Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

StructoKabiven emulsion for infusion, Biofine Container.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

StructoKabiven consists of a three chamber bag system. Each bag contains the following partial volumes depending on the pack size.

	986 ml	**1477 ml**	**1970 ml**	**Per 1000 ml**
Amino acid solution with electrolytes	500 ml	750 ml	1000 ml	508 ml
Glucose 42%	298 ml	446 ml	595 ml	302 ml
Fat emulsion	188 ml	281 ml	375 ml	190 ml

This corresponds to the following total compositions:

Active ingredients	**986 ml**	**1477ml**	**1970 ml**	**Per 1000 ml**
Purified structured triglyceride	38.00 g	56.00 g	75.00 g	38.50 g
Glucose (as monohydrate)	125.00 g	187.00 g	250.00 g	127.00 g
Alanine	7.00 g	10.50 g	14.00 g	7.10 g
Arginine	6.00 g	9.00 g	12.00 g	6.10 g
Glycine	5.50 g	8.20 g	11.00 g	5.60 g
Histidine	1.50 g	2.20 g	3.00 g	1.50 g
Isoleucine	2.50 g	3.80 g	5.00 g	2.50 g
Leucine	3.70 g	5.60 g	7.40 g	3.80 g
Lysine (as acetate)	3.30 g	5.00 g	6.60 g	3.40 g
Methionine	2.20 g	3.20 g	4.30 g	2.20 g
Phenylalanine	2.60 g	3.80 g	5.10 g	2.60 g
Proline	5.60 g	8.40 g	11.20 g	5.70 g
Serine	3.20 g	4.90 g	6.50 g	3.30 g
Taurine	0.50 g	0.75 g	1.00 g	0.50 g
Threonine	2.20 g	3.30 g	4.40 g	2.20 g
Tryptophan	1.00 g	1.50 g	2.00 g	1.00 g
Tyrosine	0.20 g	0.30 g	0.40 g	0.20 g
Valine	3.10 g	4.60 g	6.20 g	3.10 g
Calcium chloride (as Calcium chloride dihydrate)	0.28 g	0.42 g	0.56 g	0.28 g
Sodium glycerophosphate (as hydrate)	2.10 g	3.10 g	4.20 g	2.13 g
Magnesium sulphate (as Magnesium sulphate heptahydrate)	0.60 g	0.90 g	1.20 g	0.61 g
Potassium chloride	2.20 g	3.40 g	4.50 g	2.30 g
Sodium acetate (as Sodium acetate trihydrate)	1.70 g	2.60 g	3.40 g	1.70 g
Zinc sulphate (as Zinc sulphate heptahydrate)	0.0065 g	0.0097 g	0.013 g	0.0066 g

Corresponding to:

	986 ml		1477 ml		1970 ml		Per 1000ml	
o Amino acids	50	g	75	g	100	g	51	g
o Nitrogen	8	g	12	g	16	g	8	g
o Fat	38	g	56	g	75	g	38	g
o Carbohydrates								
- Glucose (anhydrous)	125	g	187	g	250	g	127	g
o Energy content								
- total approx.	1100	kcal	1600	kcal	2100	kcal		
- non protein approx.	870	kcal	1300	kcal	1735	kcal		
Electrolytes								
- sodium	40	mmol	60	mmol	80	mmol	41	mmol
- potassium	30	mmol	45	mmol	60	mmol	30	mmol
- magnesium	5	mmol	7.5	mmol	10	mmol	5	mmol
- calcium	2.5	mmol	3.8	mmol	5.0	mmol	2.5	mmol
- phosphate[1]	12	mmol	19	mmol	25	mmol	12.5	mmol
- zinc	0.04	mmol	0.06	mmol	0.08	mmol	0.04	mmol
- sulphate	5.0	mmol	7.5	mmol	10	mmol	5.1	mmol
- chloride	35	mmol	52	mmol	70	mmol	36	mmol
- acetate	104	mmol	157	mmol	209	mmol	106	mmol

- o Osmolality approx. 1800 mosmol/kg water
- o Osmolarity approx. 1500 mosmol/l
- o pH approx. 5.6

[1] Contribution from both the fat emulsion and the amino acid solution.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Emulsion for infusion.

Glucose and amino acid solutions are clear and colourless to slightly yellow and free from particles. The fat emulsion is white and homogenous.

