PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

SmofKabiven®
Amino acids with electrolytes, dextrose and lipid injectable emulsion
5.1% & 0.7% / 12.7% / 3.8%; w/v

SmofKabiven® extra Nitrogen
Amino acids with electrolytes, dextrose and lipid injectable emulsion
6.5% & 0.7% / 8.5% / 2.9%; w/v

Emulsions for Intravenous Nutrition

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION

SmofKabiven®

Amino acids with electrolytes, dextrose and lipid injectable emulsion
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SmofKabiven® extra Nitrogen
Amino acids with electrolytes, dextrose and lipid injectable emulsion
6.5% & 0.7% / 8.5% / 2.9%; w/v

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-Medicinal Ingredients
Intravenous	Injectable emulsions **SmofKabiven** [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] **SmofKabiven extra Nitrogen** [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v]	Purified egg phospholipids All-*rac*-α-tocopherol *For a complete listing, see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] and **SmofKabiven extra Nitrogen** [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v] are indicated for intravenous infusion into a central vein as parenteral nutrition for adult patients when oral or enteral nutrition is impossible, insufficient or contraindicated.

SmofKabiven and SmofKabiven extra Nitrogen are three-component products. Each component is located in a separate chamber. Before use, the seals between the chambers must be broken to mix the components.

Geriatrics:
SmofKabiven and SmofKabiven extra Nitrogen can be used in adults including geriatrics (see WARNINGS AND PRECAUTIONS section).

CONTRAINDICATIONS

SmofKabiven and SmofKabiven extra Nitrogen are contraindicated in patients with:

- Hypersensitivity to fish-, egg-, soybean- or peanut protein or to any of the active ingredients 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 hyperglycemia
- Pathologically elevated serum levels of any of the included electrolytes
- General contraindications to infusion therapy: acute pulmonary edema, hyperhydration, and decompensated cardiac insufficiency
- Hemophagocytic 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)

WARNINGS AND PRECAUTIONS

General

The infusion must be stopped immediately if any signs or symptoms of allergic reactions (such as fever, shivering, sweating, headache, skin rashes, or dyspnea) develop.

SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] and SmofKabiven extra Nitrogen [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v] should be infused 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.

To avoid risks associated with too rapid delivery, it is recommended to use a continuous and well-controlled infusion, if possible 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 of SmofKabiven and SmofKabiven extra Nitrogen.

SmofKabiven and SmofKabiven extra Nitrogen should be given with caution to patients prone to retaining electrolytes. Special monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be stopped.

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

Parenteral nutrition should be given with caution in metabolic acidosis, cellular hypoxia and increased serum osmolarity.

Parenteral nutrition infusion may be 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 parenteral nutrition. Amounts of zinc present in SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] and SmofKabiven extra Nitrogen [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v] should be taken into account.

In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary edema and congestive heart failure as well as a decrease in the serum concentration of potassium, phosphate, 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 and SmofKabiven extra Nitrogen must not be given simultaneously with transfusion blood in the same Y-on-site infusion set due to the risk of pseudoagglutination.

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.

Fat overload syndrome is a rare condition that has been reported with intravenous lipid formulations. A reduced or limited ability to metabolize the lipid contained in SmofKabiven and SmofKabiven extra Nitrogen accompanied by prolonged plasma clearance may result in a syndrome characterized by a sudden deterioration in the patient's condition accompanied by fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g. coma).

The cause of the fat overload syndrome is unclear. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped. Although it has been most frequently observed when the recommended lipid dosage was exceeded, cases have also been described where the lipid formulation was administered according to instructions.

Cardiovascular

Fluid status should be closely monitored in patients with pulmonary edema or heart failure.

Endocrine and Metabolism

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

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

Hematologic

High levels of lipids in plasma may interfere with some laboratory blood tests, e.g. hemoglobin.

Immune

This intravenous emulsion contains soybean oil, fish oil and egg phospholipids which may rarely cause allergic reactions. Allergic cross reaction has been observed between soybean and peanut oil.

If a hypersensitivity reaction occurs (signs or symptoms of anaphylactic reaction such as fever, shivering, sweating, headache, skin rash, or dyspnea) infusion of the emulsion must be stopped immediately and the appropriate treatment and supportive measures should be undertaken until the conditions have been resolved.

Renal

Use with caution in patients with renal insufficiency. Intake of electrolytes such as phosphate and potassium should be carefully controlled to prevent e.g. hyperphosphatemia and hyperkalemia.

Fluid and electrolyte status should be closely monitored in these patients.

