SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NuTRIflex® Lipid plus without electrolytes Emulsion for Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nutriflex Lipid Plus without electrolytes Emulsion for Infusion contains:

<table>
<thead>
<tr>
<th>Large upper, left chamber (500, 750 and 1000 mL)</th>
<th>in 1250 ml Size 1</th>
<th>in 1875 ml Size 2</th>
<th>in 2500 ml Size 3</th>
<th>Quantity per 1000 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose monohydrate</td>
<td>165.0</td>
<td>247.5</td>
<td>330.0</td>
<td>132.0 g</td>
</tr>
<tr>
<td>equivalent to anhydrous glucose</td>
<td>150.0 g</td>
<td>225.0 g</td>
<td>300.0 g</td>
<td>120.0 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Small upper, right chamber ((250, 375 and 500 mL))</th>
<th>in 1250 ml Size 1</th>
<th>in 1875 ml Size 2</th>
<th>in 2500 ml Size 3</th>
<th>Quantity per 1000 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soya bean oil, refined</td>
<td>25.0 g</td>
<td>37.5 g</td>
<td>50.0 g</td>
<td>20.0 g</td>
</tr>
<tr>
<td>Medium-chain triglycerides</td>
<td>25.0 g</td>
<td>37.5 g</td>
<td>50.0 g</td>
<td>20.0 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lower chamber (500, 750 and 1000 mL)</th>
<th>in 1250 ml Size 1</th>
<th>in 1875 ml Size 2</th>
<th>in 2500 ml Size 3</th>
<th>Quantity per 1000 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoleucine</td>
<td>2.82 g</td>
<td>4.23 g</td>
<td>5.64 g</td>
<td>2.26 g</td>
</tr>
<tr>
<td>Leucine</td>
<td>3.76 g</td>
<td>5.64 g</td>
<td>7.52 g</td>
<td>3.01 g</td>
</tr>
<tr>
<td>Lysine hydrate</td>
<td>3.06 g</td>
<td>4.59 g</td>
<td>6.13 g</td>
<td>2.45 g</td>
</tr>
<tr>
<td>equivalent to Lysine</td>
<td>2.73 g</td>
<td>4.10 g</td>
<td>5.46 g</td>
<td>2.18 g</td>
</tr>
<tr>
<td>Methionine</td>
<td>2.35 g</td>
<td>3.53 g</td>
<td>4.70 g</td>
<td>1.88 g</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>4.21 g</td>
<td>6.32 g</td>
<td>8.42 g</td>
<td>3.37 g</td>
</tr>
<tr>
<td>Threonine</td>
<td>2.18 g</td>
<td>3.27 g</td>
<td>4.36 g</td>
<td>1.74 g</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>0.68 g</td>
<td>1.02 g</td>
<td>1.36 g</td>
<td>0.54 g</td>
</tr>
<tr>
<td>Valine</td>
<td>3.12 g</td>
<td>4.68 g</td>
<td>6.24 g</td>
<td>2.50 g</td>
</tr>
<tr>
<td>Arginine</td>
<td>3.24 g</td>
<td>4.86 g</td>
<td>6.48 g</td>
<td>2.59 g</td>
</tr>
<tr>
<td>Histidine</td>
<td>1.50 g</td>
<td>2.25 g</td>
<td>3.00 g</td>
<td>1.20 g</td>
</tr>
<tr>
<td>Alanine</td>
<td>5.82 g</td>
<td>8.73 g</td>
<td>11.64 g</td>
<td>4.66 g</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>1.80 g</td>
<td>2.70 g</td>
<td>3.60 g</td>
<td>1.44 g</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>4.21 g</td>
<td>6.32 g</td>
<td>8.42 g</td>
<td>3.37 g</td>
</tr>
<tr>
<td>Glycine</td>
<td>1.98 g</td>
<td>2.97 g</td>
<td>3.96 g</td>
<td>1.58 g</td>
</tr>
<tr>
<td>Proline</td>
<td>4.08 g</td>
<td>6.12 g</td>
<td>8.16 g</td>
<td>3.26 g</td>
</tr>
<tr>
<td>Serine</td>
<td>3.60 g</td>
<td>5.40 g</td>
<td>7.20 g</td>
<td>2.88 g</td>
</tr>
</tbody>
</table>

| Amino acid content [g] | 48 | 72 | 96 | 38 |
| Nitrogen content [g]   | 6.8 | 10.2 | 13.6 | 5.4 |
| Carbohydrate content [g] | 150 | 225 | 300 | 120 |
| Lipid content [g]      | 50 | 75 | 100 | 40 |

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Emulsion for infusion.