- o Osmolality approx. 1800 mosmol/kg water
- o Osmolarity approx. 1500 mosmol/l
- o pH approx. 5.6

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Parenteral nutrition for adult patients when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

The ability to eliminate fat and metabolise glucose should govern the dosage and infusion rate. *See section 4.4 , Special warning and special precautions for use.*

Dosage
The dose should be individualised with regard to the patients clinical condition, body weight and nutritional requirements.
StructoKabiven is not recommended to use in children, *see section 4.4, Special warnings and special precautions for use.*

The nitrogen requirements for maintenance of body protein mass depend on the patient's condition (e.g. nutritional state and degree of catabolic stress). The requirements are 0.10-0.15 g nitrogen/kg body weight/day in the normal nutritional state or in conditions with mild metabolic stress. In patients with moderate to high metabolic stress with or without malnutrition, the requirements are in the range of 0.15-0.25 g nitrogen/kg body weight/day (0.9-1.6 g amino acid/kg body weight/day).

The dosage range of 0.10-0.25 g nitrogen/kg body weight/day (0.6-1.6 g amino acid/kg body weight/day) covers the need of the majority of the patients and corresponds to 13 ml – 31 ml StructoKabiven/kg body weight/day. For a 70-kg-patient this is equivalent to 910 ml – 2000 ml StructoKabiven per day. The corresponding commonly accepted requirements are 2.0-6.0 g/kg body weight/day for glucose and 1.0-2.0 g/kg body weight/day for fat.

The total energy requirement depends on the patient's clinical condition and is most often between 20-30 kcal/kg body weight/day. In obese patients the dose should be based on the estimated ideal weight.

StructoKabiven is available in three pack sizes intended for patients with high, moderately increased or basal nutritional requirements. To provide total parenteral nutrition, trace elements and vitamins should be added to StructoKabiven.

Infusion rate
The maximum infusion rate for glucose is 0.25 g/kg/h, for amino acid 0.1 g/kg/h, and for fat 0.15 g/kg/h.

The infusion rate should not exceed 2.0 ml/kg body weight/hour (corresponding to 0.25 g glucose, 0.10 g amino acid, and 0.08 g fat/kg body weight/hour). The recommended infusion period is 14-24 hours.

Maximum daily dose
The maximum daily dose varies with the clinical condition of the patient and may even change from day to day. The recommended maximum daily dose is 30 ml/kg/day.

Method and duration of administration
Intravenous use, infusion into a central vein.

4.3 Contraindications

Hypersensitivity to egg-, soya or peanut protein or to any of the active substances or excipients.
Severe hyperlipaemia
Severe liver insufficiency
Severe blood coagulation disorders
Congenital errors of amino acid metabolism
Severe renal insufficiency without access to hemofiltration or dialysis
Acute shock
Hyperglycemia, which requires more than 6 units insulin/h
Pathologically elevated serum levels of any of the included electrolytes.
General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, and decompensated cardiac insufficiency
Hypotonic dehydration
Hemophagocytotic syndrome
Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, metabolic acidosis, severe sepsis and hyperosmolar coma)

4.4 Special warnings and precautions for use

The ability to eliminate fat should be monitored. It is recommended that this is done by measuring serum triglycerides after a fat-free period of 5-6 hours.
The serum concentration of triglycerides should not exceed 4 mmol/l when starting the infusion.

To avoid risks associated with too rapid infusion rates, it is recommended to use a continuous and well-controlled infusion, if possible by using a volumetric pump.

Disturbances of the electrolyte and fluid balance (e.g. abnormally high or low serum levels of the electrolytes) should be corrected before starting the infusion.

StructoKabiven should be given with caution to patients with a tendency towards electrolyte retention.
Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be stopped.
Since an increased risk of infection is associated with the use of any central vein, strict aseptic precautions should be taken to avoid any contamination during catheter insertion and manipulation.

StructoKabiven should be given with caution in conditions of impaired lipid metabolism. Hypertriglyceridemia can occur in renal insufficiency, pancreatitis, impaired liver function, hypothyroidism and sepsis. If StructoKabiven is given to patients with these conditions, close monitoring of serum triglycerides is mandatory.

Serum glucose, electrolytes and osmolarity as well as fluid balance, acid-base status and liver enzyme tests (alkaline phosphatase, ALT, AST) should be monitored.

Blood cell count and coagulation should be monitored when fat is given for a longer period.

