SUMMARY OF THE PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

SmofKabiven emulsion for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

SmofKabiven consists of a three chamber bag system. Each bag contains the following partial volumes depending on the five pack sizes.

	493 ml	**986 ml**	**1477 ml**	**1970 ml**	**2463 ml**	**Per 1000 ml**
Amino acid solution with electrolytes	250 ml	500 ml	750 ml	1000 ml	1250 ml	508 ml
Glucose 42%	149 ml	298 ml	446 ml	595 ml	744 ml	302 ml
Lipid emulsion	94 ml	188 ml	281 ml	375 ml	469 ml	190 ml

This corresponds to the following total compositions:

Active ingredients	**493 ml**	**986 ml**	**1477ml**	**1970 ml**	**2463 ml**	**Per 1000 ml**
Alanine	3.5 g	7.0 g	10.5 g	14.0 g	17.5 g	7.1 g
Arginine	3.0 g	6.0 g	9.0 g	12.0 g	15.0 g	6.1 g
Glycine	2.8 g	5.5 g	8.2 g	11.0 g	13.8 g	5.6 g
Histidine	0.8 g	1.5 g	2.2 g	3.0 g	3.7 g	1.5 g
Isoleucine	1.3 g	2.5 g	3.8 g	5.0 g	6.2 g	2.5 g
Leucine	1.9 g	3.7 g	5.6 g	7.4 g	9.4 g	3.8 g
Lysine (as acetate)	1.7 g	3.3 g	5.0 g	6.6 g	8.4 g	3.4 g
Methionine	1.1 g	2.2 g	3.2 g	4.3 g	5.4 g	2.2 g
Phenylalanine	1.3 g	2.6 g	3.8 g	5.1 g	6.4 g	2.6 g
Proline	2.8 g	5.6 g	8.4 g	11.2 g	14.0 g	5.7 g
Serine	1.6 g	3.2 g	4.9 g	6.5 g	8.1 g	3.3 g
Taurine	0.25 g	0.50 g	0.75 g	1.0 g	1.2 g	0.5 g
Threonine	1.1 g	2.2 g	3.3 g	4.4 g	5.4 g	2.2 g
Tryptophan	0.5 g	1.0 g	1.5 g	2.0 g	2.5 g	1.0 g
Tyrosine	0.10 g	0.20 g	0.30 g	0.40 g	0.49 g	0.20 g
Valine	1.6 g	3.1 g	4.6 g	6.2 g	7.6 g	3.1 g
Calcium chloride (as dihydrate)	0.14 g	0.28 g	0.42 g	0.56 g	0.69 g	0.28 g
Sodium glycerophosphate (as hydrate)	1.1 g	2.1 g	3.1 g	4.2 g	5.2 g	2.1 g
Magnesium sulphate (as heptahydrate)	0.30 g	0.60 g	0.90 g	1.2 g	1.5 g	0.61 g
Potassium chloride	1.1 g	2.2 g	3.4 g	4.5 g	5.7 g	2.3 g
Sodium acetate (as trihydrate)	0.9 g	1.7 g	2.6 g	3.4 g	4.2 g	1.7 g
Zinc sulphate (as heptahydrate)	0.0033 g	0.0065 g	0.0097 g	0.013 g	0.016 g	0.0066 g
Glucose (as monohydrate)	63 g	125 g	187 g	250 g	313 g	127 g

Soya-bean oil, refined	5.6 g	11.3 g	16.9 g	22.5 g	28.1 g	11.4 g
Medium-chain triglycerides	5.6 g	11.3 g	16.9 g	22.5 g	28.1 g	11.4 g
Olive oil, refined	4.7 g	9.4 g	14.1 g	18.8 g	23.4 g	9.5 g
Fish oil, rich in omega-3-acids	2.8 g	5.6 g	8.4 g	11.3 g	14.0 g	5.7 g

