Directions for Use

B. Braun Melsungen AG · 34209 Melsungen, Germany

Lipofundin® MCT/LCT 20% emulsion for infusion

1. NAME OF THE MEDICINAL PRODUCT

Lipofundin MCT/LCT 20% emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml emulsion for infusion contain:

Soya-bean oil, refined	100.0 g
Medium-chain triglycerides (MCT)	100.0 g

Essential fatty acid content per 1000 ml:

Linoleic acid	48.0 – 58.0 g
α-Linolenic acid	5.0 – 11.0 g

Excipient(s) with known effect

Lipofundin MCT/LCT 20% contains less than 1 mmol (23 mg) sodium per litre.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for infusion
Milky-white oil-in-water emulsion

Energy [kJ/l (kcal/l)]	8095 (1935)
Theoretical osmolarity [mOsm/l]	380
Acidity or alkalinity (titration to pH 7.4) [mmol/l]	< 0.5
pH	6.5 - 8.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Energy supply including a readily utilisable lipid component (MCT)
- Supply of essential fatty acids as part of total parenteral nutrition

4.2 Posology and method of administration

Posology

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 Lipofundin MCT/LCT 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 and term newborn infants

It is recommended not to exceed a daily maximum dose of **4.0 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.

Infants, toddlers, children and adolescents

It is recommended not to exceed a daily maximum lipid dose of **3.0 g/kg b.w./d** of lipids.

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 Lipofundin MCT/LCT 20%. The amount of lipids administered then is 10.5 g per hour.

Preterm newborn infants, term newborn infants, infants and toddlers

Up to **0.17 g/kg b.w./h** lipids.

Children and adolescents

Up to **0.13 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.

The duration of administration of Lipofundin MCT/LCT 20% is usually 1 - 2 weeks. If parenteral nutrition with lipid emulsions is further indicated, Lipofundin MCT/LCT 20% can be administered over longer periods provided appropriate monitoring is employed.

When used in infants aged from preterm to 2 years old, the emulsion (including administration sets) should be protected from light exposure after preparation for infusion until administration is completed (see sections 4.4, 6.3 and 6.6).

4.3 Contraindications

- Hypersensitivity to egg or soya-bean protein, soya-bean or peanut products or to any of the active substances or the excipients listed in section 6.1.
- Severe hyperlipidaemia
- Severe coagulopathy
- Severe hepatic insufficiency
- Intrahepatic cholestasis
- Severe renal insufficiency in absence of renal replacement therapy
- Acute thromboembolic events
- Fat embolism
- Aggravating haemorrhagic diatheses
- Metabolic acidosis

General contraindications to parenteral nutrition include:

- Unstable circulatory status with vital threat (states of collapse and shock)
- Unstable metabolic conditions (e.g. severe post-aggression syndrome, severe sepsis, coma of unknown origin)
- Acute phase of myocardial infarction or stroke
- Uncorrected disorders of fluid and electrolyte balance, such as hypokalaemia and hypotonic dehydration (see also section 4.4)
- Decompensated cardiac insufficiency
- Acute pulmonary oedema

4.4 Special warnings and precautions for use

The serum triglyceride concentration should be regularly monitored during the infusion of Lipofundin MCT/LCT.
Depending on the patient's metabolic condition, occasional hypertriglyceridaemia may occur. If the plasma triglyceride concentration exceeds 4.6 mmol/l during administration of the lipid emulsion, it is recommended to reduce the infusion rate. The infusion must be interrupted if the plasma triglyceride concentration exceeds 11.4 mmol/l.
Disorders of the fluid, electrolyte or acid-base balance must be corrected before the start of infusion.

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

Hypersensitivity reactions to an ingredient of Lipofundin MCT/LCT (e.g. due to traces of protein in soya-bean oil or egg phospholipids for injection) are extremely rare, but cannot be totally excluded for sensitised patients. Infusion of Lipofundin MCT/LCT should immediately be discontinued in case of appearance of any sign of allergic reaction, e.g. fever, shivering, rash, dyspnoea.

Energy supply with lipid emulsions alone could cause metabolic acidosis. It is therefore recommended to infuse an adequate quantity of intravenous carbohydrates and amino acids 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.

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.

In solutions with higher lipid concentration (e.g. Lipofundin MCT/LCT 20%), the ratio of emulsifier (phospholipid) to oil is lower than in lower concentrated lipid emulsions. This ensures a favourable lower plasma concentration of triglycerides, phospholipids, free fatty acids as well as the pathological lipoprotein-X in the patient`s blood. Therefore higher concentrated lipid emulsions like Lipofundin MCT/LCT 20% should be preferred over lower concentrated lipid emulsions.

