Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipidem 200 mg/ml emulsion for infusion (glass bottles)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml emulsion contains:

Medium-chain triglycerides	100.0 g
Soya-bean oil, refined	80.0 g
Omega-3-acid triglycerides	20.0 g
Content of essential fatty acids per liter:	
Linoleic acid (omega-6)	38.4 - 46.4 g
Alpha-linolenic acid (omega-3)	4.0 - 8.8 g
Eicosapentaenoic acid and docosahexaenoic acid (omega-3)	8.6 - 17.2 g

200 mg/ml (20%) correspond to total content of triglycerides.

Total energy per liter	7900 kJ ≅ 1910 kcal
	6.5 - 8.5

Excipients:
1000 ml emulsion contains 2.6 mmol sodium (as sodium hydroxide and sodium oleate).
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Emulsion for infusion.
White, homogeneous emulsion.

Osmolality	approximately 410 mOsm/kg
Titration (to pH 7.4)	less than 0.5 mmol/l NaOH or HCI
pH	6.5 - 8.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Supply of lipids, including essential omega-6 fatty acids and omega-3 fatty acids, as part of a parenteral nutrition regimen for adults, when oral or enteral nutrition is impossible, insufficient or contra-indicated.

4.2 Posology and method of administration

Adults:
Dosage should be adjusted to the individual patient's needs.
Recommended dosage:

1 - 2 g fat per kg body weight per day

equivalent to:
- 5 - 10 ml of Lipidem per kg body weight per day

Infusion rate:

The infusion should be administered at the lowest possible infusion rate. During the first 15 minutes the infusion rate should only be 50% of the maximum infusion rate to be used.

Maximum infusion rate:

Up to 0.15 g lipids per kg body weight per hour,

equivalent to:
- up to 0.75 ml of Lipidem per kg body weight per hour

The infusion rate should be reduced in undernourished patients.

As clinical experience with long-term use of Lipidem is limited, it should normally not be administered for longer than one week. Only if clearly needed the emulsion may be administered longer, with careful metabolic monitoring.

Lipidem is suitable for both central and peripheral intravenous infusion.

Paediatric patients:
Safety and efficacy in children and adolescents have not been established.

4.3 Contraindications

Lipidem must not be used in any of the following conditions:

– Severe hyperlipidemia
– Severe blood coagulation disorders
– Intrahepatic cholestasis
– Severe liver failure
– Severe renal failure without access to haemofiltration or dialysis.
– Acute phase of myocardial infarction or stroke
– Acute thromboembolic disease, lipid embolism
– Hypersensitivity to egg, fish, or soya-bean protein or to any of the active substances or excipients.

The following conditions are general contraindications to infusion therapy:
– Unstable hemodynamic status with compromised vital functions (conditions of collapse and shock)
– Unstable metabolic conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, severe sepsis, acidosis)
– Acute pulmonary oedema
– Hyperhydration
– Decompensated cardiac insufficiency
– Hypotonic dehydration
– Hypokalaemia

4.4 Special warnings and precautions for use

Serum triglycerides should be monitored during the infusion of Lipidem. In patients with suspected disorders of lipid metabolism, fasting lipemia should be ruled out before the start of the infusion. Hypertriglyceridemia 12 hours after the administration of lipids is also indicative of abnormal lipid metabolism.

Transient hypertriglyceridemia or elevated blood glucose levels may arise, depending on the patient's metabolic status. If the plasma triglyceride concentration rises to more than 3 mmol/l during administration of the lipid emulsion, it is recommended to reduce the infusion rate. If the plasma triglyceride concentration remains higher than 3 mmol/l, the infusion should be stopped until the plasma triglyceride concentration is normalized.

Electrolytes, fluid balance or body weight, acid-base balance, blood glucose levels, and, during long-term administration, full blood counts, coagulation status, and liver function should be monitored.