In patients with renal insufficiency, the phosphate and potassium intake should be carefully controlled to prevent hyperphosphatemia and hyperkalaemia.

The amount of individual electrolytes to be added is governed by the clinical condition of the patient and by frequent monitoring of serum levels.

Parenteral nutrition should be given with caution in lactic acidosis, insufficient cellular oxygen supply and increased serum osmolarity.

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

The fat content of StructoKabiven may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, hemoglobin) 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.

This medicinal product contains soya-bean oil (derived from seeds of Glycine soya, Glycine max and Glycine hispida) and egg phospholipids, which may rarely cause severe allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut.

Intravenous infusion of amino acids is accompanied by increased urinary excretion of the trace elements, in particular copper and zinc. This should be considered in the dosing of trace elements, especially during long-term intravenous nutrition.

In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary oedema and congestive heart failure as well as a decrease in the serum concentration of potassium, phosphorus, magnesium and water soluble vitamins. These changes can occur within 24 to 48 hours, therefore careful and slow initiation of parenteral nutrition is recommended together with close monitoring and appropriate adjustments of fluid, electrolytes, minerals and vitamins.

StructoKabiven should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

In patients with hyperglycaemia, administration of exogenous insulin might be necessary.

Due to composition of the amino acid solution StructoKabiven is not suitable for the use in new-borns or infants below 2 years of age. There is at present no clinical experience of the use of StructoKabiven in children (age 2 years to 11 years).

4.5 Interaction with other medicinal products and other forms of interaction

Some medicinal products, like insulin, may interfere with the body's lipase system. This kind of interaction seems, however, to be of limited clinical importance.

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.

Purified structured triglycerides contains soya-bean oil which has a natural content of vitamin K_1. However, the concentration in StructoKabiven is so low that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

	Uncommon ≥1/1,000, <1/100	*Rare ≥1/10,000, <1/1,000*	*Very Rare <1/10,000*
Cardiac disorders		Tachycardia	
Respiratory, thoracic and mediastinal disorders			Respiratory symtoms
Gastrointestinal disorders			Diarrhoea
Metabolism and nutrition disorders	Elevated plasma levels of liver enzymes, ketone bodies and triglycerides		
Vascular disorders		Hypertension	
General disorders and administration site conditions	Nausea, headache, rise in body temperature		Rash, back pain, dizziness

Fat overload syndrome
An impaired capacity to eliminate Structolipid may lead to the fat overload syndrome as a result of overdosage, but also at recommended rates of infusion 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 hyperlipaemia, fever, fat infiltration, hepatomegaly, splenomegaly, anaemia, leucopenia, thrombocytopenia, blood coagulation disorders and coma. All symptoms are usually reversible if the infusion is discontinued.

Excess of amino acid infusion
As with other amino acid solutions, the Aminoven content in StructoKabiven may cause undesirable effects when the recommended infusion rate is exceeded. These effects are nausea, vomiting, shivering and sweating. Amino acid infusion may also cause a rise in body temperature. With an impaired renal function, increased levels of nitrogen containing products (e.g. creatinine, urea) may occur.

Excess of glucose infusion
If the glucose clearance capacity of the patient is exceeded, hyperglycemia will develop.

4.9 Overdose

(*See section 4.8, Undesirable effects-"Fat overload syndrome", "Excess of amino acid infusion" and "Excess of glucose infusion").*

If symptoms of overdose of fat or amino acids occur, the infusion should be slowed down or discontinued. There is no specific antidote for overdose. Emergency procedures should be general supportive measures, with particular attention to respiratory and cardiovascular systems. Close biochemical monitoring would be essential and specific abnormalities treated appropriately.

If hyperglycemia occurs, it should be treated according to the clinical situation either by appropriate insulin administration and/or adjustment of the infusion rate.

Additionally, overdose might cause fluid overload, electrolyte imbalances and hyperosmolality.

In some rare serious cases, haemodialysis, haemofiltration or haemo-diafiltration may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition.
ATC code: B05BA10

Fat emulsion
Structolipid, the fat emulsion used in StructoKabiven, provides essential and non-essential long-chain fatty acids and medium chain fatty acids which are important for energy metabolism and the structural integrity of cell membranes.

Structolipid in the recommended dosage does not cause haemodynamic changes. No clinically significant changes in pulmonary function have been described when Structolipid is used properly. The transient increase in liver enzymes seen in some patients on parenteral nutrition is reversible and disappears when parenteral nutrition is discontinued. Similar changes are also seen in parenteral nutrition without fat emulsions.

