Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

STRUCTOLIPID 20% emulsion for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

100 ml of the emulsion contains

Active ingredient	Quantity
Purified structured triglyceride	20 g

For list of excipients, see section 6.1
The active ingredient, purified structured triglyceride, can be defined as an interesterified mixture of equimolar amounts of long chain triglycerides (LCT) and medium chain triglycerides (MCT), corresponding to 64% (w/w) and 36% (w/w), respectively. The fatty acids are randomly distributed within the interesterified triglyceride molecule. Purified structured triglyceride consists mainly of mixed chain triglycerides, i.e. containing medium as well as long chain fatty acids (approx 75%) with minor proportions of LCT and MCT. MCT is a synthetic oil originated from coconut oil and/or palm kernel oil and LCT is added in the form of refined soybean oil.

Osmolality:	350 mosm/kg water
pH	Approx 8
Energy content:	8.2 MJ (1960 kcal) /1000 ml

3 PHARMACEUTICAL FORM

Emulsion for infusion
White homogenous emulsion

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

To supply energy and essential fatty acids to adult patients, as part of a parenteral nutrition regimen.

4.2 Posology and method of administration

The patient's ability to eliminate the fat infused, should govern the dosage and infusion rate, *see section 4.4, Special warnings and special precautions for use.*

Adults
The recommended dose is 1-1.5 g triglycerides/kg body weight/day, corresponding to
5-7.5 ml/kg body weight/day, normally given over 10-24 hours.
The infusion rate should not exceed 0.75 ml /kg body weight/ hour, corresponding to
0.15 g fat / kg body weight/ hour.

Children
Safety and efficacy in children have not been established.

Administration
STRUCTOLIPID should be administered by intravenous infusion as part of a parenteral nutrition regimen, including glucose, into a peripheral vein or via a central venous catheter.

4.3 Contraindications

Hypersensitivity to egg-, soya- or peanut protein or to any of the active substances or excipients
Severe hyperlipemia
Severe liver insufficiency
Hemophagocytotic syndrome
Severe blood coagulation disorders
Acute shock
General contra-indications of an infusion therapy: acute pulmonary oedema, hyperhydration and decompensated cardiac insufficiency.

4.4 Special warnings and precautions for use

Triglyceride concentrations in serum should be monitored. When disturbed fat metabolism is suspected, this should be done daily. The serum triglyceride concentration should not exceed 3 mmol/l during the infusion. The next infusion should only be started when serum triglyceride levels have returned to the baseline.

Blood glucose levels, serum electrolytes, liver function tests, fluid balance, and blood status should be monitored regularly. When acidosis is suspected or occurs, acid-base balance should be monitored as well.

This medicinal product contains soybean oil (in the form of purified structured triglycerides), which may rarely cause allergic reactions. Cross-allergic reactions have been observed between soybean and peanut.
Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.

STRUCTOLIPID should be given with caution to patients with impaired lipid metabolism such as in renal insufficiency, uncontrolled diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertriglyceridemic) and sepsis.

There is at present no clinical experience of the use of STRUCTOLIPID in children and limited experience in patients with diabetes mellitus or renal failure.

STRUCTOLIPID should be administered simultaneously with carbohydrates to avoid the occurrence of metabolic acidosis.

STRUCTOLIPID may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, Hb) if blood is sampled before fat has been adequately cleared from the bloodstream. Fat is cleared after a fat-free interval of 5-6 hours in most patients.

4.5 Interaction with other medicinal products and other forms of interaction

Some drugs, like insulin, may interfere with the body’s lipase system. However, this kind of interaction seems to have little clinical significance.

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.

Soybean oil has a natural content of vitamin K_1. However, the concentration in STRUCTOLIPID is so low that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

4.6 Pregnancy and lactation

For STRUCTOLIPID no clinical data on exposed pregnancies are available. Structolipid has not been tested in animals for effects on the conceptus beyond the period of organogenesis. Evaluation of animal data has shown reproductive toxicity (*see section 5.3, Preclinical safety data*). The clinical relevance of this data is unknown. STRUCTOLIPID should be used during pregnancy only after special consideration.

No clinical experience of use during breast-feeding is available. Women treated with STRUCTOLIPID should not breast-feed.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and operate machines are to be expected.

4.8 Undesirable effects

Structolipid infusion may cause a rise in body temperature and nausea, furthermore increases in serum-triglycerides and ketone bodies have been reported (incidence>1% in clinical trials).

Reports of adverse events in conjunction with Structolipid infusion are extremely rare and have been predominantly noted during clinical studies.

