SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NuTRIflex® Lipid peri

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amounts of active ingredients (INN names) in both sizes of the product after mixing of the chambers are given below.

Left Chamber

Composition (g)	**Size 1 1250 ml**	**Size 2 1875 ml**	**Size 3 2500 ml**
From the larger, upper compartment (500 ml, 750 ml, 1000 ml)			
Glucose monohydrate ≅ Anhydrous glucose	88.0 (80.0)	132.0 (120.0)	176.0 (160.0)
Sodium dihydrogen phosphate dihydrate	1.170	1.755	2.340
Zinc acetate dihydrate (mg)	6.6	9.9	13.2

Right Chamber

Composition (g)	**Size 1 1250 ml**	**Size 2 1875 ml**	**Size 3 2500 ml**
From the smaller, upper compartment (250 ml, 375 ml, 500 ml)			
Soya bean oil	25.0	37.5	50.0
Medium chain triglycerides	25.0	37.5	50.0

Lower Chamber

Composition (g)	**Size 1 1250 ml**	**Size 2 1875 ml**	**Size 3 2500 ml**
From the lower compartment (500 ml, 750 ml, 1000 ml)			
Isoleucine	2.34	3.51	4.68
Leucine	3.13	4.70	6.26
Lysine hydrochloride ≅ Lysine	2.84 2.26	4.26 3.39	5.68 4.53
Methionine	1.96	2.94	3.92
Phenylalanine	3.51	5.27	7.02
Threonine	1.82	2.73	3.64
Tryptophan	0.57	0.86	1.14
Valine	2.60	3.90	5.20
Arginine	2.70	4.05	5.40
Histidine hydrochloride monohydrate ≅ Histidine	1.69 1.25	2.54 1.88	3.38 2.50
Alanine	4.85	7.28	9.70
Aspartic acid	1.50	2.25	3.00
Glutamic acid	3.50	5.25	7.00
Glycine (aminoacetic acid)	1.65	2.48	3.30
Proline	3.40	5.10	6.80
Serine	3.00	4.50	6.00
Sodium hydroxide	0.800	1.200	1.600
Sodium chloride	1.081	1.622	2.162
Sodium acetatetrihydrate	0.544	0.816	1.088
Potassium acetate	2.943	4.415	5.886
Magnesium acetate tetrahydrate	0.644	0.966	1.288
Calcium chloride dihydrate	0.441	0.662	0.882

Total electrolyte concentration after mixing	**Size 1 1250 ml (mmol)**	**Size 2 1875 ml (mmol)**	**Size 3 2500 ml (mmol)**
Sodium	50	75	100
Potassium	30	45	60
Magnesium	3.0	4.5	6.0
Calcium	3.0	4.5	6.0
Zinc	0.03	0.045	0.06
Chloride	48	72	96
Acetate	40	60	80
Phosphate	7.5	11.25	15

Total substrate contents and other information	**Size 1 1250 ml**	**Size 2 1875 ml**	**3 2500 ml**
Total amino acids (g)	40	60	80
Nitrogen (g)	5.7	8.6	11.4
KJ (Kcal) from fat	1990 (475)	2985 (715)	3980 (950)
KJ (Kcal) from carbohydrate	1340 (320)	2010 (480)	2680 (640)
KJ (Kcal) from amino acids	670 (160)	1005 (240)	1340 (320)
Non-protein energy KJ (Kcal)	3330 (795)	4995 (1195)	6660 (1590)
Total energy KJ (Kcal))	4000 (955)	6000 (1435)	8000 (1910)
Osmolality (mOsm/kg)	920	920	920

3 PHARMACEUTICAL FORM

Emulsion for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral nutrition with NuTRIflex* Lipid peri is indicated when a patient requires parenteral nutritional support, i.e. when feeding via the gastrointestinal tract is either not possible or insufficient.

NuTRIflex* Lipid peri provides amino acids, electrolytes, essential fatty acids and calories in the form of carbohydrates and lipids.

4.2. Posology and Method of Administration

Adults and children
The dosage should be adjusted according to individual patient needs, however, 1250-2500 ml of NuTRIflex® Lipid peri per day are regarded as a normal dose which may be sufficient for the majority of circumstances.
The maximum daily dose is 40 ml per kg body weight.