Special Populations

Pregnant Women:
There are no data available on exposure of SmofKabiven and SmofKabiven extra Nitrogen in pregnant women. There are no studies available on reproductive toxicity in animals. Parenteral nutrition may become necessary during pregnancy. SmofKabiven and SmofKabiven extra Nitrogen should only be given to pregnant women after physicians have carefully considered the potential risks and benefits.

Nursing Women:
There are no data available on exposure of SmofKabiven and SmofKabiven extra Nitrogen in breast-feeding women. Parenteral nutrition may become necessary during lactation. SmofKabiven and SmofKabiven extra Nitrogen should only be given to breast-feeding women after physicians have carefully considered the potential risks and benefits.

Pediatrics:
No studies have been performed in the pediatric population.

Geriatrics:
Metabolism of SmofKabiven and SmofKabiven extra Nitrogen does not appear to be affected by advanced age.

Monitoring and Laboratory Tests

Fluid and electrolyte balance, serum osmolarity, serum triglycerides, acid/base balance, blood glucose (dextrose), liver and kidney function, blood count, including platelets, and coagulation parameters should be monitored throughout treatment. Daily monitoring is recommended during initiation of parenteral nutrition and until the patient and laboratory measurements are stable, followed by regular monitoring as required. Blood cell count and coagulation should be monitored when lipids are given for an extended period.

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

Individual capacity to eliminate lipids should be monitored according to standard practice. This is generally done by checking serum triglyceride levels which should not exceed 4 mmol/L during infusion. An overdose may lead to fat overload syndrome, see ADVERSE REACTIONS.

The lipid content of SmofKabiven and SmofKabiven extra Nitrogen may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, hemoglobin) if blood is sampled before lipids have been adequately cleared from the bloodstream. Lipids are cleared after a lipid-free interval of 5 to 6 hours in most patients.

ADVERSE REACTIONS

Adverse Drug Reactions Overview

See WARNINGS AND PRECAUTIONS.

Clinical Trial Adverse Drug Reaction

SmofKabiven
Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful to identify drug-related adverse events and approximate rates. An overview of the studies mentioned in this section is given in Table 12, section Clinical Trials.

The treatment emergent adverse events (TEAEs) classified as “at least possibly related” in the studies 03-3CB7-001 and 03-3CB8-001 with SmofKabiven, are presented in Table 1.

Table 1 - Drug-related TEAEs occurring in studies 03-3CB7-001 and 03-3CB8-001

Drug-related TEAEs by MedDRA preferred term, n (%) of patients	SmofKabiven pooled (N=53)	Comparator product pooled (N=52)
Number of patients with at least 1 TEAE	**17 (32.1)**	**13 (25.0)**
Vomiting	7 (13.2)	2 (3.8)
Nausea	5 (9.4)	7 (13.5)
Flatulence	4 (7.5)	1 (1.9)
Edema	1 (1.9)	-
Hyperglycemia	1 (1.9)	-
Hypertension	1 (1.9)	-
Thrombophlebitis	1 (1.9)	1 (1.9)
Abdominal pain	-	1 (1.9)
Anemia	-	1 (1.9)

Sorted by frequency in SmofKabiven pooled group.

SmofKabiven and SMOFlipid

Adverse reactions from 7 studies with SmofKabiven and SMOFlipid, the lipid emulsion component of SmofKabiven that contains 6% soybean oil / 6% medium chain triglycerides / 5% olive oil/ 3% fish oil (w/v), in adults are shown in Table 2.

Table 2 - Summary of Treatment-Emergent Adverse Drug Reactions in SmofKabiven and SMOFlipid Studies

System organ class Adverse event (preferred term)	SmofKabiven or SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Gastrointestinal disorders	**23 (7.3)**	**18 (5.7)**
Nausea	13 (4.1)	13 (4.1)
Vomiting	13 (4.1)	6 (1.9)
Flatulence	4 (1.3)	1 (0.3)
Abdominal Pain	1 (0.3)	1 (0.3)
Investigations	**10 (3.2)**	**10 (3.2)**
Blood triglycerides increased	6 (1.9)	4 (1.3)
Liver function test abnormal	2 (0.6)	3 (1.0)
Gamma-glutamyltransferase increased	1 (0.3)	3 (1.0)
Blood alkaline phosphatase increased	1 (0.3)	2 (0.6)
Blood pressure increased	1 (0.3)	0
Heart rate increased	1 (0.3)	0
Hepatic enzyme increased	0	1 (0.3)
Glucosuria	1 (0.3)	0
Metabolism and nutrition disorders	**8 (2.5)**	**6 (1.9)**
Hyperglycemia	5 (1.6)	3 (1.0)
Hypertriglyceridemia	3 (0.9)	3 (1.0)
Hyperchloremia	1 (0.3)	0
Hypernatremia	1 (0.3)	0
Metabolic acidosis	0	1 (0.3)
Hepatobiliary disorders	**6 (1.9)**	**8 (2.5)**
Hyperbilirubinemia	4 (1.3)	5 (1.6)
Cholestasis	2 (0.6)	2 (0.6)
Cytolytic hepatitis	2 (0.6)	2 (0.6)

