1. NAME OF THE MEDICINAL PRODUCT

Lipovenoes® 10% PLR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 litre contains:

Soya bean oil	100.0 g
(content of essential fatty acids:	
Linoleic acid (18 : 2ω6)	43.8 – 58.6 g
α-Linolenic acid (18 : 3ω3)	4.53 – 11.0 g)
Glycerol	25.0 g
Egg phospholipids	6.0 g
(stand. with 75 – 81% (3-sn-phosphatidyl)-cholin)	

Total energy	4522 kJ/l = 1080 kcal/l
pH-value	6.5 – 8.7
Titration acidity	< 1 mmol HCl/l or < 1 mmol NaOH/l
Theoret. Osmolarity	272 mosm/l

3. PHARMACEUTICAL FORM

Emulsion for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supply of energy and parenteral nutrition supplementation with essential fatty acids.

4.2 Posology and method of administration

Daily dose
For newborns, infants and children up to 2 years of age:
Unless otherwise prescribed, 1 to 2 g fat per kg bw per day = 10 - 20 ml Lipovenoes® 10% PLR per kg bw per day. In the case of increased energy needs up to max. 3 g fat per kg bw per day = 30 ml Lipovenoes® 10% PLR per kg bw per day.

For adults:
Unless otherwise prescribed, 1 to max. 2 g fat per kg bw per day = 10 - 20 ml Lipovenoes® 10% PLR per kg bw per day.

Infusion rate:
The infusion rate should not exceed 0.125 g fat per kg bw per hour = 1.25 ml Lipovenoes® 10% PLR per kg bw per hour. However, at the start of the parenteral nutrition with fat, a reduced dosage with a maximum of 0.05 g fat/per kg bw per hour is recommended.

For patients with a body weight of 70 kg the infusion is started with about 10 drops per minute which after 30 minutes is gradually increased to a maximum of 26 drops per minute.

Maxiumum daily dose
For newborns, infants and children up to 2 years of age:
Max. 3 g fat per kg bw per day = 30 ml Lipovenoes® 10% PLR per kg bw per day.

For adults:
Max. 2 g fat per kg bw per day = 20 ml Lipovenoes® 10% PLR per kg bw per day.

During a parenteral nutrition therapy fat emulsions should always be administered together with amino acids and carbohydrates.
The simultaneous administration of Lipovenoes® 10% PLR with amino acid solutions and/or carbohydrate solutions is carried out through separate infusion lines and veins. However, if Lipovenoes® 10% PLR is to be administered via a common infusion line (by-pass, Y-tube) the compatibility of all solutions must be ensured.

The use of filters with a pore size of 0.2 µm is not possible, because fat emulsions do not pass through these filters.

Lipovenoes® 10% PLR is administered as long as parenteral nutrition is required.

4.3 Contraindications

- disorders of the lipid metabolism
- severe haemorrhagic diathesis
- unstable diabetes mellitus
- pregnancy in the first trimester.

In addition in all cases of acute and life-threatening diseases such as:
- collapse and shock
- recent cardiac infarction
- stroke
- embolism
- undefined coma status.

General contraindications for a parenteral nutrition:
- hypokalaemia
- hyperhydration
- hypotonic dehydration
- unstable metabolism
- acidosis.

Lipovenoes® 10% PLR should not be administered to patients known to be allergic to soy beans or egg protein.

Note:
A decision to use Lipovenoes® 10% PLR in newborns and infants suffering from hyperbilrubinaemia must be based on a careful benefit-risk analysis. Close checks of bilirubin levels during infusion of fat are absolutely necessary because of the risk of kernicterus!

4.4 Special warnings and special precautions for use

The serum triglyceride level should be monitored daily, the blood sugar, the acid-base metabolism, the serum electrolyte status, fluid balance and blood count at suitable intervals. The serum triglyceride concentration should not exceed 3 mmol/l for adults or 1.7 mmol/l for children during the infusion of the fat emulsion.