Neonates, infants
See section 4.3 (Contra-indications).

The elderly
There is no evidence to suggest that dosage should be different from that recommended for other adult patients. Nevertheless, as metabolic rates and patterns can vary in the elderly, careful monitoring of this particular group of patients is always advisable.

An individual adjustment of the dosage is necessary in case of liver insufficiency.

Infusion rates
It is recommended that NuTRIflex® Lipid peri is administered by continuous infusion.
It is advisable to gradually increase the infusion rate to the desired level over approximately 30 minutes. This prevents metabolic complications.

The maximum infusion rate is 2.5 ml per kg body weight per hour. With this infusion rate, 0.08 g amino acids, 0.16 g glucose, and about 0.1 g lipids are administered per kg body weight per hour. The infusion rate should be lower, according to the body weight, in patients with reduced nutritional condition.

Duration of use
NuTRIflex® Lipid peri can be administered as long as parenteral nutrition is indicated (normally 1-2 weeks, sometimes up to 4 weeks); in cases where parenteral nutrition is further indicated, administration of NuTRIflex® Lipid peri should be accompanied by careful metabolic monitoring.

Method of Administration
NuTRIflex® Lipid peri has an osmolality of approximately 920 mOsm/kg and can be infused via a peripheral vein.

Trace element and vitamin levels should be assessed, particularly in the critically ill patients or those receiving prolonged nutrition, and supplementation may be required according to individual needs.

If other solutions (e.g., medications) are administered along with NuTRIflex® Lipid peri through a Y-connector, the possibility of incompatibilities between the solutions should be considered and excluded before the infusion.

The fluid should be warmed to room temperature before setting up the infusion.

4.3. Contra-indications

NuTRIflex® Lipid peri is contraindicated in the following conditions:

Acute shock, acute phase of myocardial and cerebral infarction, severe disorders of blood coagulation, acute thrombo-embolism or fat embolism, irreversible liver damage, intrahepatic cholestasis, severe uraemia when dialysis facilities are not available, disorders of lipid metabolism such as pathological hyperlipaemia and conditions associated with trigylceride accumulation during parenteral nutrition, inborn errors of amino acid metabolism, untreated or complicated diabetes mellitus, especially in the presence of coma related to keto-acidosis or diabetic precoma.

Due to the different nutritional requirements NuTRIflex® Lipid peri should not be given to neonates and infants up to the age of 24 months.

4.4. Special Warnings and Precautions for Use

As with all large volume infusion fluids, NuTRIflex® Lipid peri should be administered with caution to patients with cardiac or renal dysfunction. Disorders of the fluid, electrolyte, and acid-base balance, e.g., overhydration, hyperkalaemia, acidosis, should be corrected before administration. Too rapid infusion can cause fluid overloading resulting in pathological serum electrolyte concentrations, overhydration, congested states, pulmonary oedema, impaired pulmonary diffusion capacity.

NuTRIflex® Lipid peri should be given with caution in conditions of impaired lipid metabolism as in renal insufficiency, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertriglyceridaemic), and sepsis. NuTRIflex® Lipid peri should also be given with caution in conditions of altered amino acid metabolism.

As with other solutions containing glucose, administration of NuTRIflex® Lipid peri may lead to hyperglycaemia. Blood glucose levels should be monitored and the rate of infusion adjusted or insulin should be administered if hyperglycaemia occurs.

When NuTRIflex® Lipid peri is administered, the patient´s capacity to eliminate the infused fat from the circulation should be monitored. Especially where the product is administered for extended periods of time, the patient´s haemogram, blood coagulation, liver function, and platelet count should be regularly monitored.

In patients suspected to have disorders of fat metabolism, fasting lipaemia should be excluded. In this case of fasting hypertriglyceridaemia the administration of fat is contraindicated. Likewise, hypertriglyceridaemia 12 hours after fat infusion indicates disorders of fat metabolism.

Fluid, electrolyte, and acid-base balance should be monitored.

As with all parenteral solutions administered through a peripheral venous catheter, strict aseptic precautions should be taken when NuTRIflex® Lipid peri is infused. Care should be taken to avoid complications of catheterisation including air embolism and venous thrombosis.