Table 2 - Summary of Treatment-Emergent Adverse Drug Reactions in SmofKabiven and SMOFlipid Studies (continued)

System organ class Adverse event (preferred term)	SmofKabiven or SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Nervous system disorders	**3 (0.9)**	**2 (0.6)**
Dysgeusia	2 (0.6)	0
Headache	1 (0.3)	1 (0.3)
Tremor	0	1 (0.3)
General disorders and administration site conditions	**2 (0.6)**	**3 (1.0)**
Edema	1 (0.3)	0
Pyrexia	1 (0.3)	0
Infusion site erythema	0	1 (0.3)
Infusion site swelling	0	1 (0.3)
Chest discomfort	0	1 (0.3)
Pain	0	1 (0.3)
Vascular disorders	**2 (0.6)**	**1 (0.3)**
Thrombophlebitis	1 (0.3)	1 (0.3)
Hypertension	1 (0.3)	0
Injury, poisoning and procedural complications	**0**	**2 (0.6)**
Accidental overdose	0	1 (0.3)
Post gastric surgery syndrome	0	1 (0.3)
Infections and infestations	0	1 (0.3)
Enterobacter sepsis	0	1 (0.3)
Blood and lymphatic system disorders	**0**	**1 (0.3)**
Anemia	0	1 (0.3)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.3)**
Muscle spasms	0	1 (0.3)

Note, that numbers in each column cannot be added because a subject may have had more than one adverse event.
*Total number of patients treated.

Less common Clinical Trial Adverse Drug Reactions (<1%)
Not applicable. There were no other ADRs reported from clinical studies than the ones reported in Table 1.

Abnormal Hematological and Clinical Chemistry Findings
No clinically relevant changes indicating impairment of body functions were seen over the course of the study and no notable differences were observed between the treatment groups.

The amino acid component of SmofKabiven and SmofKabiven extra Nitrogen was compared in a clinical study to another amino acid solution that is approved in Europe. In the Aminoven 10% study (AS-CS-01-FR), the incidence of adverse drug reactions was comparable between the Aminoven 10% and the Nutrilamine 16 group among 30 ICU patients evaluated for safety.

Table 3 - Adverse Drug Reactions in the Aminoven 10% Study AS-CS-01-FR

Body system	Aminoven 10% group	Comparator group
Liver disorders Alkaline phosphatase elevation	1 (7.5%)	1 (7.5%)
Metabolic disorders Hyperglycemia + osmotic polyuria	1 (7.5%)	-

Post-Marketing Adverse Drug Reactions

Adverse Drug Reactions observed during administration of emulsions for intravenous nutrition in general, including SmofKabiven, and reported spontaneously from post-marketing experience consisted of:

Table 4 - Frequency of Adverse Drug Reactions for lipid emulsions*

System Organ Class	Adverse Drug Reaction	Frequency of Occurrence
Cardiac disorders	Tachycardia	Rare (> 0.01% – ≤ 0.1%)
Vascular disorders	Hypotension, hypertension	Rare (> 0.01% – ≤ 0.1%)
Respiratory, thoracic and mediastinal disorders	Dyspnea	Rare (> 0.01% – ≤ 0.1%)
Gastrointestinal disorders	Lack of appetite, nausea, vomiting	Uncommon (≥ 0.1% – < 1%)
Metabolism and nutrition disorders	Elevated plasma levels of liver enzymes	Uncommon (≥ 0.1% – < 1%)
Reproductive system and breast disorders	Priapism	Very rare (≤ 0.01%)
General disorders and administration site conditions	Slight increase in body temperature	Common (≥ 1% – < 10%)
	Chills, dizziness, headache	Uncommon (≥ 0.1% – < 1%)
	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	Rare (>0.01% – ≤ 0.1%)

*This applies to lipid emulsions in general and therefore to lipid-containing parenteral nutrition.

