SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lipoplus 20%

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of emulsion contains:

Medium-chain triglycerides	100.0 mg
Soya-bean oil, refined	80.0 mg
Omega-3-acid triglycerides	20.0 mg

Content of triglycerides 200 mg/ml (20%)

Content of essential fatty acids per l

Linoleic acid (omega-6) 38.4 - 46.4 g/l

Alpha-linolenic acid (omega-3) 4.0 - 8.8 g/l

Eicosapentaenoic acid and docosahexaenoic acid (omega-3) 8.6 - 17.2 g/l

Excipient(s) with known effect:

1000 ml emulsion contains 2.6 mmol sodium (as sodium hydroxide and sodium oleate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for infusion

A white, milky oil-in-water emulsion

Energy	7990 kJ/l ≙ 1910 kcal/l
Osmolality	approximately 410 mOsm/kg
Acidity or alkalinity (titration to pH 7.4)	less than 0.5 mmol NaOH/l or HCl/l
pH	6.0 - 8.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Supply of energy, including a readily utilisable lipid component (medium-chain triglycerides) and essential omega-6 fatty acids and omega-3 fatty acids, as part of parenteral nutrition when oral or enteral nutrition is impossible, insufficient or contraindicated.

Lipoplus is indicated in adults, preterm and term neonates, infants and toddlers, children and adolescents.

4.2 Posology and method of administration

Posology

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

Maximum daily doses should only be administered after stepwise increase with careful monitoring of the tolerance of the infusions.

The utilisation of intravenous lipids depends on e.g. the severity of underlying disease, body weight, gestational and postnatal age and specific body functions.

Depending on energy requirements, the following daily doses are recommended:

Adults

The usual dose is 0.7 to 1.5 g lipids/kg body weight (b.w.) per day. A maximum dose of 2.0 g lipids/kg b.w./d, for instance when energy requirements are high or fat utilisation is increased (e.g. oncology patients), should not be exceeded For long-term home parenteral nutrition treatment (> 6 months) and in patients with short bowel syndrome the provision of intravenous lipids should not exceed 1.0 g/kg b.w./d.
For a patient weighing 70 kg a daily dose of 2.0 g/kg b.w./d corresponds to a maximum daily dose of 700 ml Lipoplus 20%.

Paediatric population

A gradual increase of lipid intake in increments of 0.5 – 1.0 g/kg b.w./d may be beneficial regarding the possibility to monitor the increase of the plasma triglyceride level and prevent hyperlipidaemia.

Preterm newborn infants, term newborn infants, infants and toddlers
It is recommended not to exceed a daily dose of 2.0 – 3.0 g/kg b.w./d of lipids.
In preterm newborn infants, term newborn infants, infants and toddlers, the daily dose of lipids should be infused continuously over about 24 hours.

Children and adolescents
It is recommended not to exceed a daily lipid dose of 2.0 – 3.0 g/kg b.w./d.

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
See section 4.4.

Patients with hepatic impairment
See section 4.4 (‘(‘Patients with impaired lipid metabolism’).

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.
The patient should be monitored closely for the occurrence of adverse reactions.

Maximum infusion rate

Adults
Up to 0.15 g/kg b.w./h lipids.

For a patient weighing 70 kg this corresponds to a maximum infusion rate of 52.5 ml per hour Lipoplus 20%. The amount of lipids administered then is 10.5 g per hour.

Preterm newborn infants, term newborn infants, infants and toddlers
Up to 0.15 g/kg b.w./h lipids.

Children and adolescents
Up to 0.15 g/kg b.w./h
lipids.

Method of administration
Intravenous use.
Lipid emulsions are suitable for peripheral venous administration and can also be administered separately via peripheral veins as part of total parenteral nutrition.
The Y- or the bypass connector should be placed as close to the patient as possible if lipid emulsions are co-administered with amino acid and carbohydrate solutions.
For further instructions on handling of the medicinal product before administration, see section 6.6.

When used in neonates and children below 2 years, the solution (in bottles and administration sets) should be protected from light exposure until administration is completed (see sections 4.4, 6.3 and 6.6).

Duration of treatment
As clinical experience with long-term use of Lipoplus 20% is limited, it should normally not be administered for longer than one week. If parenteral nutrition with lipid emulsions is further indicated, Lipoplus 20% can be administered over longer periods provided appropriate monitoring is employed.