4.5. Interactions with other Medicaments and other forms of Interaction

The electrolytes contained in NuTRIflex® Lipid peri might cause interactive effects with medications (e.g., cardiac glycoside treatment, potassium sparing effects of diuretics, hyperpotassaemia induced by ACE-inhibitors).

In general, solutions containing amino acids, carbohydrates, and lipids should not be mixed with other solutions due to the risk for incompatibilities or microbial contamination. However, in the case of concomitant infusion with medicines, possible incompatibilities with NuTRIflex® Lipid peri should be excluded before administration.

4.6. Pregnancy and Lactation

The safety of NuTRIflex® Lipid peri during pregnancy and lactation has not been assessed, but its use during these periods is not considered to constitute a hazard. Nevertheless, medicines should not be used in pregnancy, especially during the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus.

4.7. Effects on Ability to Drive and Use Machines

Not applicable

4.8. Undesirable Effects

Undesirable effects related to the components of NuTRIflex® Lipid peri are rare. Those that do occur are usually reversible and subside when therapy is discontinued.

Nausea or vomiting may occasionally occur. In the event of a forced infusion an osmotic diuresis might occur as a result of the high osmolarity.

During infusion of NuTRIflex® Lipid peri in very rare cases the amino acids might cause hyperazotaemia and acidosis.

Immediate (acute) reactions related to the lipid are dyspnoea, cyanosis, allergic reactions, hyperlipaemia, hypercoagulability of the blood, nausea, vomiting, headache, flushing, hyperthermia, sweating, chills, sleepiness, chest and back pain. The infusion should be stopped in these cases. The infusion can be resumed after the disappearance of the symptoms and/or the elevated serum triglyceride levels with reduced dose and/or reduced infusion rate. Close monitoring of the patient´s general condition and his/her plasma triglyceride levels is recommended.

4.9. Overdose

In general, significant overdosage is unlikely to occur during infusion of NuTRIflex® Lipid peri.

Signs of overdosage of fluid and electrolytes are hypertonic overhydration, and pulmonary oedema. An osmotic diuresis with a simultaneous loss of amino acids, accompanied by dizziness and nausea, may occur.

Signs of overdosage of amino acids are renal losses of amino acids and subsequent imbalances in the amino acid pool. Shivering, nausea, and vomiting may occur.

Signs of overdosage of glucose are hyperglycaemia, glucosuria, dehydration, hyperosmolarity, hyperglycaemic, hyperosmolar coma. It should be considered that the glucose tolerance is reduced in the post-aggression phase. This effect is more obvious in patients with higher age, more severe diseases, trauma or surgery. Therefore, in these patients a clinical condition resembling a diabetic status can develop more easy.

In rare instances, overdose of fat, especially after prolonged administration, may lead to the overloading syndrome.

In the case of overdose, the infusion should be stopped and appropriate corrective measures should be taken according to the prevailing clinical or metabolic situation. Emergency procedures would include general supportive measures as well as therapy of respiratory and cardiovascular disorders. Close metabolic monitoring is essential and specific abnormalities must be treated appropriately. Later on, after normalisation of the patient´s condition, the infusion of NuTRIflex® Lipid peri may be resumed with careful adjustment of the infusion rate and tight monitoring of the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Parenteral nutrition must supply the body with all the components necessary for growth and tissue regeneration. The amino acids play a prominent role, since they are the basic components for protein synthesis. However, in order to ensure optimal utilisation of the amino acids the administration of an energy source is required. This can be fulfilled partly in the form of carbohydrates. As glucose can be utilised directly, it is the carbohydrate of choice.

In addition, further energy and essential (polyunsaturated) fatty acids are supplemented in the form of lipids. Medium-chain triglycerides are cleared from the bloodstream at a faster rate and are oxidised more completely for energy production than long-chain triglycerides. For that reason they serve as preferential fuel for the body, especially in conditions where the oxidation of long-chain triglycerides is impaired, e.g. due to long carnitine deficiency or diminished carnitine palmitoyltransferase activity, respectively.

The polyunsaturated fatty acids, which are only provided by long-chain triglycerides, will prevent the biochemical disorders of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

Electrolytes are administered for the maintenance of metabolic and physiological functions. They ensure a complete parenteral nutrition regime with NuTRIflex® Lipid peri.