The lower chamber and the larger upper chamber (amino acids and glucose solutions): clear, colourless up to faintly straw-coloured solutions.  
The smaller top chamber (lipid emulsion): oil-in-water emulsion, milky white.

Physico-chemical characteristics of Nutriflex Lipid peri after mixing the chamber contents:

<table>
<thead>
<tr>
<th></th>
<th>in 1250 ml (Size 1)</th>
<th>in 1875 ml (Size 2)</th>
<th>in 2500 ml (Size 3)</th>
<th>Quantity per 1000 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy in the form of lipid [kJ (kcal)]</td>
<td>1990 (475)</td>
<td>2985 (715)</td>
<td>3980 (950)</td>
<td>1590 (380)</td>
</tr>
<tr>
<td>Energy in the form of carbohydrate [kJ (kcal)]</td>
<td>2510 (600)</td>
<td>3765 (900)</td>
<td>5020 (1200)</td>
<td>2010 (480)</td>
</tr>
<tr>
<td>Energy in the form of amino acids [kJ (kcal)]</td>
<td>800 (190)</td>
<td>1200 (285)</td>
<td>1600 (380)</td>
<td>635 (150)</td>
</tr>
<tr>
<td>Non-protein energy [kJ (kcal)]</td>
<td>4500 (1075)</td>
<td>6750 (1615)</td>
<td>9000 (2155)</td>
<td>3600 (860)</td>
</tr>
<tr>
<td>Total energy [kJ (kcal)]</td>
<td>5300 (1265)</td>
<td>7950 (1900)</td>
<td>10600 (2530)</td>
<td>4235 (1010)</td>
</tr>
<tr>
<td>Osmolality [mOsm/kg]</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
<td>1350</td>
</tr>
<tr>
<td>Theoretical osmolarity [mOsm/l]</td>
<td>1055</td>
<td>1055</td>
<td>1055</td>
<td>1055</td>
</tr>
<tr>
<td>pH</td>
<td>5.0 - 6.0</td>
<td>5.0 - 6.0</td>
<td>5.0 - 6.0</td>
<td>5.0 - 6.0</td>
</tr>
</tbody>
</table>

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supply of energy, essential fatty acids, amino acids and fluids in the setting of parenteral nutrition of patients in states of moderately severe catabolism when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

The dosage is adapted to the patients’ individual requirements.

It is recommended that Nutriflex Lipid plus without electrolytes be administered continuously. A stepwise increase of the infusion rate over the first 30 minutes up to the desired infusion rate avoids possible complications.

Adolescents from 14 years of age and 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 a maximum infusion rate of 140 ml per hour. The amount of substrate administered is then 5.4 g of amino acids per hour, 16.8 g of glucose per hour and 5.6 g of lipids per hour.

**Paediatric population**

Newborn infants, infants and toddlers less than two years of age
Nutriflex Lipid plus without electrolytes is contraindicated in newborn infants, infants and toddlers < 2 years of age (see section 4.3).

Children from 2 to 13 years of age
The given dosage recommendations are guiding data based on average requirements. The dosage should be individually adapted according to age, developmental 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 for 2 – 4 years of age:
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 for 5 – 13 years of age:
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.

Due to the individual needs of paediatric patients, Nutriflex Lipid plus without electrolytes may not cover sufficiently the total energy and fluid requirements. In such cases carbohydrates and/or lipids and/or fluids must be provided in addition, as appropriate.

**Patients with renal/hepatic impairment**
The doses should be adjusted individually in patients with hepatic or renal insufficiency (see also section 4.4).

**Duration of treatment**
The duration of treatment for the indications stated is not limited. During long-term administration of Nutriflex Lipid plus without electrolytes it is necessary to provide for appropriate supply of electrolytes, trace elements and vitamins.

**Method of administration**
Intravenous use. For central venous infusion only.
4.3 Contraindications

- hypersensitivity to the active substances, to egg, peanut or soya protein or to any of the excipients listed in section 6.1.
- congenital disorders of amino acid metabolism
- severe hyperlipidaemia
- hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour
- acidosis
- intrahepatic cholestasis
- severe hepatic insufficiency
- severe renal insufficiency in absence of renal replacement therapy
- aggravating haemorrhagic diatheses
- acute thrombo-embolic events, lipid embolism.