In the case of hypokalaemia and/or hyponatraemia adequate quantities of potassium and/or sodium should be administered simultaneously with Lipovenoes® 10% PLR.

The choice of a peripheral venous or a central venous administration depends on the osmolarity of the mixture to be administered. Infusion solutions with an osmolarity of more than 800 mosm/l should be administered via a central vein.

There are indications that during phototherapy and the simultaneous administration of fatty emulsions, a peroxide formation in the infusion solution due to the effect of light cannot be completely ruled out. Where this therapy is used on newborns, it is, therefore recommended as a precautionary measure to protect the fat emulsion from light.

4.5 Interaction with other medicinal products and other forms of interaction

None known.

4.6 Pregnancy and lactation

Lipovenoes® 10% PLR should not be used in the first trimester of the pregnancy (see point 4.3 “Contraindications”). Because of the lack of specific experiences Lipovenoes® 10% PLR should only be used during the remaining period of pregnancy and lactation after a careful benefit risk evaluation.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Possible early reactions during the administration of fat emulsions are:

- slight rise in body temperature
- heat sensation - cold sensation
- chills
- flush, cyanosis
- lack of appetite, nausea, vomiting
- dyspnoea
- headache, pain in the back, bones, chest and loins
- hypotension, hypertension
- hypersensitivity reactions (e.g. anaphylactoid reactions, skin rash)
- priapism (in very rare cases).

Should these side effects occur or should the triglyceride level during lipid infusion rises above 3 mmol/l for adults or 1.7 mmol/l for children, the lipid infusion should be stopped or, if necessary, continued at a reduced dosage.

Possible signs of metabolic overload must be observed. This can appear with varying rapidity and following different dosages because of genetically caused, individually different metabolic conditions and in view of different previous illnesses.

Metabolic overload might give the following symptoms:

- hepatomegaly with and without icterus
- change or reduction of some coagulation parameters (e.g. bleeding time, coagulation time, prothrombin time, platelet count etc.)
- splenomegaly
- anaemia, leucopenia, thrombocytopenia

- bleedings and tendency to bleed
- pathological liver function tests
- hyperlipidaemia
- headache, abdominal pain, fever, fatigue.

4.9 Overdose

Overdosage (triglyceride level rises above 3 mmol/l in adults or 1.7 mmol/l in children) may lead to the side-effects mentioned under the section 4.8 ”Undesirable effects”. In these cases the lipid infusion should be stopped or, if necessary, be continued at a reduced dosage.The administration of fat has also to be stopped if a marked increase in blood glucose levels occurs during infusion of Lipovenoes® 10% PLR. A severe overdosage of Lipovenoes® 10% PLR. Without simultaneous administration of a carbohydrate solution, may lead to metabolic acidosis.

The following effects may be observed when fatty emulsions are applied:

- reactive hyperglycaemia, especially in the post aggression phase
- hyperlipidaemia
- rise in body temperature
- heat sensation - cold sensation
- chills
- flush or cyanosis
- lack of appetite, nausea, vomiting
- dyspnoea
- headache, pain in the back, bones, chest and loins.

Where overdosage occurs, in rare cases a metabolic overload (see point 4.8 ”Undesirable effects”) may occur, but has been observed mainly with the use of cottonseed oil emulsions.

5. PHARMACOLOGICAL PROPERTIES

Lipovenoes® 10% PLR is a sterile and pyrogen-free fatty emulsion for parenteral nutrition. The use of Lipovenoes® 10% PLR in the framework of a parenteral nutrition enables the following therapeutic goals to be achieved:

Meeting energy needs
During parenteral nutrition it is recommended that 30 - 40%, in isolated cases up to 50%, of the total energy supply should be administered with fat.

Meeting the need for essential fatty acids
Because of the use of soya bean oil as an ingredient, Lipovenoes® 10% PLR contains a high content of the essential fatty acids, linoleic acid and linolenic acid.