As with all parenteral infusions, extravasation may occur and should be treated according to symptoms.

In case these side effects occur during the infusion of SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] and SmofKabiven extra Nitrogen [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v], the infusion should be stopped or, if necessary, continued at a reduced dosage.

Adverse Drug Reactions observed during administration of emulsion for intravenous nutrition in general, including SMOFlipid, and reported spontaneously from post-marketing experience are displayed in Table 4.

DRUG INTERACTIONS

Drug-Drug Interactions

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.

Intravenous heparin infused in clinical doses and some non-steroidal anti-inflammatory drugs (NSAIDs) cause a transient increase in lipoprotein lipase release into the circulation. This may initially result in increased plasma lipolysis, followed by a transient decrease in triglyceride clearance.

Table 5 - Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Heparin, NSAIDs	T	A possible transient decrease in triglyceride clearance	These findings are based on basic research and not reported as adverse events in clinical practice.
Insulin	T	May interfere with the body's lipase system	These findings are based on basic research and not reported as adverse events in clinical practice.
Coumarin derivatives	T	May decrease anticoagulant effect	Soybean oil has a natural content of vitamin K_1. However, the content is so low in SmofKabiven and SmofKabiven extra Nitrogen that it is not expected to impair the therapeutic effects of coumarin derivatives on coagulation.

Legend: NSAID: non-steroidal anti-inflammatory drugs; T = Theoretical

Drug-Food Interactions

No SmofKabiven or SmofKabiven extra Nitrogen-food interaction studies have been performed.

Drug-Herb Interactions

No SmofKabiven or SmofKabiven extra Nitrogen-herb interaction studies have been performed.

Drug-Laboratory Interactions

High plasma levels of lipids may interfere with some laboratory blood tests, e.g. hemoglobin.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The patient's ability to eliminate lipids as well as metabolize nitrogen and glucose, and the nutritional requirements should govern the dosage and infusion rate. The dose should be individualized 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 0.6 – 0.9 g amino acids/kg bw/day (0.10 – 0.15 g nitrogen/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 0.9 – 1.6 g amino acids/kg bw/day (0.15 – 0.25 g nitrogen/kg bw/day). In some very special conditions (e.g. burns or marked anabolism) the nitrogen need may be even higher.

Recommended Dose and Dosage Adjustment

Dosage
The dosage range of 13 – 31 mL SmofKabiven /kg bw/day corresponds to 0.6 – 1.6 g amino acids/kg bw/day (0.10 – 0.25 g nitrogen/kg bw/day) and 14 – 35 kcal/kg bw/day of total energy (12 – 27 kcal/kg bw/day of non-protein energy).

The dosage range of 13 – 31 mL SmofKabiven extra Nitrogen /kg bw/day corresponds to 0.85 – 2.0 g amino acids/kg bw/day (0.14 – 0.32 g nitrogen/kg bw/day) and 12 – 28 kcal/kg bw/day of total energy (8 – 19 kcal/kg bw/day of non-protein energy).

Dosing with either SmofKabiven or SmofKabiven extra Nitrogen covers the needs for the majority of the critically and non-critically ill patients. In obese patients, the dose should be based on the estimated ideal weight.

Infusion rate
The maximum infusion rate for dextrose (glucose) is 0.25 g/kg bw/h, for amino acid 0.10 g/kg bw/h, and for lipids 0.15 g/kg bw/h.

The infusion rate of SmofKabiven should not exceed 2.0 mL/kg bw/h providing 0.25 g dextrose (glucose), 0.10 g amino acids, and 0.08 g lipids/kg bw/h.

The infusion rate of SmofKabiven extra Nitrogen should not exceed 1.5 mL/kg bw/h, providing 0.13 g dextrose (glucose), 0.10 g amino acids, and 0.04 g lipids/kg/ bw/h.

The recommended infusion period is 14 – 24 hours.

Maximum daily dose
The recommended maximum daily dose of SmofKabiven is 35 mL/kg bw/day providing 1.8 g amino acids/kg bw/day (corresponding to 0.28 g nitrogen/kg bw/day), 4.5 g dextrose (glucose)/kg bw/day, 1.33 g lipids/kg bw/day and a total energy of 39 kcal/kg bw/day (corresponding to 31 kcal/kg bw/day of non-protein energy).

The recommended maximum daily dose of SmofKabiven extra Nitrogen is 31 mL/kg bw/day, providing 2.0 g amino acids/kg bw/day (corresponding to 0.32 g nitrogen/kg bw/day), 2.6 g glucose/kg bw/day, 0.9 g lipids/kg bw/day and a total energy content of 28 kcal/kg bw/day (corresponding to 19 kcal/kg bw/day of non-protein energy).