	Frequency	**Symptoms**
Metabolism and nutrition disorders	Common (>1/100, <1/10)	Hypertriglyceridaemia Ketosis
Nervous system disorders	Very rare (<1/10 000)	Dizziness
Cardiac disorders	Very rare (<1/10 000)	Tachycardia Hypertension
Respiratory, thoracic and mediastinal disorders	Very rare (<1/10 000)	Respiratory distress i.e. respiratory symptoms
Gastrointestinal disorders	Uncommon (>1/1000, <1/100)	Diarrhoea Vomiting
Hepatobiliary disorders	Very rare (<1/10 000)	Transient increase in liver function test
Skin and subcutaneous tissue disorders	Very rare (<1/10 000)	Rash
Musculoskeletal and connective tissue disorders	Uncommon (>1/1000, <1/100)	Back pain
General disorders and administration site conditions	Common (>1/100, <1/10)	Headache Nausea
	Uncommon (>1/1000, <1/100)	Rise in body temperature Shivering

Liver function tests may show increased levels during parenteral nutrition regardless of whether fat is included or not.

Fat overload syndrome

An impaired capacity to eliminate triglycerides may lead to the fat overload syndrome as a result of overdosage. However, this syndrome may appear also during severe hypertriglyceridemia even at the recommended infusion rate, 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 and disorders in various organs and coma. All symptoms are usually reversible if the infusion of the fat emulsion is discontinued.

4.9 Overdose

See *section 4.8, Undesirable effects*, Fat overload syndrome
Severe overdose of fat emulsions containing MCT can, specially if carbohydrates are not administered simultaneously, lead to metabolic acidosis

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: B05BA02

Fat emulsion for intravenous nutrition STRUCTOLIPID is a fat emulsion with particle size and biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, STRUCTOLIPID does not contain cholesterol esters and apolipoproteins.

Another difference compared with chylomicrons is that STRUCTOLIPID is a mixture of long and medium chain fatty acids on the same glycerol molecule.

The emulsion provides both essential fatty acids (long chain fatty acids, LCFA) and energy substrate in the form of both LCFA and medium chain fatty acids (MCFA).

To prevent essential fatty acid deficiency, at least 20% of the nonprotein energy should be supplied in the form of fat emulsions with an adequate amount of linoleic and linolenic acid such as STRUCTOLIPID.

5.2 Pharmacokinetic properties

A study in healthy volunteers has shown that STRUCTOLIPID is eliminated faster than emulsions containing only triglycerides with long chain fatty acids.

Retrospectively analysed data from studies in patients suggest a faster elimination of STRUCTOLIPID than that of emulsions containing only LCT or a physical mixture of LCT and MCT.

Due to the metabolism of STRUCTOLIPID, increased plasma levels of medium chain fatty acids, dicarboxylic acids and 3-hydroxy fatty acids will be generated. Studies in healthy volunteers have shown that the amounts of these metabolites are lower after infusion of STRUCTOLIPID compared with after infusion of equimolar doses of fat in a physical mixture of LCT and MCT. These metabolites were found to be completely eliminated in a blood sample drawn 16 hours after completion of the infusion. Dicarboxylic acids are excreted in the urine.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. The carcinogenic potential of STRUCTOLIPID has not been evaluated.

No teratogenic or embryotoxic potential was evident in rabbits after infusions of STRUCTOLIPID at a dosage of 3 g (TG) /kg/day (0.75 g TG/kg/h) over 4 hours.
At a dosage of 4.5 g TG/kg/day (1.12 g TG/kg/h), a possible embryotoxic effect was evidenced by a slight increase in embryonic/fetal loss. The dosage and infusion rate were
3 and 7 times higher, respectively, than recommended for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified egg phospholipids, Glycerol, Sodium hydroxide, Water for injections.

6.2 Incompatibilities

This medicinal product should not be mixed with other products than those mentioned in *Section 6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal products and other handling of the product* unless full compatibility of Stuctolipid with the product has been demonstrated.

Additives may only be added to STRUCTOLIPID in cases where compatibility has been documented. The compatibility with solutions administered simultaneously via a common port (Y-connector) must be ensured.

6.3 Shelf Life

Shelf-life in the product as packaged for sale
2 years

Shelf-life after first opening the container
The emulsion should be used directly due to the risk of micobiological contamination. Any unused emulsion should be discarded.

Shelf-life after addition or mixing according to directions
See section 6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal products and other handling of the product Stability

6.4 Special precautions for storage

Do not store above 25 ^{o}C. Do not freeze

6.5 Nature and contents of container

Pack sizes:
1 x 250 ml, 10 x 250 ml.
1 x 500 ml, 12 x 500 ml.

Not all pack sizes may be marketed.