With the exception of the desired pharmacological effects, which are similar to those achieved by enteral administration of same substrates, safety investigations did not reveal any specific effects.

5.2. Pharmacokinetic Properties

Following intravenous infusion, the constituents of NuTRIflex® Lipid peri are immediately available for metabolism. Therefore, no investigations on the bioavailability were necessary.

A portion of the amino acids is used for protein synthesis, the rest being broken down as follows: The amino groups are separated by transamination and the carbon moiety is either oxidised to CO_2 in the citrate cycle or utilised in the liver as a substrate for gluconeogenesis. The amino groups resulting from protein breakdown in muscle tissue are transported to the liver, where urea is synthesised.

Glucose is metabolised through the known physiological pathways ending at CO_2 and H_2O. A portion of the ingested glucose may also be utilised for the synthesis of fat.

The administered fat dose, as well as infusion rate, metabolic situation, and individual factors are of major importance for the serum triglyceride

concentration resulting from the infusion of NuTRIflex® Lipid peri. With appropriate administration these levels should normally not exceed 5 mmol/l. Both medium-chain and long-chain triglycerides are normally completely bound to albumin and therefore do not pass the blood-brain barrier or into the liquor. No data are available concerning the passage into breast milk or into the placenta. The lipids are completely metabolised through the known physiological pathways and elimination as an unchanged substrate is not to be expected.

5.3. Preclinical Safety Data

There are no data to be stated which may be relevant in the context of the normal clinical use of the product.

The ingredients of NuTRIflex® Lipid peri are naturally occurring substances or metabolic intermediates and their concentration after appropriate infusion is similar to physiological levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate, egg lecithin, glycerol, sodium oleate, water for injections.

6.2. Incompatibilities

An additive port is provided for admixing supplements to NuTRIflex® Lipid peri. However, only mixtures of known compatibility should be prepared. Information on compatibility is available from the manufacturer.

The mixing of NuTRIflex® Lipid peri with solutions containing ethanol should be avoided. A further addition of calcium, phosphate, or bicarbonate to NuTRIflex® Lipid peri might cause precipitation.

6.3. Shelf Life

In unopened state NuTRIflex® Lipid peri has a shelf life of 24 months.

It is recommended that the product should be administered immediately after mixing. Otherwise the storage period after mixing must not exceed 4 days at 4-8 °C plus 48 hours at room temperature (the latter covering the warming-up and infusion time).

6.4. Special Precautions for Storage

Store below 25°C. Refrigeration is not necessary.
Protect the bag from freezing. If accidentally frozen, discard the bag.

Storage conditions after mixing, see section 6.3. above.

6.5. Nature and Contents of Container

NuTRIflex® Lipid peri is available in flexible plastic bags of 1250 ml, 1875 ml or 2500 ml.
The containers are divided into three compartments, separated by internal peel seals.
The design of the bag permits the mixing of amino acids, glucose, lipids, and electrolytes in the lower chamber.
On breaking the seals, aseptic mixing of the solutions and the emulsion occurs.

6.6. Instructions for Use/Handling

Immediately before use the internal seals between the upper and the lower compartments are broken allowing the respective contents to be aseptically mixed. It is recommended to mix the lipid emulsion and the amino acids prior to adding the glucose solution. The contents of the bag should then be thoroughly mixed to ensure they are homogenous.

Only completely clear amino acid and glucose solutions from undamaged containers are to be used. Do not use any bag in which there appears to be a separation (oiling out) of the emulsion in the chamber containing the fat emulsion (smaller upper compartment).

NuTRIflex® Lipid peri is supplied in single dose containers. Unused contents must be discarded and should not be stored for later use. Do not reconnect partially used bags.

Only filters allowing the passage of fat emulsions can be used in connection with infusions of NuTRIflex® Lipid peri.

Preparation of the all-in-one solution

- Place the unfolded bag on a hard and flat surface.
- Open the peelseam by applying pressure with both hands on one of the upper compartments, one after the other. Mix the bag contents.
- The homogenous solution is then ready to use and the infusion may be conducted according to the usual techniques.

7. MARKETING AUTHORISATION HOLDER

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Carl-Braun-Str. 1
D-34212 Melsungen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

PL 03551/0028

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10 DATE OF REVISION OF THE TEXT

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