Corresponding to

	493 ml	**986 ml**	**1477 ml**	**1970 ml**	**2463 ml**	**Per 1000 ml**
• Amino acids	25 g	50 g	75 g	100 g	125 g	51 g
• Nitrogen	4 g	8 g	12 g	16 g	20 g	8 g
• Electrolytes						
- sodium	20 mmol	40 mmol	60 mmol	80 mmol	100 mmol	41 mmol
- potassium	15 mmol	30 mmol	45 mmol	60 mmol	74 mmol	30 mmol
- magnesium	2.5 mmol	5.0 mmol	7.5 mmol	10 mmol	12 mmol	5.1 mmol
- calcium	1.3 mmol	2.5 mmol	3.8 mmol	5.0 mmol	6.2 mmol	2.5 mmol
- phosphate[1]	6 mmol	12 mmol	19 mmol	25 mmol	31 mmol	13 mmol
- zinc	0.02 mmol	0.04 mmol	0.06 mmol	0.08 mmol	0.1 mmol	0.04 mmol
- sulphate	2.5 mmol	5.0 mmol	7.5 mmol	10 mmol	13 mmol	5.1 mmol
- chloride	18 mmol	35 mmol	52 mmol	70 mmol	89 mmol	36 mmol
- acetate	52 mmol	104 mmol	157 mmol	209 mmol	261 mmol	106 mmol
• Carbohydrates						
- Glucose (anhydrous)	63 g	125 g	187 g	250 g	313 g	127 g
• Lipids	19 g	38 g	56 g	75 g	94 g	38 g
• Energy content						
- total (approx.)	550 kcal 2.3 MJ	1100 kcal 4.6 MJ	1600 kcal 6.7 MJ	2200 kcal 9.2 MJ	2700 kcal 11.3 MJ	
- non protein (approx.)	450 kcal 1.9 MJ	900 kcal 3.8 MJ	1300 kcal 5.4 MJ	1800 kcal 7.5 MJ	2200 kcal 9.2 MJ	

- Osmolality approx. 1800 mosmol/kg water
- Osmolarity approx. 1500 mosmol/l
- pH (after mixing) approx. 5.6

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

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Emulsion for infusion.

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

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 appearance of the product after mixing the 3 chambers is a white emulsion.

The patient's ability to eliminate fat and metabolise nitrogen and glucose, and the nutritional requirements should govern the dosage and infusion rate, see section 4.4.

The dose should be individualised with regard to the patient's clinical condition and body weight (bw).
The nitrogen requirements for maintenance of body protein mass depend on the patient's condition (e.g. nutritional state and degree of catabolic stress or anabolism).

The requirements are 0.10-0.15 g nitrogen/kg bw/day (0.6-0.9 g amino acids/kg bw/day) in the normal nutritional state or in conditions with mild catabolic 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 bw/day (0.9-1.6 g amino acids/kg bw/day). In some very special conditions (e.g. burns or marked anabolism) the nitrogen need may be even higher.

Dosage
The dosage range of 13 ml – 31 ml SmofKabiven/kg bw/day corresponds to 0.10-0.25 g nitrogen/kg bw/day (0.6-1.6 g amino acids/kg bw/day) and 14-35 kcal/kg bw/day of total energy (12-27 kcal/kg bw/day of non-protein energy). This covers the need of the majority of the patients. In obese patients the dose should be based on the estimated ideal weight.

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

The infusion rate should not exceed 2.0 ml/kg bw/h (corresponding to 0.25 g glucose, 0.10 g amino acids, and 0.08 g fat/kg bw/h). 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 35 ml/kg bw/day.

The recommended maximum daily dose of 35 ml/kg bw/day will provide 0.28 g nitrogen/kg bw/day (corresponding to 1.8 g amino acids/kg bw/day), 4.5 g glucose/kg bw/day, 1.33 g fat/kg bw/day and a total energy of 39 kcal/kg bw/day (corresponding to 31 kcal/kg bw/day of non-protein energy).

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

The five different package sizes of SmofKabiven are intended for patients with high, moderately increased or basal nutritional requirements. To provide total parenteral nutrition, trace elements, vitamins and possibly electrolytes (taking into account the electrolytes already present in SmofKabiven) should be added to SmofKabiven according to the patients need.