4.3 Contraindications

– Hypersensitivity to the active substances, to egg, fish, peanut or soya protein or to any of the excipients listed in section 6.1

– Severe hyperlipidaemia characterized by hypertriglyceridaemia (≥ 1000 mg/dl or 11.4 mmol/l)
– Severe coagulopathy
– Intrahepatic cholestasis
– Severe hepatic insufficiency
– Severe renal insufficiency in absence of renal replacement therapy
– Acute thromboembolic events, fat embolism
– Acidosis

General contraindications to parenteral nutrition include:

– Unstable circulatory status with vital threat (states of collapse and shock)
– Acute phases of cardiac infarction or stroke
– Unstable metabolic conditions (e.g. decompensated diabetes mellitus, severe sepsis, 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

The serum triglyceride concentration should be monitored when infusing Lipoplus 20%.

In patients with suspected disorders of lipid metabolism, fasting hyperlipidaemia should be ruled out before the start of the infusion.

Depending on the patient's metabolic condition, occasional hypertriglyceridaemia may occur. If the plasma triglyceride concentration exceeds 4.6 mmol/l (400 mg/dl) in adults during administration of lipids it is recommended to reduce the infusion rate. The infusion must be interrupted if the plasma triglyceride concentration exceeds 11.4 mmol/l (1000 mg/dl), as these levels have been associated with an increased risk for acute pancreatitis.

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

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.

Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and renal function are necessary.

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

Energy supply with lipid emulsions only could cause metabolic acidosis. It is therefore recommended to infuse an adequate quantity of intravenous carbohydrates or carbohydrate- containing amino acid solutions along with the fat emulsion.

For patients requiring complete parenteral nutrition, complementary carbohydrate, amino acid, electrolyte, vitamin, and trace element supplements are required. Also, an adequate total fluid intake has to be ensured.

Impaired capacity to eliminate triglycerides can lead to "fat overload syndrome" which may be caused by overdose (see section 4.8 and 4.9.).

Mixing with incompatible substances might lead to breaking of the emulsion or to precipitation of particles (see sections 6.2 and 6.6), both resulting in a high risk of embolism.

There is as yet only limited experience of the use of Lipoplus 20% for periods longer than seven days.

As with all intravenous solutions, especially for parenteral nutrition, strict aseptic precautions are necessary for the infusion of Lipoplus 20%.

Patients with diabetes mellitus, impaired cardiac or renal function
Like all large-volume infusion solutions, Lipoplus 20% 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
Lipoplus 20% should be administered cautiously to patients with disturbances of lipid metabolism with increased serum triglycerides, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired hepatic function, hypothyroidism (with hypertriglyceridaemia), sepsis, and metabolic syndrome. If Lipoplus 20% is given to patients with these conditions, more frequent monitoring of serum triglycerides is necessary to assure triglyceride elimination and stable triglyceride levels below 11.4 mmol/l (1000 mg/dl).
In combined hyperlipidaemias and in metabolic syndrome, triglyceride levels react to glucose, lipids and overnutrition. Adjust dose accordingly. Assess and monitor other lipid and glucose sources, and drugs interfering with their metabolism.
The presence of hypertriglyceridaemia 12 hours after the administration of lipids also indicates disturbance of lipid metabolism.

Paediatric population
Free fatty acids (FFA) compete with bilirubin for albumin binding sites. Especially very premature infants may be at increased risk of hyperbilirubinaemia due to high levels of FFA released from triglycerides resulting in a high FFA/albumin ratio. In parenterally fed infants at risk of hyperbilirubinaemia, serum triglyceride and bilirubin levels should be monitored and lipid infusion rate be adjusted if deemed necessary.
During infusion Lipoplus 20% should be protected from phototherapy light to decrease the formation of potentially harmful triglyceride hydroperoxides.
The serum triglyceride concentration should be regularly monitored during the infusion of Lipoplus 20%, (especially in very small preterm infants), especially if there is an increased risk of hyperlipidaemia (e.g. in situations of stress or infection). A stepwise increase of the daily dose may be advisable.
Depending on the patient's metabolic condition, occasional hypertriglyceridaemia may occur. In infants dose reduction should be considered if the plasma triglyceride concentration during infusion exceeds 2.8 mmol/l (250 mg/dl). In older children and adolescents dose reduction should be considered if the plasma triglyceride concentration during infusion exceeds 4.6 mmol/l (400 mg/dl).

Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, Lipoplus 20% should be protected from ambient light until administration is completed (see sections 4.2, 6.3 and 6.6).

