07.2022

רופא/ה רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלון לרופא בעקבות "אימוץ עלון כלשונו" עבור התכשיר:

Lipofundin MCT/LCT 20 %

חומר פעיל :

TRIGLYCERIDES, MEDIUM-CHAIN 100 G/L
SOYA OIL 100 G/L

התוויה מאושרת:
Source of calories and essential fatty oils for patients requiring parenteral nutrition

להלן עלונים לרופא כפי שאומץ מעלון אסמכתא כלשונו (טקסט מסומן ירוק משמעותו עדכון ,טקסט מסומן צהוב משמעותו החמרה):

8 Hashita Street, P.O. Box 3552, Caesarea Industrial Park 3088900, Israel
Tel.: + 972-4-6309630 Fax: +972-4-6309631

LAPIDOT MEDICAL

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lipofundin MCT/LCT 20 %

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1000 ml emulsion for infusion contain:	
Soya-bean oil	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 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	6.0 - 8.5

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Lipofundin MCT/LCT is indicated as a source of calories and essential fatty oils for patients requiring parenteral nutrition.

4.2 Posology and method of administration

8 Hashita Street, P.O. Box 3552, Caesarea Industrial Park 3088900, Israel
Tel.: + 972-4-6309630 Fax: +972-4-6309631

Posology

The dosage and infusion rate should be within the ranges recommended below and should be governed by the patient's ability to utilise fat.

1. Adults and school-age children

1-2 g fat per kg body weight per day, corresponding to 10-20 ml of Lipofundin MCT/LCT 10% or 5-10 ml of Lipofundin MCT/LCT 20% per kg body weight per day.

2. Neonates, infants and pre-school children.

Dosage is governed by the maturity and birth-weight of the infant. Neonates 2.5-3 g (up to 4 g) of fat per kg body weight per day, corresponding to 25-30 ml (up to 40 ml) of Lipofundin MCT/LCT 10% or 12.5-15 ml (up to 20 ml) of Lipofundin MCT/LCT 20% per kg body weight per day.

Especially in preterm infants and low-birth-weight neonates, the ability to eliminate infused lipids is not yet fully developed. Therefore maximum fat doses should not be administered to these patients. The infant's ability to eliminate infused fat from the circulation should be checked daily. Measuring serum triglycerides is the only reliable method. If lipaemia is present re-testing should be carried out after an interval of four hours.

At the end of the daily fat-free interval, the fat must have been cleared from the serum.

Infants and pre-school children

0.5-3 g of fat per kg body weight per day, corresponding to 5-30 ml of Lipofundin MCT/LCT 10% or 2.5-15 ml of Lipofundin MCT/LCT 20% per kg body weight per day.

3. Elderly

Age per se requires no adjustment of the adult dosage. However, caution should be exercised in the "frail" and indeed in all patients with poor renal, cardiac or liver function, where smaller volumes should be used depending on the individual's requirements and condition.

Infusion rates

In general, fat emulsions should be infused at as low a rate as possible. During the first 15 minutes the infusion rate should not exceed 0.05-0.1 g of fat per kg body weight and hour, corresponding to 0.5-1.0 ml of Lipofundin MCT/LCT 10% or 0.25-0.5 ml of Lipofundin MCT/LCT 20% per kg body weight and hour. If no adverse reactions are observed during this initial phase, the infusion rate may be increased to 0.15-0.2 g fat per kg body weight per hour, corresponding to 1.5-2.0 ml of Lipofundin MCT/LCT 10% or 0.75-1.0 ml of Lipofundin MCT/LCT 20% per kg body weight and hour. The daily fat infusions should be administered over not less than 16 hours, preferably as continuous infusion over 24 hours. To premature and low birth-weight infants Lipofundin MCT/LCT should be administered continuously during 24 hours/day. The dose can only be increased up to a maximum of 4.0 g/kg/24 hours by concomittant careful monitoring by following the triglyceride levels, liver function tests and oxygen saturation. The rates given are maximum rates and no attempt should be made to exceed these in order to compensate for missed doses.

Duration of use

8 Hashita Street, P.O. Box 3552, Caesarea Industrial Park 3088900, Israel
Tel.: + 972-4-6309630 Fax: +972-4-6309631

In total parenteral nutrition, Lipofundin MCT/LCT is normally administered over 1-2 weeks. If fat infusions are further indicated and appropriate monitoring is instituted, the period of use of Lipofundin MCT/LCT may be extended.

Method of administration

Lipofundin MCT/LCT should be administered by intravenous infusion as part of a total parenteral nutrition regimen via a peripheral vein or central venous catheter. Lipofundin MCT/LCT can be infused into the same central or peripheral vein as the carbohydrate and amino acid solutions by means of a short Y-connector near the infusion site. This allows for mixing of the solutions immediately before entering the vein. Flow rates for each solution should be controlled separately by infusion pumps, if these are used.
For safe administration of intravenous fluids from non-collapsible containers a giving set with an integral airway is recommended.
Infusion sets with in-line filters are not to be used for administration of fat emulsions.