Pediatric patients
SmofKabiven is not recommended for use in children, see section 4.4.

4.3 Contraindications

- Hypersensitivity to fish-, egg, soya- or peanut protein or to any of the active substances or excipients
- Severe hyperlipidemia

- Severe liver insufficiency
- Severe blood coagulation disorders
- Congenital errors of amino acid metabolism
- Severe renal insufficiency without access to hemofiltration or dialysis
- Acute shock
- Uncontrolled hyperglycaemia
- Pathologically elevated serum levels of any of the included electrolytes
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, and decompensated cardiac insufficiency
- Hemophagocytotic syndrome
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis, severe sepsis, hypotonic dehydration and hyperosmolar coma)

4.4 Special warnings and precautions for use

The capacity to eliminate fat is individual and should therefore be monitored according to the routines of the clinician. This is in general done by checking the triglyceride levels. The concentration of triglycerides in serum should not exceed 4 mmol/l during infusion. An overdose may lead to fat overload syndrome, see section 4.8.

SmofKabiven should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with renal failure, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism and sepsis.

This medicinal product contains soya-bean oil, fish oil and egg phospholipids, which may rarely cause allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut

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.

SmofKabiven 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.

Serum glucose, electrolytes and osmolarity as well as fluid balance, acid-base status and liver enzyme tests 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 SmofKabiven 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.

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. Amounts of zinc administered with SmofKabiven should be taken into account.

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 in this patient group, together with close monitoring and appropriate adjustments of fluid, electrolytes, minerals and vitamins.

SmofKabiven 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 in SmofKabiven it 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 SmofKabiven 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.

Soya-bean oil has a natural content of vitamin K_1. However, the concentration in SmofKabiven 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

There are no data available on exposure of SmofKabiven in pregnant or breast-feeding women. There are no studies available on reproductive toxicity in animals. Parenteral

nutrition may become necessary during pregnancy and lactation. SmofKabiven should only be given to pregnant and breast-feeding women after careful consideration.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

	Common *≥ 1/100, <1/10*	*Uncommon* *≥ 1/1000, <1/100*	*Rare* *≥ 1/10000, <1/1000*
Cardiac disorders			Tachycardia
Respiratory, thoracic and mediastinal disorders			Dyspnoea
Gastrointestinal disorders		Lack of appetite, nausea, vomiting	
Metabolism and nutrition disorders		Elevated plasma levels of liver enzymes	
Vascular disorders			Hypotension, hypertension
General disorders and administration site conditions	Slight increase in body temperature	Chills, dizziness, headache	Hypersensitivity-reactions (e.g. anaphylactic or anaphylactoid reactions, skin rash, urticaria, flush, headache), heat or cold sensation, paleness, cyanosis, pain in the neck, back, bones, chest and loins.

Should these side-effects occur the infusion of SmofKabiven should be stopped or, if necessary, continued at a reduced dosage.

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 illnesses. This syndrome may also appear during severe hypertriglyceridemia, 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 hyperlipemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorder, hemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the lipid emulsion is discontinued.

Excess of amino acid infusion
As with other amino acid solutions, the amino acid content in SmofKabiven 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 metabolites (e.g. creatinine, urea) may occur.

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

4.9 Overdose

See section 4.8 “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 hyperglycaemia 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.

PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Lipid emulsion
The lipid emulsion of SmofKabiven is composed of Smoflipid and has a particle size and biological properties similar to those of endogenous chylomicrons. The constituents of SmofKabiven; soya-bean oil, medium-chain triglycerides, olive oil and fish oil have except for their energy contents, their own pharmacodynamic properties.

Soya-bean oil has a high content of essential fatty acids. The omega-6 fatty acid linoleic acid is the most abundant (approx. 55-60%). Alpha-linolenic acid, an omega-3 fatty acid, constitutes about 8 %. This part of SmofKabiven provides the necessary amount of essential fatty acids.

Medium-chain fatty acids are rapidly oxidised and provide the body with a form of immediately available energy.

Olive oil mainly provides energy in the form of mono-unsaturated fatty acids, which are much less prone to peroxidation than the corresponding amount of poly-unsaturated fatty acids.