Infusion of Lipidem should be discontinued in case of appearance of any sign of allergic reaction, e.g. fever, shivering, rash, dyspnoea.
An overdose may lead to fat overload syndrome, see sections 4.8 and 4.9.

There is as yet no clinical experience of the use of Lipidem in children and adolescents, and there is only limited experience of its use in patients with diabetes mellitus or renal failure.

There is as yet only limited experience of the use of Lipidem for periods longer than seven days.

Caution should be exercised in patients with conditions associated with disturbed lipid metabolism, such as renal insufficiency, diabetes mellitus, pancreatitis, hepatic insufficiency, hypothyroidism (in the presence of hyper-triglyceridemia), pulmonary disease and sepsis.

Lipids may interfere with certain laboratory tests (such as bilirubin, lactate dehydrogenase, oxygen saturation, haemoglobin measurement) when the blood sample is taken before the lipids have been eliminated from the bloodstream. In most patients the lipids are eliminated within 5 to 6 hours after the end of the infusion.

Energy supply with lipid emulsions only could cause metabolic acidosis. This may be avoided by the concurrent administration of carbohydrates. It is therefore recommended to infuse an adequate quantity of intravenous carbo-hydrates or carbohydrate-containing amino acid solutions along with the fat emulsion.

Vitamin E can interfere with the effect of vitamin K in clotting factor synthesis. This should be considered in patients with blood coagulation disorders or suspected vitamin K deficiency.

Lipidem contains 2.6 mmol/l sodium. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Heparin induces a transient release of lipoprotein lipase into the bloodstream. This may initially lead to increased plasma lipolysis, followed by a transient decrease in triglyceride clearance.

Soya-bean oil has a natural content of vitamin K1. The content is however so low in Lipidem that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives. Nevertheless, the coagulation status should be monitored in patients treated concomitantly with anticoagulants.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Lipidem in pregnant women. No evidence of embryotoxicity or teratogenicity was seen in a reproductive study (see section 5.3).
Parenteral nutrition may become necessary during pregnancy. Lipidem should only be given to pregnant women after careful consideration.

Lactation
There is no experience of the use of Lipidem in nursing mothers.
It is unknown if Lipidem is excreted in human breast milk. The excretion of Lipdiem in milk has not been studied in animals.
Breast-feeding is in general not recommended to mothers on parenteral nutrition.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. All adverse drug reactions with the emulsion are very rare (<1/10,000).

Blood and lymphatic system disorders
Very rare: Hypercoagulation

Immune system disorders
Very rare: Allergic reactions

Metabolism and nutrition disorders
Very rare: Hyperlipidemia, hyperglycaemia, metabolic acidosis, ketoacidosis
However, the frequency of the undesirable effects listed here is dose-dependent. They are likely to occur as symptoms of absolute or relative overdose. A.m. frequency applies to conditions of correct use, in terms of dosing monitoring, observation of safety restrictions and instructions.

Nervous system disorders
Very rare: Drowsiness

Vascular disorders
Very rare: Hypertension or hypotension

Respiratory, thoracic, and mediastinal disorders
Very rare: Dyspnoea, cyanosis

Gastrointestinal disorders
Very rare: Nausea, vomiting

General disorders and/or administration site conditions
Very rare: Headache, flushing / erythema, elevated body temperature, sweating, chills, chest and back pain, Fat overload syndrome (see below).

Should these adverse reactions occur or should the triglyceride level rise above 3 mmol/l during infusion, the infusion of Lipidem 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.

Triglycerides that contain omega-3 fatty acids may increase bleeding time and inhibit platelet aggregation. In patients with aspirin - induced asthma, pulmonary function may deteriorate as well.

Lipidem should always be a part of a complete parenteral nutritional treatment including amino acids and glucose. Nausea, vomiting, lack of appetite and hyperglycaemia are symptoms related to conditions indicating parenteral nutrition and may sometimes 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 hypertriglyceridemia, 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 hyperlipemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorder, hemolysis 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 Lipidem should be discontinued immediately.

