: Tremor**

Gastrointestinal disorders

Not known: Diarrhoea**, vomiting**, nausea**

Skin and subcutaneous tissue disorders

Not known: Erythema**, excessive sweating**

Musculoskeletal, connective tissue and bone disorders

Not known: Pain in extremities**, muscle spasm**

General disorders and administration site conditions

Not known: Shivering**, extravasation in the infusion site**, pain in the infusion site**#, swelling/edema in the infusion site**#, vesicles in the infusion site**#, catheter-related phlebitis**#, localized edema**#, peripheral edema**#, pyrexia**, paresthesias**, acedia**, inflammation**, necrosis/ulcer in the infusion site**, reaction in the infusion site**

Injury, poisoning and procedural complications

Not known: Fat overload syndrome

* Adverse effects reported during clinical trials. Only 286 patients were included in these studies.

** Adverse effects reported in the post-marketing experience with the original product.

Adverse reactions that may be associated with extravasation.

Class Reactions

The following undesirable effects have been reported with other similar products:

- Vascular disorders (frequency not known - cannot be estimated from the available data): Pulmonary vascular precipitates (pulmonary vascular embolism and respiratory distress) (see section 4.4)
- Diseases of the blood and lymphatic system (frequency unknown): Thrombocytopenia
- Hepatobiliary disorders (frequency unknown): Cholestasis, hepatomegaly, jaundice
- Diseases of the immune system (frequency unknown): Hypersensitivity
- Investigations (frequency unknown): High level of Gamma-glutamyltransferase, hepatic enzyme (including aspartate-aminotransferase, alanine-aminotransferase, transaminase), blood triglyceride, blood alkaline phosphatase and blood bilirubin
- Renal and urinary disorders (frequency unknown): Azotemia

Description of selected adverse reactions:

- Fat overload syndrome

Fat overload syndrome has been reported with similar products. Improper use (eg. as can be seen as a result of an overdose and/or a higher than recommended infusion rate), it can be seen from the beginning of the infusion, even if the product is used according to the instructions. The reduced or limited ability to metabolise the lipids contained in FRINUTRI product may result in a "fat overload syndrome" which may be caused by overdose; however, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions. This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterized by typical symptoms such as hyperlipidemia, fever, liver fatty infiltration (hepatomegaly), worsen liver function, anemia, leukopenia, thrombocytopenia, coagulation disorders and symptoms of the central nervous system requiring hospitalization (eg. coma). The syndrome is usually reversible when infusion of the lipid emulsion is stopped.

Pediatric Population

Thrombocytopenia was reported in children receiving lipid infusion.

4.9. Overdose

In the event of inappropriate administration (overdose and/or infusion rate higher than recommended), signs of hypervolaemia and acidosis may occur.

An excessively fast administration of total parenteral nutrition (TPN) solutions, including FRINUTRI, had serious and fatal outcomes.

Hyperglycaemia, glucosuria, and a hyperosmolar syndrome may develop if glucose infusion rate exceeds clearance.

An excessively fast infusion or administration of an inappropriately large volume of the product may cause nausea, vomiting, shivering and electrolyte disturbances. In such situations the infusion must be stopped immediately.

The reduced or limited ability to metabolise lipids may result in a "fat overload syndrome". The symptoms are usually reversible after the infusion of the lipid emulsion is stopped (see also section 4.8).

In some serious cases, haemodialysis, haemofiltration or haemodiafiltration may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition/mixtures

ATC Code: B05BA10

This is a ternary mixture enabling the nitrogen/energy balance to be maintained from the nitrogen source (L series amino acids) and energy in the form of glucose and essential fatty acids. In addition, this formulation contains electrolytes.

The amino acid solution contains 15 L series amino acids (including 8 essential amino acids), which are indispensable for protein synthesis.

The amino acids also represent an energy source, their oxidation resulting in excretion of nitrogen in the form of urea.

The amino acid profile is as follows:

- Essential amino acids/total amino acids: 40,5%
- Essential amino acids (g)/total nitrogen (g): 2,5
- Branched-chain amino acids/total amino acids: 19%

The carbohydrate source is glucose (80 g/L).