Elderly patients

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 impaired lipid metabolism

Lipofundin MCT/LCT 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 Lipofundin MCT/LCT is administered to patients with these conditions, close monitoring of serum triglycerides is necessary. The dose should be adjusted to the metabolic tolerance. The presence of hypertriglyceridaemia 12 hours after lipid administration also indicates a 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 Lipofundin MCT/LCT 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 Lipofundin MCT/LCT, especially if there is an increased risk of hyperlipidaemia. 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. In older children dose reduction should be considered if the plasma triglyceride concentration during infusion exceeds 4.5 mmol/l.

Light exposure of mixtures 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 infants aged from preterm to 2 years old, Lipofundin MCT/LCT should be protected from light exposure after preparation for infusion until administration is completed (see sections 4.2, 6.3 and 6.6).

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

• Heparin

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.

• Coumarin derivatives

Soya-bean oil has a natural content of vitamin K_1. The content is however so low in Lipofundin MCT/LCT that it is not expected to influence the coagulation process significantly in patients treated with coumarin derivatives. Nevertheless, the coagulation status should be monitored in patients treated concomitantly with coumarins.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Lipofundin MCT/LCT in pregnant women. Animal data are insufficient with respect to reproductive toxicity (see section 5.3).

Parenteral nutrition may become necessary during pregnancy. Lipofundin MCT/LCT should only be administered to pregnant women after careful benefit-risk consideration.

Breast-feeding

Components/metabolites of Lipofundin MCT/LCT are excreted in human milk, but at therapeutic doses no effects on the breastfed newborns/infants are anticipated. In general, breast-feeding is not recommended to mothers receiving parenteral nutrition.

Fertility

No human data available. Animal studies have indicated no evidence of an effect on fertility.

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 Lipofundin MCT/LCT. 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).

Listing of undesirable effects

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

Very rare: Hypercoagulability
Not known: Leucopenia, thrombocytopenia

Immune system disorders

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

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Metabolism and nutrition disorders

Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, ketoacidosis, loss of appetite
The frequency of these adverse reactions is dose-dependent and may be higher under conditions of absolute or relative overdose.

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

Hepatobiliary disorders

Not known: Cholestasis

Skin and subcutaneous tissue disorders

Very rare: Erythema, sweating

Musculoskeletal and connective tissue disorders

Very rare: Pain in the back, bones, chest and lumbar region

General disorders and administration site conditions

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

If adverse reactions occur, the infusion of Lipofundin MCT/LCT must be stopped or, if necessary, continued at a reduced dosage.

If the infusion is restarted, the patient must 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 related to conditions constituting an indication for parenteral nutrition and may sometimes be associated with parenteral nutrition.

Fat overload syndrome

Overdose of lipid emulsion or impaired capacity to eliminate triglycerides can lead to "fat overload syndrome". 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 Lipofundin MCT/LCT must be discontinued immediately.

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 the particular symptoms and their severity.

When the infusion is recommenced after 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, fat emulsions
ATC code: B05B A02

Mechanism of action, pharmacodynamic effect

Lipofundin MCT/LCT is intended to provide energy and polyunsaturated ("essential") fatty acids as part of parenteral nutrition. For this purpose Lipofundin MCT/LCT contains medium-chain triglycerides, long-chain triglycerides (soya-bean oil), phosphatides (egg phospholipids for injection) and glycerol.

Medium-chain triglycerides are more rapidly hydrolysed, 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 cases of lipoprotein lipase deficiency, deficiency of lipoprotein lipase cofactors, carnitine deficit and impairment of the carnitine-dependent transport system.

Only the long-chain triglycerides provide unsaturated fatty acids, so these are primarily included for prophylaxis and therapy of essential fatty acid deficiency and, only secondarily, as a source of energy.

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.

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

Absorption

Bioavailability: Because of intravenous administration, the bioavailability of the constituents of Lipofundin MCT/LCT is 100 per cent.

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. On administration according to the instructions and observance of the dosage guidelines the triglyceride concentrations should not generally exceed 4.6 mmol/l.