4.9 Overdose

Overdose leading to fat overload syndrome may occur as a result of a too rapid infusion rate, or chronically at recommended rates of infusion in association with a change in the patients clinical conditions e.g. renal function impairment or infection. Overdosage may lead to undesirable effects (see section 4.8).

Substantial overdosage with a fat emulsion that contains medium-chain triglycerides may lead to metabolic acidosis, especially when no carbohydrates are given concomitantly.

Treatment: In case of an overdose, the infusion must be stopped immediately. Other therapeutic measures will depend on a patient's specific symptoms and their severity. If the infusion is restarted after symptoms have subsided, the infusion rate should be increased gradually with close monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition, fat emulsions
ATC code: B05BA02

Lipidem is intended for supply of energy and polyunsaturated ("essential") omega-6 and omega-3 fatty acids as part of parenteral nutrition regimens. Lipidem therefore contains medium-chain triglycerides, soya-bean oil (medium-chain triglycerides), and triglycerides containing omega-3 fatty acids (long-chain triglycerides).
Medium-chain triglycerides are hydrolyzed faster, eliminated faster from the bloodstream, and oxidized faster than long-chain triglycerides.
Only the long-chain omega-6 and omega-3 triglycerides supply polyunsaturated fatty acids. They are primarily intended for the prevention and treatment of essential fatty acid deficiency, but also as a source of calories. Lipidem supplies essential omega-6 fatty acids, mainly in the form of linoleic acid, and omega-3 fatty acids in the form of alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid.
The ratio of omega-6/omega-3 fatty acids in Lipidem is approximately 3:1.

5.2 Pharmacokinetic properties

The dose, the infusion rate, the patient's metabolic status and other individual factors (such as fasting levels) should be considered when the maximum serum triglyceride concentration is determined.
Medium-chain fatty acids have lower affinity for albumin than long-chain fatty acids. When administered in accordance with the dosing guidelines, however, plasma albumin binding of both types of fatty acid is almost 100%. When the dosing guidelines are complied with, neither medium-chain nor long-chain fatty acids therefore cross the blood-brain barrier or pass into the cerebrospinal fluid.

5.3 Preclinical safety data

Preclinical studies with a developmental version of Lipidem (containing twice the amount of omega-3 acid triglycerides present in the final product and a correspondingly smaller amount of long chain triglycerides) revealed no effects other than those expected following administration of high doses of lipids. In a rabbit reproductive toxicity study no evidence of embryotoxicity or teratogenicity was seen at a dose of 2g lipid/kg body weight per day for 12 days.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Egg Lecithin
Glycerol
Sodium Oleate
Ascorbyl Palmitate
all-rac-α-Tocopherol
Sodium Hydroxide for (pH adjustment)
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 2 years

After first opening the medicinal product should be used immediately.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package**,** in order to protect from light.
Do not freeze.

6.5 Nature and contents of container

The emulsion is packed in a Type II glass bottle with a butyl rubber stopper.

Pack Sizes:
Glass bottle

10 x 100 ml
1 x 250 ml
10 x 250 ml
1 x 500 ml
10 x 500 ml
1 x 1000 ml
6 x 1000 ml

Not all pack sizes may be marketed.

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

Use only if the emulsion is homogeneous from intact containers. Inspect the emulsion visually for phase separation prior to administration.
For single use only. Any unused emulsion should be discarded.
Products that have been frozen should be discarded.

Before infusing a lipid emulsion together with other solutions via a Y connector or bypass set, the compatibility of these fluids should be checked, especially when co-administering carrier solutions to which drugs have been added. Particular caution should be exercised when co-infusing solutions that contain divalent electrolytes (such as calcium).

The emulsion should always be brought to room temperature prior to infusion.

If filters are used, these must be permeable to lipids.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 736/21/1

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