Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NuTRIflex Lipid plus Emulsion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The ready-for-use emulsion for intravenous infusion contains after mixing the chamber contents:

from the upper, left-hand chamber (glucose solution)	in 1250 ml	in 1875 ml	in 2500 ml
Glucose monohydrate ≙ anhydrous glucose	165.0 g 150.0 g	247.5 g 225.0 g	330.0 g 300.0 g
Sodium dihydrogen phosphate $2H_2O$	2.340 g	3.510 g	4.680 g
Zinc acetate $2H_2O$	6.580 mg	9.870 mg	13.160 mg

from the upper, right-hand chamber (fat emulsion)	in 1250 ml	in 1875 ml	in 2500 ml
Soya-bean oil	25.0 g	37.5 g	50.0 g
Medium-chain triglycerides	25.0 g	37.5 g	50.0 g

from the lower chamber (amino acid solution)	in 1250 ml	in 1875 ml	in 2500 ml
Isoleucine	2.82 g	4.23 g	5.64 g
Leucine	3.76 g	5.64 g	7.52 g
Lysine hydrochloride ≙ Lysine	3.41 g 2.73 g	5.12 g 4.10 g	6.82 g 5.46 g
Methionine	2.35 g	3.53 g	4.70 g
Phenylalanine	4.21 g	6.32 g	8.42 g
Threonine	2.18 g	3.27 g	4.36 g
Tryptophan	0.68 g	1.02 g	1.36 g
Valine	3.12 g	4.68 g	6.24 g
Arginine	3.24 g	4.86 g	6.48 g
Histidine hydrochloride monohydrate ≙ Histidine	2.03 g 1.50 g	3.05 g 2.25 g	4.06 g 3.00 g
Alanine	5.82 g	8.73 g	11.64 g
Aspartic acid	1.80 g	2.70 g	3.60 g
Glutamic acid	4.21 g	6.32 g	8.42 g
Glycine	1.98 g	2.97 g	3.96 g
Proline	4.08 g	6.12 g	8.16 g
Serine	3.60 g	5.40 g	7.20 g
Sodium hydroxide	0.976 g	1.464 g	1.952 g
Sodium chloride	0.503 g	0.755 g	1.006 g
Sodium acetate	0.277 g	0.416 g	0.554 g
Potassium acetate	3.434 g	5.151 g	6.868 g
Magnesium acetate 4 H_2O	0.858 g	1.287 g	1.716 g
Calcium chloride	0.588 g	0.882 g	1.176 g

	in 1250 ml	in 1875 ml	in 2500 ml
Amino acid content (g)	48	72	96

Total nitrogen content (g)	6.8	10.2	13.6
Carbohydrate content (g)	150	225	300
Lipid content (g)	50	75	100

Energy in the form of lipid (kJ/kcal)	1990 (475)	2985 (715)	3980 (950)
Energy in the from of carbohydrate (kJ/kcal)	2510 (600)	3765 (900)	5020 (1200)
Energy in the from of amino acids (kJ/kcal)	800 (190)	1200 (285)	1600 (380)
Non-protein energy (kJ/kcal)	4500 (1075)	6750 (1615)	9000 (2155)
Total energy (kJ/kcal))	5300 (1265)	7950 (1900)	10600 (2530)

Osmolality (mOsm/kg)	1540	1540	1540
pH	5.0 - 6.0	5.0 - 6.0	5.0 - 6.0

Electrolytes (mmol)			
Sodium	50	75	100
Potassium	35	52.5	70
Magnesium	4.0	6.0	8.0
Calcium	4.0	6.0	8.0
Zinc	0.03	0.045	0.06
Chloride	45	67.5	90
Acetate	45	67.5	90
Phosphate	15	22.5	30

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for infusion.