On account of its composition, Nutriflex Lipid plus without electrolytes must not be used in newborn infants, infants and toddlers under 2 years of age.

General contraindications to parenteral nutrition include:
- unstable circulatory status with vital threat (states of collapse and shock)
- acute phases of cardiac infarction and stroke
- unstable metabolic condition (e.g. severe postaggression syndrome, coma of unknown origin)
- inadequate cellular oxygen supply
- disturbances of the electrolyte and fluid balance
- acute pulmonary oedema
- decompensated cardiac insufficiency.

4.4 Special warnings and precautions for use

Caution should be exercised in cases of increased serum osmolarity.

Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentration, hyperhydration and pulmonary oedema.

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

The serum triglyceride concentration should be monitored when infusing Nutriflex Lipid plus without electrolytes.

Depending on the patient’s metabolic condition, occasional hypertriglyceridaemia may occur. If the plasma triglyceride concentration rises to above 3 mmol/l during administration of lipids it is recommended that the infusion rate be reduced. Should the plasma triglyceride concentration remain above 3 mmol/l, the administration should be stopped until the level normalises.

Like all solutions containing carbohydrates the administration of Nutriflex Lipid plus without Electrolytes 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 If the patient is receiving other intravenous glucose solutions concurrently, the amount of additionally administered glucose has to be taken into account.

An interruption of administration of the emulsion may be indicated if the blood glucose concentration rises to above 14 mmol/l (250 mg/dl) during administration.
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.

Refeeding or repletion of malnourished or depleted patients may cause hypokalaemia, hypophosphataemia and hypomagnesaemia. Adequate supplementation of electrolytes according to deviations from normal values is necessary.

Nutriflex Lipid plus without electrolytes should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

**Elderly patients**

Basically the same dosage as for adults applies, but caution should be exercised in patients suffering from further diseases like cardiac insufficiency or renal insufficiency that may frequently be associated with advanced age.

**Patients with diabetes mellitus, impaired cardiac or renal function**

Like all large-volume infusion solutions Nutriflex Lipid plus without electrolytes should be administered with caution to patients with impaired cardiac or renal function.

There is only limited experience of its use in patients with diabetes mellitus or renal failure.

**Patients with impaired lipid metabolism**

Nutriflex Lipid plus without electrolytes should be administered cautiously to patients with disturbances of lipid metabolism, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired hepatic function, hypothyroidism (with hypertriglyceridaemia) and sepsis. If Nutriflex Lipid plus without electrolytes is given to patients with these conditions, monitoring of serum triglycerides is necessary. The presence of hypertriglyceridaemia 12 hours after lipid administration also indicates a disturbance of lipid metabolism.

Disturbance of the fluid, electrolyte or acid-base balance must be corrected before the start of the infusion.

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

This product does not contain electrolytes. Therefore sufficient amounts of electrolytes must be administered together with Nutriflex Lipid plus without electrolytes according to the patients’ requirements. A sufficient potassium substitution has to be ensured. It may be necessary to supply also trace elements and vitamins.

Close monitoring of serum electrolytes is mandatory. This applies especially for re-feeding or repletion of malnourished or depleted patients who are at special risk to develop hypokalaemia, hypophosphataemia and hypomagnesaemia.

As with all intravenous solutions, strict aseptic precautions are necessary for the infusion of Nutriflex® Lipid plus without Electrolytes.

Nutriflex Lipid plus without electrolytes is a preparation of complex composition. It is, therefore, strongly advisable not to add other solutions (as long as compatibility is not proven – see section 6.2).

**Interference with laboratory tests**
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 cleared from the blood stream.

**Special warnings/precautions regarding excipients**

This medicinal product contains less than 1 mmol sodium (23 mg) per multichamber bag, i.e. it is essentially ‘sodium- free’.

### 4.5 Interactions 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

**Pregnancy**

There are no or limited amount of data from the use of Nutriflex Lipid plus without electrolytes in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Parenteral nutrition may become necessary during pregnancy. Nutriflex Lipid plus without electrolytes should only be given to pregnant women after careful consideration.

**Breast-feeding**

Components/metabolites of Nutriflex Lipid plus without electrolytes are excreted in human milk, but at therapeutic doses no effects on the breastfed newborns/infants are anticipated. Nevertheless breast-feeding is not recommended for mothers on parenteral nutrition.