The lipid emulsion is an association of refined olive oil and refined soya oil (ratio 80/20), with the following approximate distribution of fatty acids:

- 15% saturated fatty acids (SFA)
- 65% monounsaturated fatty acids (MUFA)
- 20% polyunsaturated essential fatty acids (PUFA)

The phospholipid/triglyceride ratio is 0,06.

The moderate essential fatty acid (EFA) content improves the status of their upper derivatives while correcting EFA deficiency.

Olive oil contains significant amount of alpha tocopherol which, combined with a moderate PUFA intake, contributes to improve vitamin E status and reduce lipid peroxidation.

5.2. Pharmacokinetic properties

General properties:

The ingredients of the emulsion for infusion (amino acids, electrolytes, glucose, lipids) are distributed, metabolised and removed in the same way as if they had been administered individually.

The pharmacokinetic properties of the amino acids administered intravenously are principally the same as those of amino acids supplied by oral feeding. Amino acids from food proteins, however, first pass through the vena porta before reaching the systemic circulation.

Absorption

Since this drug is administered intravenously, it is not applicable.

Distribution

The components of the formulation are distributed to all cells in the body.

Biotransformation

Amino acids, dextrose and triglycerides are metabolized by all cells in the body. Dextrose and triglycerides are metabolized to carbon dioxide. Electrolytes are not metabolized.

Elimination

Nitrogen waste is converted into urea in the liver and excreted by the kidneys. Carbon dioxide waste is excreted by the lungs. Electrolytes are stored in the body or excreted by the liver, intestines, kidneys or skin.

The elimination rate of lipid emulsions depends on particle size. Small lipid particles appear to delay clearance whereas they increase lipolysis by lipoprotein lipase.

The size of the lipid particles in the emulsion contained in FRINUTRI is close to that of chylomicrons and this emulsion therefore has a similar elimination rate.

Lineer/Non-lineer State

None

5.3. Preclinical safety data

No preclinical study has been performed with reference product. However, studies performed using the solutions of amino acids and glucose contained in FRINUTRI of different qualitative compositions and concentrations have not, however, revealed any specific toxicity.

Preclinical studies performed using the lipid emulsion contained in FRINUTRI have identified typical changes associated with a high intake of a lipid emulsion. These are fatty liver, thrombocytopenia and elevated cholesterol.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

Lipid emulsion compartment:

- Purified egg phosphatide (derived from chicken)
- Glycerol
- Sodium oleate
- Sodium hydroxide (for pH adjustment)
- Water for injections

Amino acid solution compartment:

- Glacial acetic acid (for pH adjustment)
- Water for injections

Glucose solution compartment:

- Hydrochloric acid (for pH adjustment)
- Water for injection

6.2. Incompatibilities

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular the stability of the lipid emulsion or formation of precipitates) (see section 6.6).

As with any parenteral nutrition admixture, calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in formation of calcium phosphate precipitates.

Incompatibilities may be produced for example by excessive acidity (low pH) or inappropriate content of divalent cations (Ca^{2+} and Mg^{2+}), which may de-stabilise the lipid emulsion.

Ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including FRINUTRI, through the same infusion line (e.g., via Y-connector) because of the risk of precipitation of ceftriaxone-calcium salt (see section 4.4 and 4.5).

Check compatibility with solutions administered simultaneously through the same administration set, catheter or cannula.

Do not administer before, simultaneously with or after blood through the same equipment because of the risk of pseudoagglutination.

FRINUTRI contains calcium ions which pose additional risk of coagulation precipitates in citrate anticoagulated/preserved blood or components.

6.3. Shelf-life

24 months if the overwrap is not damaged.

It is recommended that the product is used immediately after the nonpermanent seals between the 3 compartments have been opened. The reconstituted emulsion has, however, been shown to be stable for a maximum of 7 days at between 2° C and 8°C followed by a maximum of 48 h at temperatures not exceeding 25°C.

After addition of supplements (electrolytes, organic phosphate, trace elements, vitamins; see section 6.6):

For specific admixtures, chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8°C followed by 48 hours below 25°C. From a microbiological point of view, any admixture should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless addition of supplements has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store at room temperature below 25°C.

Do not freeze.