Infusion bag with three compartments.
Amino acids and glucose solutions: clear, colourless up to faintly straw-coloured solutions.
Lipid emulsion: white, milky oil-in-water emulsion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Supply of energy, essential fatty acids, amino acids, electrolytes and fluid during parenteral nutrition for patients with moderately severe catabolism when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

4.2.1 Recommended dosage schedule

The dosage has to be adapted to the individual requirements of the patients.

It is recommended that NuTRIflex Lipid plus be administered continuously. A stepwise increase of the infusion rate over the first 30 minutes up to the desired infusion rate avoids possible complications.

Adults:
The maximum daily dose amounts to 40 ml/kg body weight, corresponding to
1.54 g amino acids /kg body weight per day
4.8 g glucose /kg body weight per day

1.6 g lipid /kg body weight per day.

The maximum rate of infusion is 2.0 ml/kg body weight per hour, corresponding to
0.08 g amino acids /kg body weight per hour
0.24 g glucose /kg body weight per hour
0.08 g lipid /kg body weight per hour

For a patient weighing 70 kg this corresponds to an infusion rate of 140 ml per hour. The amount of amino acid administered is then 5.4 g/hour, of glucose 16.8 g/hour and of lipid 5.6 g/hour.

In general, it is recommended that the maximum amount of energy should not exceed 40 kcal/kg BW and day. If specially indicated e.g. for burned patients higher dosage is possible.

Children over 2 years of age:
The given dosage recommendations are guiding data based on average requirements. The dosage should be individually adapted, according to age, development stage and illness. For calculation of dosage account must be taken of the hydration status of the paediatric patient.
For children, it might be necessary to start the nutritional therapy with half of the target dosage. The dosage should be increased stepwise according to the individual metabolic capacity up the maximum dosage.

Daily dose during 3rd – 5th year of life:
40 ml/kg body weight, corresponding to
1.54 g amino acids /kg body weight per day
4.8 g glucose /kg body weight per day
1.6 g lipid /kg body weight per day.

Daily dose during 6th – 14th year of life:
25 ml/kg body weight, corresponding to
0.96 g amino acids /kg body weight per day
3.0 g glucose /kg body weight per day
1.0 g lipid /kg body weight per day.

The maximum rate of infusion is 2.0 ml/kg body weight per hour, corresponding to
0.08 g amino acids /kg body weight per hour
0.24 g glucose /kg body weight per hour
0.08 g lipid /kg body weight per hour.

Additional energy that may be required for paediatric patients should be administered in the form of glucose solutions or fat emulsions, as appropriate.

Duration of use

The duration of treatment for the indications stated is not limited. During long-term administration of NuTRIflex Lipid plus it is necessary to supply appropriate replacement of trace elements and vitamins.

4.2.2 Method of and route of Administration

For central venous infusion only.

4.3 Contraindications

This product must not be administered in the following conditions

- disturbances of amino acid metabolism,
- disturbances of lipid metabolism,
- hyperkalaemia; hypernatraemia,
- unstable metabolism (e.g. severe postaggression syndrome, unstabilized diabetic metabolic situation, coma of unknown origin),
- hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour,
- acidosis,
- intrahepatic cholestasis,
- severe hepatic insufficiency,
- severe renal insufficiency,
- manifest cardiac insufficiency,
- aggravating haemorrhagic diatheses,
- acute phases of cardiac infarction and stroke,
- acute thrombo-embolic events, lipid embolism,
- known hypersensitivity to egg – or soy protein, peanut oil or to any of the excipients.

On account of its composition NuTRIflex Lipid plus should not be used for neonates, infants and children under 2 years of age.

General contra-indications to parenteral nutrition are:

- unstable circulatory status with vital threat (states of collapse and shock),
- inadequate cellular oxygen supply,
- states of hyperhydration,
- disturbances of the electrolyte and fluid balance,
- acute pulmonary oedema, decompensated cardiac insufficiency

4.4 Special warnings and precautions for use

Due to the individual needs of paediatric patients, NuTRIflex Lipid plus may not cover sufficiently the total energy requirements. In such cases carbohydrates and / or lipids must be provided in addition, as appropriate.