5.1 Pharmacodynamic properties

The metabolisation of the free fatty acids can take place on the following metabolic pathways:

- Absorption into the fatty tissue cells, re-esterification, storage
- Absorption into the liver and muscle cells, catabolism via β oxidation (predominantly in the mitochondria) to generate energy
- Synthesis of triglyceride-rich lipoproteins (VLDL) in the liver cell and release into the plasma
- Substrate for the synthesis of biologically highly active molecules (arachidonic acid derivatives).

Glycerol is either metabolised via glycolysis to produce energy or is re-esterified with free fatty acids to form tryglycerides particularly in the liver.

Phospholids are hydrolysed or incorporated unaltered into the cell membranes where they are essential for the maintenance of membrane integrity.

5.2 Pharmacokinetic properties

Absorption and distribution
The lipid particles infused with Lipovenoes® 10% PLR are similar in composition and size distribution to physiological chylomicrons and exhibit comparable elimination kinetics. Triglycerides are hydrolysed by lipoproteinlipase (LPL), releasing fatty acids and glycerol.

At a medium to high dosage, intravenous administration of fat lead to a temporary lipaemia which like postprandial lipaemia can be considered as “physiological”.

The limiting factor in the metabolism of the triglycerides is not their splitting into free fatty acids and glycerol leading to a decrease in the triglyceride concentration but the transport of the free fatty acids into the cell.

5.3 Preclinical safety data

- Preclinical data of Lipovenoes® 10% PLR are not available. Tests over 4 weeks with high doses of Lipovenoes® 10% PLR and 20% (9 -12 g fat/kg body weight/day) in dogs resulted in changes in the blood count as well as to clinico-chemical changes in the lipid metabolism parameters, bilirubin and alkaline phosphatase levels. Histopathological findings showed substance-induced changes in the liver, kidneys and spleen. At the highest dosage there was an increase in organ weight of the liver and spleen as well as a clear increase in total lipids. The bilirubin, phospholipid and cholesterol levels had clearly increased in the bile acids.

- Studies on reproduction toxicity as well as mutagenic and carcinogenic potential are not available.

- Different vegetable oils, particularly soya bean oil, can contain phyto-oestrogens, such as β-sitosterol. An impairment of fertility was established when β-sitosterol was administered subcutaneously and intravaginally to rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium oleate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Incompatibilities can occur through the addition of polyvalent cations (e.g. calcium) especially when combined with heparin. Lipovenoes® 10% PLR should not be mixed with other infusion solutions, electrolyte concentrations or other drugs unless the compatibility of the solutions used has been proven.

Lipovenoes® 10% PLR should not be stored after the addition of other components!

6.3 Shelf-life

18 months

6.4 Special precautions for storage

Do not store above 25°C.
Do not freeze!

6.5 Nature and contents of container

Glass bottles containing: 100 ml
250 ml
500 ml

Packs of: 10 x 100 ml
10 x 250 ml
10 x 500 ml

6.6 Instruction for use / handling

Do not use Lipovenoes® 10% PLR after expiry date printed on the package.

Shake before use.

Use only if the emulsion is homogenous and the container is undamaged.

To be used immediately after opening the bottle.

Any emulsion for infusion remaining after infusion must be discarded.

Fat emulsions should not be mixed with other medicinal products, except for parenteral nutrition products, due to the increased risk of microbiological contamination and incompatibilities. When mixing with other nutrients like electrolytes, vitamins or trace elements to Lipovenoes® 10% PLR for complete parenteral nutrition, care should be given to aseptic techniques, thorough mixing and, in particular, to compatibility. Under no circumstances Lipovenoes® 10% PLR should be stored after addition of other components. Unless no other stability data are available, admixtures should be used within 24 hours.

7. MARKETING AUTHORISATION HOLDER

Name or style and permanent address of registered place of business of holder of marketing authorisation

Fresenius Kabi Deutschland GmbH
61346 Bad Homburg v.d.H.
Germany

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