Medium-chain fatty acids have a low affinity to albumin. In animal experiments administering pure medium-chain triglyceride emulsions, it has been shown that medium-chain fatty acids can cross the blood-brain barrier, if overdosed. No adverse effects were observed with an emulsion providing a mixture of medium-chain triglycerides and long-chain triglycerides, as long-chain triglycerides have an inhibiting effect on medium-chain triglyceride hydrolysis. Therefore, toxic effects on the brain can be excluded after the administration of Lipofundin MCT/LCT.

Placental tissue preferentially takes up long-chain polyunsaturated fatty acids from the maternal circulation and regulates their transfer to the foetal circulation. The placental transfer of fatty acids is a very complex process that involves numerous membrane-bound and cytosolic fatty acid-binding proteins, although the mechanisms are still uncertain. The placenta takes up the maternal circulating nonesterified fatty acids and fatty acids released by maternal lipoprotein lipase and endothelial lipase. These nonesterified fatty acids enter the cell through passive diffusion or by membrane carrier proteins. Nonesterified fatty acids bind to cytosolic fatty-acid-binding proteins to interact with subcellular organelles, including the endoplasmic reticulum, mitochondria, lipid droplets and peroxisomes.

Biotransformation

After infusion triglycerides are hydrolysed to glycerol and fatty acids. Both are incorporated into physiological pathways for energy production, synthesis of biologically active molecules, gluconeogenesis and resynthesis of lipids.

Elimination

The plasma half-life of Lipofundin MCT/LCT is approximately 9 minutes.

Both the triglycerides of soya-bean oil and medium-chain triglycerides are completely metabolised to CO_2 and H_2O. 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

Preclinical data with Lipofundin MCT/LCT are available only to a limited extent.

Effects in non-clinical examinations were observed only at exposures being 2- to 3-fold the maximum human daily dose. It should be considered that in these examinations excessive infusion rates were applied which are far above the recommended infusion rates (29-fold in dogs and 353-fold in rats and mice).

Repeated-dose toxicity

Six-week toxicity tests have been carried out in dogs and rabbits. The highest i.v. dose tested in the rabbit was 4.6 g lipid/kg body weight and in the dog 6 g lipid/kg body weight. Apart from a slight effect on the general behaviour there were no toxic symptoms; in particular, no biochemical or histological indications of damage to the liver or to other organs were detected.

Mutagenic and tumorigenic potential

The mutagenic and tumorigenic potential was not investigated because the components of Lipofundin MCT/LCT are natural nutrients and/or intermediates in physiological metabolism.

Reproduction toxicity

Animal experiments carried out at dose levels envisaged for human administration did not provide any evidence of an influence on the fertility or breeding performance.

Teratogenic effects were not specifically investigated since the components of Lipofundin MCT/LCT are natural substances and/or intermediates in physiological metabolism that are not assumed to possess teratogenic properties.

Sensitising properties

Appropriate toxicological investigations did not reveal that Lipofundin MCT/LCT possessed any sensitising properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Egg phospholipids for injection
all-rac-α-Tocopherol
Sodium oleate (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Lipofundin MCT/LCT must not be used as carrier solution for electrolyte concentrates or other pharmaceuticals nor must the emulsion be mixed with other infusion solutions in an uncontrolled manner, since adequate stability of the emulsion would no longer be guaranteed.

Combined regimens are only to be used for parenteral nutrition after their pharmaceutical compatibility has been controlled and guaranteed.

6.3 Shelf life

Unopened

2 years

After first opening the container

After first opening the medicinal product should be used immediately.
When used in infants aged from preterm to 2 years old, the emulsion (including administration sets) should be protected from light exposure after preparation for infusion until administration is completed (see sections 4.2, 4.4 and 6.6).

After reconstitution or dilution

Not applicable, see section 6.2.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.
Keep the bottles in the outer carton in order to protect from light.

6.5 Nature and contents of container

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

Contents: 100 ml, available in packs of 10 x 100 ml
250 ml, available in packs of 10 x 250 ml
500 ml, available in packs of 10 x 500 ml
1000 ml, available in packs of 6 x 1000 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

When using product packed in flexible bags, the air vent of the giving set must be closed.

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 electrolytes (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. Any unused emulsion should be discarded.

Products that have been frozen should be discarded.

Only use containers that are undamaged and in which the emulsion is homogenous and milky white. Inspect the emulsion visually for phase separation prior to administration.

When used in infants aged from preterm to 2 years old, parenteral nutrition mixtures containing Lipofundin MCT/LCT should be protected from light exposure, after preparation for infusion until administration is completed. Exposure of such mixtures to 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. DATE OF REVISION OF THE TEXT

10/2021

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