Caution should be exercised in cases of increased serum osmolarity.

As for all large-volume infusion solutions NuTRIflex Lipid plus should be administered with caution to patients with impaired cardiac or renal function. Disturbances of the fluid, electrolyte or acid-base balance, e.g. hyperhydration, hyperkalaemia, acidosis, should be corrected before the start of infusion. Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration and pulmonary oedema.

The serum triglyceride concentration should be monitored when infusing NuTRIflex Lipid plus. Fasting lipaemia should be excluded in patients with suspected disturbances of lipid metabolism before starting infusion. The administration of lipids is contra-indicated if there is fasting lipaemia. The presence of hypertriglyceridaemia 12 hours after lipid administration also indicates a disturbance of lipid metabolism.

NuTRIflex Lipid plus should be administered cautiously to patients with disturbances of lipid metabolism, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired hepatic function, hypothyroidism (with hypertriglyceridemia) and sepsis. If NuTRIflex Lipid plus is given to patients with these conditions, close monitoring of serum triglycerides is mandatory.

Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.

Depending on the patient´s metabolic condition, occasional hypertriglyceridaemia or increases of the blood glucose concentration may occur. If the plasma triglyceride concentration rises to more than 3 mmol/l during administration of lipid it is recommended that the infusion rate should be reduced. Should the plasma triglyceride concentration remain above 3 mmol/l the administration should be stopped until the level normalizes.

A dose reduction or interruption of administration is also indicated if the blood glucose concentration rises to more than 14 mmol/l (250 mg/dl) when administering the product.

As with all solutions containing carbohydrates the administration of NuTRIflex Lipid plus can lead to hyperglycaemia. The blood glucose level should be monitored. If there is hyperglycaemia the rate of infusion should be reduced or insulin should be administered.

Intravenous infusion of amino acids is accompanied by increased urinary excretion of the trace elements, especially copper and, in particular, zinc. This should be considered in the dosing of trace elements, especially during long-term intravenous nutrition.

NuTRIflex Lipid plus should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

Moreover controls of the serum ionogramme, the water balance, the acid-base balance and -during long-term administration - of blood cell counts, coagulation status and hepatic function are necessary.

The fat content may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation) if blood is sampled before fat has been adequately cleard from the blood stream.

Substitution of electrolytes, vitamins and trace elements may be necessary as required.
As NuTRIflex Lipid plus contains zinc and magnesium, care should be taken when it is coadministered with solutions containing these elements.

As with all intravenous solutions strict aseptic precautions are necessary for the infusion of NuTRIflex Lipid plus.

NuTRIflex Lipid plus is a preparation of complex composition. It is, therefore, strongly advisable not to add other solutions.

4.5 Interaction with other medicinal products and other forms of interaction

Some drugs, like insulin, may interfere with the body’s lipase system. This kind of interaction seems, however, to be of only limited clinical importance.

Heparin given in clinical doses causes a transient release of lipoprotein lipase into the circulation. This may result initially in increased plasma lipolysis followed by a transient decrease in triglyceride clearance.

Soya-bean oil has a natural content of vitamin K1. This may interfere with the therapeutic effect of coumarin derivatives which should be closely monitored in patients treated with such drugs.

4.6 Fertility, pregnancy and lactation

Preclinical studies have not been performed with NuTRIflex Lipid plus. The prescriber should consider the benefit/ risk relationship before administering NuTRIflex Lipid plus to pregnant women.

Breast-feeding is not recommended if women need parenteral nutrition in that time.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Possible early reactions on the administration of lipid emulsions are: slight increase in temperature, flush, cold feeling, shivering, loss of appetite, nausea, vomiting, respiratory distress, headache, pain in the back, bones, chest and lumbar region, fall or increase in blood pressure (hypotension, hypertension), hypersensitivity reactions (e.g. anaphylactic reactions, dermal eruptions).

Hot flushes or bluish discoloration of the skin, because of reduced oxygen content of the blood (cyanosis), can occur as side effects.