Special warnings/precautions regarding excipients
This medicinal product contains 59.8 mg sodium per 1000 ml, equivalent to 3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interference with laboratory tests
Lipids may interfere with certain laboratory tests (such as bilirubin, lactate dehydrogenase, oxygen saturation) when the blood sample is taken before the lipids have been eliminated from the bloodstream, this may take 4 to 6 hours.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Heparin given in clinical doses causes 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 K_1. 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 Lipoplus 20% in pregnant women. Animal studies undertaken with a lipid emulsion containing twice the amount of omega-3 acid triglycerides and a correspondingly smaller amount of omega-6-acid triglycerides as compared to Lipoplus 20% do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Parenteral nutrition may become necessary during pregnancy. Lipoplus 20% should only be administered to pregnant women after careful benefit-risk consideration.

Breastfeeding

Components/metabolites of Lipoplus 20% are excreted in human milk, but at therapeutic doses of Lipoplus 20% no effects on the breastfed newborns/infants are anticipated. In general, breastfeeding is not recommended to mothers on parenteral nutrition.

Fertility

No data from the use of Lipoplus 20% 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 adverse reactions that may be associated with the use of Lipoplus 20%. Under the conditions of correct use, in terms of dosing, monitoring, observation of safety restrictions and instructions, most of them are very rare (< 1/10,000).

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 (cannot be estimated from the available data)

Blood and lymphatic system disorders

Very rare: Hypercoagulation

Not known: Leucopenia, thrombocytopenia

Immune system disorders

Very rare: Allergic reactions (e.g. anaphylactic reactions, dermal eruptions, laryngeal, oral and facial oedema)

Metabolism and nutrition disorders

Very rare: Hyperlipidaemia, metabolic acidosis

The frequency of these adverse reactions is dose-dependent and may be higher under conditions of absolute or relative overdose.

Very rare: Hyperglycaemia

Nervous system disorders

Very rare: Headache, drowsiness

Vascular disorders

Very rare: Hypertension or hypotension, flush

Respiratory, thoracic and mediastinal disorders

Very rare: Dyspnoea, cyanosis

Gastrointestinal disorders

Very rare: Nausea, vomiting, loss of appetite

Skin and subcutaneous tissue disorders

Very rare: Erythema, sweating

Hepatobiliary disorders

Not known: Cholestasis

Musculoskeletal and connective tissue disorders

Rare: Back, bones, chest and lumbar region pain

General disorders and administration site conditions

Very rare: Elevated body temperature, feeling cold, chills, fat overload syndrome (see below).

Should adverse reactions occur, the infusion must be stopped.

Should the triglyceride level rise to above 11.4 mmol/l (1000 mg/dl) during infusion, the infusion must be stopped. With levels above 4.6 mmol/l (400 mg/dl), the infusion may be continued at a reduced dosage (see section 4.4).

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 and lack of appetite are symptoms often related to conditions for which parenteral nutrition is indicated, and may be associated with parenteral nutrition at the same time.

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 diseases. 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, leucopenia, 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 Lipoplus 20% must 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

4.9 Overdose

Symptoms

Hyperlipidaemia, metabolic acidosis.

Also, a fat overload syndrome may occur. See section 4.8.

Treatment

Immediate cessation of infusion is indicated for overdose. Other therapeutic measures will depend on a patient's specific symptoms and their severity. When the infusion is recommenced after symptoms have declined, it is recommended that the infusion rate should be raised gradually with monitoring at frequent intervals.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition, fat emulsions
ATC code: B05B A02

Lipoplus 20% is intended to provide energy and polyunsaturated ("essential") omega-6 and omega-3 fatty acids as part of parenteral nutrition. For this purpose Lipoplus 20% contains medium-chain triglycerides, soya-bean oil (long-chain triglycerides, mainly omega-6), and triglycerides containing omega-3 fatty acids (long-chain triglycerides).

Medium-chain triglycerides are more rapidly hydrolysed, faster eliminated from the circulation, and more completely oxidised than long-chain triglycerides. Hence they are a preferred energy substrate, particularly when there are disturbances of the degradation and/or utilisation of long-chain triglycerides, e.g. in case of lipoprotein lipase deficiency, deficiency of lipoprotein lipase cofactors, carnitine deficit and impairment of the carnitine-dependent transport system.