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 un-known origin)
- Acute phase of myocardial infarction or stroke
- Uncorrected disorders of fluid and electrolyte balance, such as hypokalaemia and hypotonic dehy-dration (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 20%.

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 20% (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 20% 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 20% 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 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 Lipofundin MCT/LCT 20%, 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 to 2 years old, Lipofundin MCT/LCT 20% 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 K1. The content is however so low in Lipofundin MCT/LCT 20% 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 20% 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 20% should only be administered to pregnant women after careful benefit-risk consideration.

Breastfeeding
Components / metabolites of Lipofundin MCT/LCT 20% are excreted in human milk, but at therapeutic doses no effects on the breastfed newborns / infants are anticipated. In general, breastfeeding 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 applicable.

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 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).

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)

Metabolism and nutrition disorders
Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, ketoacidosis
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, loss of appetite

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 20% 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 syn-drome”. 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, 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 Lipofundin MCT/LCT 20% must be discon-tinued 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 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

Lipofundin MT/LCT 20% provides a source of energy and essential (polyunsaturated) fatty acids for the patient requiring parenteral nutrition. Medium-chain triglycerides are cleared from the bloodstream at a faster rate and are oxidised more completely for energy production than long-chain triglycerides. For that reason they serve as preferential fuel for the body, especially in conditions where the oxidation of long-chain triglycerides is impaired, eg due to carnitine deficiency or diminished carnitine palmitoyl-transferase activity, resp.

The polyunsaturated fatty acids, which are only provided by long-chain triglycerides, will prevent the biochemical disorders of essential fatty acid deficiency (EFAD), and correct the clinical manifestations of the EFAD syndrome.

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

5.2. Pharmacokinetic properties

Because of the I.V administration of Lipofundin MCT/LCT 20%, no data on absorption are provided; for the same reason, the bio-availability is 100 per cent.

The maximum serum triglyceride concentrations during infusion of Lipofundin MCT/LCT mainly depend on the actual dose and infusion rate as well as on the patient's individual metabolic status and other patient-related factors, e.g. the fasting triglyceride level. In general, however, serum triglyceride concentrations will not exceed 5 µmol/l as long as recommended doses and all other directions for use are observed.

The plasma half-life time of triglycerides infused in the form of Lipofundin MCT/LCT 20% is approx 9 minutes. Although the affinity of long-chain fatty acids to albumin is somewhat greater than that of medium-chain fatty acids, albumin binding of both types of fatty acids is virtually complete, provided the recommended doses are not exceeded. Therefore, medium- and long-chain fatty acids do not pass over the cerebrospinal fluid. No data are presently available as to passage across the placental barrier and into breastmilk.

Triglycerides and free fatty acids are not excreted via the kidneys. In view of the intended nutritive effects of Lipofundin MCT/LCT 20% , such excretion is not even desirable. Poisoning requiring rapid elimination of the toxic agent is not to be expected with Lipofundin MCT/LCT 20% because this product only contains physiological nutrient substances.

5.3. Preclinical safety data

The pharmacological and toxicological studies conducted with the product did not reveal any effects indicating specific pharmacological activity or toxicity of the product relevant to its use in man at the recommended dose levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol: 25.0 g/l
Egg Lecithin: 12.0 g/l
α-Tocopherol: 0.20 g/l

Sodium oleate (for pH-adjustment): 0.30 g/l
Water for injection: 739 g/l

6.2 Incompatibilities

Lipofundin MCT/LCT 20 % must not be used as carrier solutions for electrolyte concentrates or other pharmaceuticals nor must the emulsion be mixed with other infusion solutions, 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.

The combination of Lipofundin MCT/LCT 20 % with alcohol-containing infusion or injection solutions must be avoided.

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 infants aged 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

Store below 25 °C.
Do not freeze.
Store in original package, in order to protect from light.

6.5 Nature and contents of container

- Glass bottles (type II glass) sealed with rubber stoppers:

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 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 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 MANUFACTURER

B. Braun Melsungen AG
Carl-Braun-Straße 1
D-34212 Melsungen
Germany

8. REGISTRATION HOLDER

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

9 MARKETING AUTHORISATION NUMBER

112-08-29445-00

Revised in July 2022 according to MOH guidelines

העלון לרופא נשלח למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתו לאתר וניתן לקבלו מודפס על ידי פניה לבעל הרישום Lapidot Medical Import & Marketing Ltd, רח' השיטה 8, פארק התעשיה קיסריה 3088900 ישראל.

בברכה
גאי וגנר
רוקח ממונה

8 Hashita Street, P.O. Box 3552, Caesarea Industrial Park 3088900, Israel
Tel.: + 972-4-6309630 Fax: +972-4-6309631