If these side effects occur the infusion should be discontinued or, if appropriate, the infusion should be continued at a lower dose level.

Attention should be paid to the possibility of an overloading syndrome This can occur as a result of individually varying, genetically determined metabolic conditions and can occur at different rates and after differing doses depending on previous disorders.

Overloading syndrome is associated with the following symptoms: enlargement of the liver (hepatomegaly) with and without jaundice (icterus), enlargement of the spleen (splenomegaly), fatty infiltration of the organs, pathological hepatic function parameters, anaemia, reduction of white cell count (leucopenia), reduction of platelet count (thrombocytopenia), a tendency to haemorrhage and haemorrhages, alterations or reduction in the blood coagulation factors (bleeding time, coagulation time, prothrombin time etc.), fever, hyperlipidaemia, headache, stomach-ache, fatigue.

4.9 Overdose

4.9.1. Symptoms

Overdose of NuTRIflex Lipid plus is not to be expected on proper administration.

Symptoms of fluid and electrolyte overdose:
Hypertonic hyperhydration, electrolyte imbalance and pulmonary oedema.

Symptoms of amino acid overdose:
Renal amino acid losses with consecutive amino acid imbalances, sickness, vomiting and shivering.

Symptoms of glucose overdose:
Hyperglycaemia, glucosuria, dehydration, hyperosmolality, hyperglycaemic and hyperosmolar coma.

Symptoms of lipid overdose:
Lipid overdose may lead to the overload syndrome, characterized (for example) by fever, headache, stomach-ache, fatigue, hyperlipidaemia, hepatomegaly with or without jaundice, splenomegaly, pathological disturbances of hepatic function, anaemia, reduction in platelet count, reduction in white cell count, haemorrhagic diathesis or and haemorrhage, alteration or depression of blood coagulation factors (bleeding time, coagulation time, prothrombin time etc.). The plasma triglyceride concentration should not exceed 3 mmol/l during infusion.

4.9.2. Emergency treatment, antidotes

Immediate cessation of infusion is indicated for overdose. Further therapeutic measures depend on the particular symptoms and their severity. When infusion is recommenced after the symptoms have declined it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: The ATC code is B 05BA10 (Solution for parenteral nutrition, combination).

The purpose of parenteral nutrition is to supply all necessary nutrients for the growth and regeneration of tissue.

Here the amino acids are of particular importance since some of them are essential components for protein synthesis. The simultaneous administration of energy sources (carbohydrates/lipids) is necessary to avoid false energetic utilization of amino acids while still providing for the further energy-consuming processes.

Glucose is ubiquitously metabolized within the organism. Some tissues and organs, such as CNS, bone marrow, erythrocytes, tubular epithelium, cover their energy requirement exclusively from glucose. In addition glucose acts as a structural building block for various cell substances.

On account of their high energy density lipids are an efficient form of energy supply and provide the organism with essential fatty acids for the synthesis of cell components and prostaglandins. For this purpose the lipid emulsion contains medium-chain and long-chain triglycerides (soya-bean oil).

Medium-chain triglycerides are more rapidly hydrolyzed, eliminated from the circulation and completely oxidized than long-chain triglycerides. They are a favoured energy substrate, particularly when there is disturbance of the degradation and/or utilization of long-chain triglycerides, e.g. when there is a lipoprotein lipase deficiency and/or a deficiency in lipoprotein lipase cofactors.

Unsaturated fatty acids are only supplied by long-chain triglycerides, which, serve primarily for prophylaxis and treatment of essential fatty acid deficiency and only secondarily as energy suppliers.

5.2 Pharmacokinetic properties

NuTRIflex Lipid plus is infused intravenously. Hence, all substrates are available for metabolism immediately.

Amino acids, that do not enter protein synthesis, are metabolized as follows. The amino group is separated from the carbon skeleton by transamination. The carbon chain is either oxidized directly to CO_2 or utilized as substrate for gluconeogenesis in the liver. The amino group is also metabolized in the liver to urea.