The Excel inner bag is the primary container for the STRUCTOLIPID. The overpouch provides protection during storage by contributing barrier properties towards water and oxygen to the STRUCTOLIPID container system. The oxygen absorber will absorb and bind oxygen remaining between the inner bag and overpouch. The integrity indicator (Oxalert™) will react with free oxygen and change from clear to black in case of a damage in the overpouch.

- The Excel inner bag consists of a poly(propylene/ethylene) copolymer, a thermoplastic elastomer and a copolyester.
- The oxygen barrier overpouch consists of polypropylene, polyethylene terephtalate and poly (ethyl vinyl) alcohol.
- The oxygen absorber consists of iron powder in a polymer sachet.

The overpouch, the oxygen absorber and the integrity indicator should be discarded after opening of the overpouch.

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

The integrity indicator (Oxalert) should be inspected before removing the overpouch.
If the indicator is black, oxygen has penetrated the overpouch and the product should be discarded.

COMPATIBILITY

Additives

Only medicinal, nutritional or electrolyte solutions for which compatibility has been documented may be added to STRUCTOLIPID.

Additions should be made aseptically.

The normal daily requirement of water-soluble and fat-soluble vitamins, i.e. one bottle of SOLIVITO N and one ampoule of VITLIPID N ADULT, can be added to STRUCTOLIPID.

Before being added, SOLIVITO N is reconstituted in either 10 ml of sterile water, STRUCTOLIPID or VITLIPID N ADULT.

Mixing in plastic bag, (phthalate-free film)

The plastic bag used for admixing has to be sterile and be made of phthalate-free film.

Mixtures made up with STRUCTOLIPID should be prepared in a controlled and validated aseptic area.

STRUCTOLIPID can be mixed with the amino acid solutions GLAMIN, VAMIN 18 ELECTROLYTE FREE or INTRAFUSIN 22, glucose solutions, trace elements in the form of ADDITRACE, vitamins, i.e. SOLIVITO N and VITLIPID N ADULT, and electrolytes in the amounts indicated below.

ADDITRACE and electrolytes are added to the amino acid solution.

ADDIPHOS or any other inorganic phosphate source should be added to the glucose solution. The amino acid and glucose solutions with the additives are transferred to a plastic bag (phthalate-free film).

Vitamins, i.e. SOLIVITO N and VITLIPID N ADULT can be added to STRUCTOLIPID.

Finally, STRUCTOLIPID with additives is transferred to the plastic bag which is turned with caution until a homogeneous mixture is obtained.

The content of vitamin C in the mixture decreases due to oxidation. Vitamin C deficiency in prolonged intravenous nutrition including SOLIVITO N, has not been reported, however.
Limits for mixture components.

Structolipid	250-750 ml
Glamin/Vamin 18 Electrolyte Free/	
Intrafusin 22	500-1000 ml
Glucose10% /	1000 ml
Glucose 20% /	1000-1500 ml
Glucose 30% /	500-1000 ml
Glucose 40% /	500 ml
Glucose 50%	500*-750**ml
Additrace	0-10 ml
Vitlipid N Adult	0-10 ml
Solivito N	0-1 vial

Electrolyte limits in ready-mixed bags

mmol/1000 ml	
Sodium	0-150
Potassium	0-150
Calcium	1-5
Magnesium	0.5-5
Phosphate ***	0-15

* For stability reasons, 500 ml glucose 50% can only be mixed with 500-750 ml Structolipid when Glamin or Vamin 18 Electrolyte Free is used.

** For stability reasons, 750 ml glucose 50% can only be mixed with

1000 ml Glamin, Vamin 18 Electrolyte Free or Intrafusin 15%
500-750 ml Structolipid.

*** Includes the amount from Structolipid.

STABILITY

Without additives

After opening the container, the emulsion should be used directly due to the risk of microbiological contamination. The left-over contents of an opened bag should be discarded and not saved for later use.

Additives

When additions are made to STRUCTOLIPID, the infusion should be used directly after preparation due to the risk of microbiological contamination.

The left-over contents of an opened bag should be discarded and not saved for later use.
Mixing in plastic bag (phthalate-free film).

The physical in-use stability has been demonstrated for 72 hours in a refrigerator (2-8°C) followed by an infusion period of up to 24 hours. From a microbiological point of view, the product should be used immediately after supplementation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should normally not be longer than 24 h at 2-8°C unless additions have taken place in controlled and validated aseptic conditions.

If the admixtures have been stored after mixing a cream layer can be presented. Turn gently until a homogenous mixture is obtained before use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0566/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 28 February 2007

10 DATE OF REVISION OF THE TEXT

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