**Fertility**

No data available.

### 4.7 Effects on ability to drive and use machines

Not relevant

### 4.8 Undesirable effects

The following listing includes a number of systemic reactions that may be associated with the use of Nutriflex Lipid plus without electrolytes. Under conditions of correct use, in terms of dosing monitoring, observation of safety restrictions and instructions, most of them are rare (≥ 1/10,000 to < 1/1,000).

Undesirable effects are listed according to their frequencies as follows:

- **Very common** (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders
Rare: Hypercoagulation

Immune system disorders
Rare: Allergic reactions (e.g. anaphylactic reactions, dermal eruptions, laryngeal, oral and facial oedema)

Metabolism and nutrition disorders
Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, ketoacidosis
The frequency of these undesirable effects is dose-dependent and may be higher under the condition of absolute or relative lipid overdose.

Nervous system disorders
Rare: Drowsiness

Vascular disorders
Rare: Hypertension or hypotension, flush

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea, cyanosis

Gastrointestinal disorders
Uncommon: Nausea, vomiting, loss of appetite

Skin and subcutaneous tissue disorders
Rare: Erythema

General disorders and administration site conditions
Rare: Headache, elevated body temperature, sweating, feeling cold, chills, pain in the back, bones, chest and lumbar region

Very rare: Fat overload syndrome (details see below)

Should adverse reactions occur or should the triglyceride level rise to above 3 mmol/l during infusion, the infusion should be stopped or, if necessary, continued at a reduced dosage.

If the infusion is restarted, the patient should be carefully monitored, especially at the beginning, and serum triglycerides should be determined at short intervals.

Information on particular undesirable effects

Nausea, vomiting, lack of appetite and hyperglycaemia are symptoms often related to conditions indicating parenteral nutrition or may be associated with parenteral nutrition.

Fat overload syndrome
Impaired capacity to eliminate triglycerides can lead to ‘fat overload syndrome’ which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient’s clinical condition, such as renal function impairment or infection. The fat overload syndrome is characterised
by hyperlipidaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued.

Should signs of a fat overload syndrome occur, the infusion of Nutriflex Lipid plus without electrolytes should be discontinued immediately.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

### 4.9 Overdose

**Symptoms of fluid overdose**
Hyperhydration 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-hyperosmolar coma.

**Symptoms of lipid overdose**
See section 4.8.

**Treatment**
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 group: Solutions for parenteral nutrition, combinations

ATC code: B 05BA10

**Mechanism of action**

The purpose of parenteral nutrition is to supply all necessary nutrients for the growth and regeneration of tissue as well as energy necessary to maintain all body functions.

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 utilisation of amino acids while still providing for the further energy-consuming processes.
Glucose is ubiquitously metabolised 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. Long-chain triglycerides provide the organism with essential fatty acids for the synthesis of cell components. For these purposes the lipid emulsion contains medium-chain and long-chain triglycerides (deriving from soya-bean oil).

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

Unsaturated fatty acids derived from the long-chain triglyceride fraction serve primarily for prophylaxis and treatment of essential fatty acid deficiency.

5.2 Pharmacokinetic properties

Absorption
Nutriflex Lipid plus without electrolytes is infused intravenously. Hence, all substrates are available for metabolism immediately.

Distribution
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.

When the dosage guidelines are followed medium-chain fatty acids and long-chain fatty acids are practically completely bound to plasma albumin. Therefore, when the dosage guidelines are followed medium- and long-chain fatty acids do not pass the blood-brain barrier and, hence, do not pass into the cerebrospinal fluid.

Amino acids are incorporated in a variety of proteins in different organs of the body. In addition each amino acid is maintained as free amino acid in the blood and inside cells.

As glucose is water soluble, it is distributed with the blood over the whole body. At first, the glucose solution is distributed in the intravascular space and then it is taken up into the intracellular space.

No data are available concerning transport of the components through the placental barrier.

Biotransformation
Amino acids that do not enter protein synthesis, are metabolised as follows. The amino group is separated from the carbon skeleton by transamination. The carbon chain is either oxidised directly to CO₂ or utilised as substrate for gluconeogenesis in the liver. The amino group is also metabolised in the liver to urea.

Glucose is metabolised to CO₂ and H₂O via the known metabolic routes. Some glucose is utilised for lipid synthesis.
After infusion triglycerides are hydrolysed to glycerol and fatty acids. Both are incorporated in physiological pathways for energy production, synthesis of biological active molecules, gluconeogenesis and resynthesis of lipids.