Glucose is metabolized to CO_2 and H_2O via the known metabolic routes. Some glucose is utilized for lipid synthesis.

When the dosage guidelines are followed medium-chain fatty acids and long-chain fatty acids are practically completely bound to the plasma albumin.

Therefore, when the dosage guidelines are followed medium-chain and long-chain fatty acids do not pass the blood-brain barrier and, hence, do not pass into the cerebrospinal fluid.

No data are available concerning transport through the placental barrier and passage into the breast milk.

The dose, rate of infusion, metabolic situation and individual factors of the patient (level of fasting) are of decisive importance for the maximum triglyceride concentrations reached. When used according to the instructions with due regard to the dosage guidelines the triglyceride concentrations do not, in general, exceed 3 mmol/l.

5.3 Preclinical safety data

Preclinical studies have not been performed with NuTRIflex Lipid plus.

Toxic effects of mixtures of nutrients given as substitution therapy at the recommended dosage are not to be expected.

Reproductive Toxicity
Phytoestrogens such as β-sitosterol can be contained in various vegetable oils, especially in soya-bean oil. When β-sitosterol is administered subcutaneous and intravaginal an impairment of fertility was determined in rats and rabbits. The observed effects in animals are not of clinical relevance according to our experiences.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Egg lecithin
Glycerol
Sodium oleate
Water for injections

6.2 Incompatibilities

NuTRIflex Lipid plus must not be used as a carrier solution for pharmaceuticals or be mixed with other infusion solutions without testing, since it is not possible to guarantee adequate stability of the emulsion.

6.3 Shelf life

- *In unopened container:*
  NuTRIflex Lipid plus has a shelf life of 2 years and should not be used after the expiry date.

- *Shelf life after removing the protective pack and after mixing of the contents of the bag:*
  The emulsion can be stored at 2 – 8 °C over 4 days, plus 48 hours at 25 °C.

- *After opening of the container:*
  The emulsion is to be used immediately after opening of the container.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze! If accidentally frozen, discard the bag.

Keep the bags in the outer carton in order to protect from light.

6.5 Nature and contents of container

NuTRIflex Lipid plus is supplied in flexible multichamber bags containing:
- 1250 ml **(**500 ml of amino acids solution + 250 ml of fat emulsion + 500 ml of glucose solution),
- 1875 ml (750 ml of amino acids solution + 375 ml of fat emulsion + 750 ml of glucose solution),
- 2500 ml (1000 ml of amino acids solution + 500 ml of fat emulsion + 1000 ml of glusose solution)

in a flexible three-chambered bag (Polyamide/Polypropylene). The two upper chambers can be connected with the lower chamber by opening the intermediate seal (peel seal).

The design of the bag permits mixing of the amino acids, glucose, lipid and electrolytes in a single chamber. Opening the peel seal results in sterile mixing to form an emulsion.

The different container sizes are presented in cartons containing five bags.
Package sizes: 5 x 1250 ml, 5 x 1875 ml and 5 x 2500 ml

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Preparation of the mixed emulsion:
Remove the bag from its protective pack and proceed as follows:
- Open out the bag and lay on a solid surface.

- Open the peel seals to the two upper chambers by using pressure with both hands.
- Briefly mix the contents of the bag together.

Preparation for infusion:
- Fold the two empty chambers backwards.
- Hang the mixing bag on the infusion stand by the centre hanging loop.
- Remove the protective cap from the run-out port and carry out infusion using the standard technique.

Only use bags that are undamaged and in which the amino acid and glucose solutions are clear. Do not use bags where there is discernible phase separation (oil drops) in the chamber containing lipid emulsion.

NuTRIflex Lipid plus is supplied in single dose containers. Unused residues must be discarded.
If filters are used they must be lipid-permeable.

7 MARKETING AUTHORISATION HOLDER

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Carl-Braun Strasse. 1
34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA 736/14/1

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