Amino acids and electrolytes
The amino acids, constituents of protein in ordinary food, are utilised for tissue protein synthesis and any surplus is channelled to a number of metabolic pathways. Studies have shown a thermogenic effect of amino acid infusion.

Glucose
Glucose should have no pharmacodynamic effects apart from contributing to maintain or replete the normal nutritional status.

5.2 Pharmacokinetic properties

Fat emulsion
Structolipid has biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, Structolipid does not contain cholesterol esters or apolipoproteins, while its phospholipid content is significantly higher.

Structolipid is eliminated from the circulation via a pathway similar to that of endogenous chylomicrons. The exogenous fat particle is primarily hydrolysed in the circulation and taken up by LDL receptors peripherally and by the liver. The elimination rate is determined by the composition of the fat particles, the nutritional status, the disease and the rate of infusion. In healthy volunteers, the maximum clearance rate of Structolipid after fasting overnight is faster than emulsions containing only triglycerides with long chain fatty acid.
Both the elimination and the oxidation rates are dependent on the patient's clinical condition; elimination is faster and utilisation is increased in postoperative patients and in trauma, while patients with renal failure and hypertriglyceridaemia show lower utilisation of exogenous fat emulsions.

Amino acids and electrolytes
The principal pharmacokinetic properties of the infused amino acids and electrolytes are essentially the same as for amino acids and electrolytes supplied by ordinary food. However, the amino acids of dietary protein first enter the portal vein and then the systemic circulation, while intravenously infused amino acids reach the systemic circulation directly.

Glucose
The pharmacokinetic properties of infused glucose are essentially the same as those of glucose supplied by ordinary food.

5.3 Preclinical safety data

Preclinical safety studies with StructoKabiven have not been performed. However, preclinical data for Structolipid as well as amino acids and glucose solutions of various compositions and concentrations 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 triglycerides (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 (pH adjuster)
Acetic acid, glacial (pH adjuster)
Hydrochloric acid 1 M (pH adjuster)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *(see section6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product).*

6.3 Shelf life

Shelf-life of the product as packaged for sale
2 years.

Shelf-life after mixing
Chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 36 hours at 25°C. From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

Shelf-life after mixing with additives
Chemical and physical in-use stability, *see section 6.6, Special precautions for disposal and other handling.*
From a microbiological point of view, the product should be used immediately when additions have been made. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze. Store in overpouch.

For storage conditions of the reconstituted medicinal product, *(see section 6.3, Shelf life and section 6.6, Instructions for use and handling and disposal).*

6.5 Nature and contents of container

The container consists of a multichamber inner bag and an overpouch. The inner bag is separated into three chambers by peelable seals. An oxygen absorber is placed between the inner bag and the overpouch.

The inner bag is made of a multilayer polymer film, Biofine.

The Biofine inner bag film consists of poly(propylene-co-ethylene), synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) and synthetic rubber poly(styrene-block-isoprene) (SIS). The infusion and additive ports are made of polypropylene and synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) equipped with synthetic polyisoprene (latex-free) stoppers. The blind port, which is only used during manufacturing, is made of polypropylene equipped with a synthetic polyisoprene (latex-free) stopper.

Pack sizes:

1 x 986 ml, 4 x 986 ml
1 x1477 ml, 4 x 1477 ml
1 x 1970 ml, 2 x 1970 ml (Excel), 4 x 1970 (Biofine)

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

Do not use if package is damaged. Use only if the amino acid and glucose solutions are clear and colourless or slightly yellow and the fat emulsion is white and homogenous. The contents of the three separate chambers have to be mixed before use.

After separation of the peelable seals the bag should be inverted on a number of occasions to ensure a homogenous mixture which does not show any evidence of phase separation.

Storage after mixing with additives
After opening the peelable seals and mixing of the three solutions, additions can be made via the additive port.

Compatibility
Only medicinal or nutrition solutions for which compatibility has been documented may be added to StructoKabiven. Compatibility for different additives and the storage time of the different admixtures will be available upon request.

Addition should be made aseptically.

For single use only. Any mixture remaining after infusion must be discarded.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited
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8 MARKETING AUTHORISATION NUMBER

PA 0566/033/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 July 2006

Date of last renewal: 10 January 2008

10 DATE OF REVISION OF THE TEXT

February 2008