Elimination

Only minor amounts of amino acids are excreted unchanged in urine.

Excess glucose is excreted in urine only if the renal threshold of glucose is reached.

Both the triglycerides of soya-bean oil and medium-chain triglycerides are completely metabolised to CO₂ and H₂O. Small amounts of lipids are lost only during sloughing of cells from skin and other epithelial membranes. Renal excretion does virtually not occur.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

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 found in various vegetable oils, especially in soya-bean oil. Impairment of fertility was determined in rats and rabbits after subcutaneous and intravaginal administration of β-sitosterol. According to the current state of knowledge the observed effects in animals do not seem to have relevance for clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (for pH adjustment)
Egg lecithin
Glycerol
Sodium oleate
Water for injections

6.2 Incompatibilities

Nutriflex Lipid plus without electrolytes may only be mixed with medicinal products for which compatibility has been documented and which are mentioned in section 6.6.

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

In case the concentrations of added calcium and/or phosphate exceed the values recommended in section 6.6 precipitation and/or destabilisation of the emulsion may occur.

6.3 Shelf life
Unopened
2 years

After removing the protective overwrap and after mixing of contents of the bag
Chemical and physical in-use stability after mixing the contents has been demonstrated for 4
days at 2-8°C plus 48 hours at 25°C.

After admixture of compatible additives
From a microbiological point of view, the product should be used immediately after
admixture of additives. If not used immediately after admixture of additives, in-use storage
times and conditions prior to use are the responsibility of the user.

After first opening (spiking of the infusion port)
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.
Keep the bag in the outer carton in order to protect from light.

6.5 Nature and contents of container

Nutriflex Lipid plus without electrolytes is supplied in flexible multichamber bags of polyamide/polypropylene 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 glucose solution)
The multichamber bag is packed in a protective overwrap. An oxygen absorber is placed between the bag and the overwrap; the sachet of inert material contains powdered iron.

The two upper chambers can be connected with the lower chamber by opening the intermediate seam (peel seam).

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Preparation of the mixed emulsion:
Remove inner bag from its protective overwrap and proceed as follows:
- put the bag on a solid, flat surface
- mix glucose with amino acids by pressing the upper left chamber against the peel seam, then add the fat emulsion by pressing the upper right chamber against the peel seam
- mix the contents of the bag thoroughly.

Preparation for infusion:
- fold the bag and hang it on the infusion stand by the centre hanging loop
- remove the protective cap from the infusion port and carry out infusion using the standard technique.

The mixture is a milky white homogenous oil-in-water emulsion.

Only use bags that are undamaged and in which the amino acid and glucose solutions are clear and colourless up to straw-coloured solutions. Do not use bags where there is a discolouration or discernible phase separation (oil drops) in the chamber containing lipid emulsion.

Nutriflex Lipid plus without electrolytes is supplied in single dose containers. Container and unused residues must be discarded after use.

Do not reconnect partially used containers.

The emulsion should always be brought to room temperature prior to infusion. If filters are used they must be lipid-permeable.

If accidentally frozen discard the bag.

Additions
The capacity of the bag is sufficient to enable additions such as vitamins, electrolytes, and trace elements and alanyl-glutamin.

The bag enables a mixing of the glucose and amino acid chamber first before the non-permanent seals of the lipid chamber have been opened. Additions may be made after all 3 compartments (glucose, amino acid and lipid) have been mixed.

Nutriflex Lipid plus without electrolytes may be supplemented with:
- Electrolytes: take account of the electrolytes already present in the bag; stability has been demonstrated up to a total quantity of 200 mmol/l of sodium + potassium, 10 mmol/l of magnesium and 6.4 mmol/l of calcium in the ternary mixture.
- Phosphate: stability has been demonstrated up to a maximum concentration of 20 mmol/l for inorganic phosphate or up to a maximum concentration of 30 mmol/l for organic phosphate (not both at the same time).
- Alanyl-Glutamin up to 24 g/l.
- Trace elements: stability has been demonstrated with commercially available formulations of trace elements, details of which can be obtained from the manufacturer.
- Vitamins: stability has been demonstrated with commercially available formulations of vitamins, details of which can be obtained from the manufacturer.
MARKETING AUTHORISATION HOLDER

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Carl Braun Str. 1
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Marketing Authorisation Number

PL 03551/0030

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