Fish oil is characterised by a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is an important structural component of cell membranes, whereas EPA is a precursor of eicosanoids as prostaglandines, thromboxanes and leucotrienes.

Two studies providing home parenteral nutrition in patients in need of long-term nutrition support have been performed. The primary objective in both studies was to show safety. Efficacy was the secondary objective in one of the studies, which was done in paediatric patients. This study was stratified by age groups (1 month - <2 years, and 2 – 11 years respectively). Both studies showed that Smoflipid has the same safety profile as the comparator (Intralipid 20%). Efficacy in the paediatric study was measured by weight gain, height, body mass index, pre-albumin, retinol binding protein and fatty acid profile. There was no difference between the groups in any of the parameters except the fatty acid profile after 4 weeks treatment. The fatty acid profile in the Smoflipid patients revealed an increase in omega-3 fatty acids in plasma lipoproteins and red blood cells phospholipids and hence reflects the composition of the infused lipid emulsion.

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

Lipid emulsion
The individual triglycerides in Smoflipid have different clearance rate but Smoflipid as a mixture is eliminated faster than long chain triglycerides (LCT). Olive oil has the slowest clearance rate of the components (somewhat slower than LCT) and medium chain triglycerides (MCT) the fastest. Fish oil in a mixture with LCT has the same clearance rate as LCT alone.

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 SmofKabiven have not been performed. However, preclinical data for Smoflipid as well as amino acid and glucose solutions of various concentrations and sodium glycerophosphate reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. No teratogenic effects or other embryotoxic injuries could be observed in rabbits with amino acid solutions and are not

to be expected from fat emulsions and sodium glycerophosphate when giving at the recommended doses as substitution therapy.Nutritional products (amino acid solutions, fat emulsions, and sodium glycerophosphate) used in replacement therapy at physiological levels are not expected to be embryotoxic, teratogenic, or to influence reproductive performance or fertility.

In a test on guinea pigs (maximisation test) fish oil emulsion showed moderate dermal sensitisation. A systemic antigenicity test gave no indication of evidence of anaphylactic potential of fish oil.
In a local tolerance study in rabbits with Smoflipid a slight, transient inflammation after intra-arterial, paravenous or subcutaneous administration was observed. After intra-muscular administration a moderate transient inflammation and tissue necrosis were seen in some animals.

PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Purified egg phospholipids
all-*rac*-α-Tocopherol
Sodium hydroxide (pH adjuster)
Sodium oleate
Acetic acid, glacial (pH adjuster)
Hydrochloric acid (pH adjuster)
Water for injections

6.2 Incompatibilities

SmofKabiven may only be mixed with other medicinal products for which compatibility has been documented.

6.3 Shelf life

Shelf life of the medicinal 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
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.

Shelf life after mixing: See section 6.3.

Shelf life after mixing with additives: See section 6.3.

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, alternatively Excel or Biofine. The Excel innerbag film consists of three layers. The inner layer consists of poly (propylene/ethylene) copolymer and styrene/ethylene/butylene/styrene thermoplastic elastomer (SEBS). The middle layer consists of SEBS and the outer layer consists of copolyester-ether. The infusion port is equipped with a polyolefine cap. The additive port is equipped with a synthetic polyisoprene (latex-free) stopper.

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 493 ml, 6 x 493 ml
1 x 986 ml, 4 x 986 ml
1 x 1477 ml, 4 x 1477 ml
1 x 1970 ml, 2 x 1970 ml (Excel), 4 x 1970 ml (Biofine)
1 x 2463 ml, 2 x 2463 ml (Excel), 3 x 2463 ml (Biofine)

Not all pack sizes may be marketed.

6.6 Special precaution for disposal

Instructions for use
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 lipid emulsion is white and homogenous. The contents of the three separate chambers have to be mixed before use, and before any additions are made via the additive port.

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.

Compatibility
Only medicinal or nutrition solutions for which compatibility has been documented may be added to SmofKabiven. 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

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

June 21, 2007

10. DATE OF REVISION OF THE TEXT

May 02, 2012