Keep container in the outer carton to protect from light. For storage of the reconstituted emulsion, see section 6.3

6.5. Nature and contents of container

The 3 compartment bag is a multi-layer plastic bag. The inner (contact) layer of the bag material is made of a blend of polyolefinic copolymers and is compatible with amino acid solutions, glucose solutions and lipid emulsions. Other layers are made of EVA (poly(ethylene-vinyl acetate)), and of a copolyester.

3-Compartment bag is in an oxygen barrier overpouch. There is an oxygen absorber sachet between the overpouch and the multilayer bag.

There is 1 port in each compartment. The administration port is in the amino acid compartment and is indicated by a sign on the packaging.

Once the seals are removed, the capacity of the bag is sufficient to add vitamins, electrolytes and trace elements.

Package content:

- 1000 ml in a 3 compartment bag (400 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 400 ml 20% glucose solution (corresponding to 20g/100ml) + 200 ml 10% lipid emulsion (corresponding to 10g/100ml))
- 1500 ml in a 3 compartment bag (600 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 600 ml 20% glucose solution (corresponding to 20g/100ml) + 300 ml 10% lipid emulsion (corresponding to 10g/100ml))
- 2000 ml in a 3 compartment bag (800 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 800 ml 20% glucose solution (corresponding to 20g/100ml) + 400 ml 10% lipid emulsion (corresponding to 10g/100ml))

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

Directions for use

a. To open:

- Tear the protective overwrap.
- When present, discard the oxygen absorber sachet after removing the overwrap.
- Confirm the integrity of the bag and of the non-permanent seals.
- Use only if the bag is not damaged, if the non-permanent seals are intact (i.e. no mixture of the contents of the three compartments) and if the amino acids solution and the glucose solution are clear, colorless, or slightly yellow, practically free of visible particles, and if the lipid emulsion is a homogeneous liquid with a milky appearance.

b. Mixing the solutions and the emulsion:

- Ensure that the product is at ambient temperature when breaking the non-permanent seals.
- Manually roll the bag onto itself, starting at the top of the bag (hanger end).
- The nonpermanent seals will disappear from the side near the inlets. Continue to roll until the seals are open along half of their length.
- Mix by inverting the bag at least 3 times.

c. Preparation of the infusion:

- Aseptic conditions must be observed.

- Suspend the bag.
- Remove the plastic protector from the administration outlet.
- Firmly insert the spike of the infusion set into the administration outlet.

d. Additions:

The capacity of the bag is sufficient to enable additions such as, vitamins, electrolytes, and trace elements. Any additions (including vitamins) may be made into the reconstituted mixture (after the non-permanent seals have been opened and the contents of the three compartments have been mixed).

Vitamins may also be added into the glucose compartment before the mixture has been reconstituted (before opening the non-permanent seals and before mixing the solutions and the emulsion).

When making additions to the formulation, the final osmolarity of the mixture should be measured before administration via a peripheral vein.

FRINUTRI may be supplemented with:

- Electrolytes: electrolytes already present in the bag should be taken into account: stability has been demonstrated up to a total quantity of 150 mmol of sodium, 150 mmol of potassium, 5.6 mmol of magnesium and 5 mmol of calcium per litre of the ternary mixture.
- Organic phosphate: stability has been demonstrated for additions of up to: 15 mmol per bag.
- Trace elements and vitamins: Stability has been demonstrated with commercially available preparations of vitamins and trace elements (containing up to 1 mg of iron). Compatibility for other additives is available upon request.

Additions must be performed by qualified personnel under aseptic conditions. These additions are made into the injection site using a needle:

- Prepare the injection site.
- Puncture the injection site and inject
- Mix the content of the bag and the additive.

a. Administration:

For single use only.

Only administer the product after the non-permanent seals between the 3 compartments have been broken and the contents of the 3 compartments have been mixed.

Ensure that the final emulsion for infusion does not show any evidence of phase separation.

After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion.

Do not reconnect any partially used bag.

Do not connect bags in series in order to avoid the of air embolism due to air contained in the primary bag.

Any unused product or waste material and all necessary devices must be discarded.

Do not store any partially used bags and discard all devices after use.

7. PHARMACEUTICAL COMPANY

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8. MANUFACTURER

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9. DATE OF REVISION OF THE TEXT

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