In detail, long-chain omega-3 polyunsaturated fatty acids are precursors for anti-inflammatory eicosanoids. They reduce pro-inflammatory cytokine production from arachidonic acid and increasing anti-inflammatory cytokine production from eicosapentaenoic acid and docosahexaenoic acid. This may be of benefit in patients at risk of developing a hyperinflammatory state and sepsis.

Only the long-chain omega-6 and omega-3 triglycerides supply polyunsaturated fatty acids, so these are primarily included for prophylaxis and therapy of essential fatty acid deficiency and, only secondarily, as a source of energy. Lipoplus 20% 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.

Phosphatides, besides their function as emulsifier for the triglycerides, are components of the cell membranes and guarantee their fluidity and biological functions.

Glycerol, which has been added with the aim to render the emulsion isotonic to blood, is a physiological intermediate in the metabolism of glucose and lipids: it is metabolised to yield energy or is utilised for the synthesis of glucose, glycogen and triglycerides.

The ratio of omega-6/omega-3 fatty acids in Lipoplus 20% is approximately 2.5:1.

Safety pharmacological investigations have not revealed any specific effects other than the above-mentioned nutritive effects, which are the same as when the particular substrates were administered orally.

5.2 Pharmacokinetic properties

Distribution

The dose, rate of infusion, metabolic state and individual factors concerning the patient (level of fasting) are the most relevant factors determining the maximum serum triglyceride concentration-

Placental tissue preferentially takes up long-chain polyunsaturated fatty acids from the maternal circulation and regulates their transfer to the foetal circulation.

Biotransformation

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

Both the triglycerides of soya-bean oil and medium-chain triglycerides are completely metabolised to CO_2 and H_2O. Omega-3 acid triglycerides are either completely oxidised to CO_2 and water or incorporated in cell membranes and then metabolised to eicosanoids and cytokines. Up to 30% to 70% of the infused lipids are oxidised within 24 h, whereas the elimination rate largely depends on nutritional state, hormonal balance, simultaneous infusion of glucose solution, etc. Renal excretion does virtually not occur.

5.3 Preclinical safety data

Preclinical studies including safety pharmacology, reproductive and developmental toxicity studies with a lipid emulsion containing twice the amount of omega-3 acid triglycerides present in the final product and a correspondingly smaller amount of long chain omega-6 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 2 g lipid/kg body weight per day for 12 days.

Phytoestrogens such as ß-sitosterol can be found in various vegetable oils, especially in soya-bean oil. Impairment of fertility was observed in rats and rabbits after subcutaneous and intravaginal administration of ß-sitosterol. After administration of pure ß-sitosterol a decrease of the testicular weight and a reduction of the sperm concentration in male rats and a lowered pregnancy rate in female rabbits were recorded. However, 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

Glycerol
Egg phospholipids for injection
Sodium oleate
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
The expiry date of the product is indicated on the packaging materials.

After first opening the container
After first opening the medicinal product should be used immediately.

When used in neonates and children below 2 years, the solution (in bottles and administration sets) should be protected from light exposure until administration is completed (see sections 4.2, 4.4 and 6.6).

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.

6.4 Special precautions for storage

Do not store above 25 °C.

Do not freeze. If accidentally frozen, discard the container.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Glass bottle (type II glass) with a halogen butyl rubber stopper.

Pack sizes:

100 ml, available in packs of 10 x 100 ml
250 ml, available in packs of 1 x 250 ml and 10 x 250 ml
500 ml, available in packs of 1 x 500 ml and 10 x 500 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

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 cations (such as calcium or magnesium).

Shake gently prior to use.

The emulsion has to be brought to room temperature unaided prior to infusion, i.e., the product should not be put in a heating device (such as oven or microwave).

For single use only. Container and unused residues must be discarded after use.
Do not reconnect partially used containers.

Only use containers that are undamaged and in which the emulsion is homogeneous and milky-white. Inspect the emulsion visually for phase separation and discoloration prior to administration (oil drops, oil layer).

When used in neonates and children below 2 years, protect from light exposure, until administration is completed. Exposure of Lipoplus 20% to ambient light, especially after admixture with trace elements and/ or vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure (see sections 4.2, 4.4 and 6.3).

7 MARKETING AUTHORISATION HOLDER

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Carl-Braun-Straße 1
34209
Melsungen Germany

8 REGISTRATION HOLDER

Lapidot Medical Import and Marketing Ltd.
8 Hashita Street, Industrial Park Caesarea 3088900, ISRAEL

9 MARKETING AUTHORISATION NUMBER

170-27-36704-99

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