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

Administration

SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] and SmofKabiven extra Nitrogen [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v] are intended for infusion into a central vein once the vertical and horizontal seals have been broken and compartments thoroughly mixed. (See SPECIAL HANDLING INSTRUCTIONS)

SmofKabiven and SmofKabiven extra Nitrogen may only be mixed with other medicinal products for which compatibility has been documented (see SPECIAL HANDLING INSTRUCTIONS).

Ceftriaxone must not be administered simultaneously with intravenous calcium containing solutions through the same infusion line (e.g. via Y-site) because of the risk of precipitation of ceftriaxone-calcium salt. If the same infusion line is used for sequential administration, the line must be thoroughly flushed with a compatible fluid between infusions.

OVERDOSAGE

If symptoms of overdose of lipids or amino acids occur, the infusion should be reduced 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 serum

hyperosmolarity.

In rare serious cases, renal replacement therapy may be considered.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The primary goal of parenteral nutrition is to provide adequate calories and protein to supply required nutrients and to prevent malnutrition with its associated complications when the patient is unable to receive adequate oral or enteral nutrition. SmofKabiven and SmofKabiven extra Nitrogen provide the three macronutrients: glucose (as dextrose), amino acids, and lipids consisting of saturated fatty acids especially MCT (medium-chain triglycerides), monounsaturated and polyunsaturated fatty acids (essential fatty acids), with the electrolytes (sodium, potassium, magnesium, calcium, phosphate, zinc, sulphate, chloride, and acetate).

Amino acids provide the basic substrates for protein synthesis in all tissues and are metabolic precursors and intermediates of numerous other molecules and biochemical pathways. Amino acids provided in excess of requirements are not stored but are used as metabolic fuel. The alpha amino group is removed and the remaining carbon skeleton is transformed into acetyl CoA, acetoacetyl CoA, pyruvate, alpha-ketoglutarate, succinate fumarate, or oxaloacetate.

An adequate supply of amino acids is required for protein synthesis and reduced protein breakdown, especially in metabolic situations with increased endogenous protein degradation, as in many acute or chronic catabolic diseases.

Dextrose (glucose) is the primary source of energy for cells. All body cells have the capacity to metabolize dextrose (glucose) into pyruvate (glycolysis), which may then be oxidized in mitochondria when present, or converted anaerobically to lactate. Channels for entrance of dextrose into body cells may be activated by insulin or, as in red blood cells, be independent from insulin. Dextrose can be stored in the liver as glycogen under the influence of insulin, and converted back as required.

Lipids should be an integral part of a parenteral nutrition regimen. Fatty acids are the most calorically dense form of energy available (9 kilocalories per gram vs approx. 4 kilocalories per gram glucose and amino acids). Fatty acids may be oxidized or incorporated in cell membranes and act as precursors for prostaglandins, leukotrienes, thromboxanes, other bioactive molecules as regulators of gene expression, and as modulators of hormonal functions. Fatty acids also have a role in the propagation of nerve impulses, and in absorption of fat-soluble vitamins from the diet.

The two essential fatty acids (EFA) linoleic acid, an omega-6 polyunsaturated fatty acid (PUFA) and α-linolenic acid, an omega-3 polyunsaturated fatty acid, have to be provided intravenously if

the gut is dysfunctional. Long-chain omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil, contribute directly to higher levels of eicosanoids without the need of elongation from α-linolenic acid, showing beneficial effects on cell membranes and inflammatory processes.

Stored fat becomes the major fuel source once the carbohydrate store (glycogen) has been depleted. Long-chain fatty acids bypass portal circulation and are presented to the periphery and stored in adipose tissue until needed. Responding to a decrease in insulin levels, long-chain FAs are released and are used by muscle tissue for energy production.

Electrolytes are important to all cells and perform vital functions in the body. Sodium and chloride are the predominant electrolytes in extracellular fluid and are essential in fluid and acid-base balance. Potassium is the most predominant intracellular electrolyte and is important in protein synthesis and nerve transmission. Calcium is required for bone formation, cellular signaling and various enzyme reactions. Phosphate is important in bone maintenance as well as formation of energy compounds. Magnesium regulates many enzymatic reactions. Several enzymes depend on zinc for catalytic activity.

Pharmacodynamics

The lipid emulsion of SmofKabiven and SmofKabiven extra Nitrogen is composed of SMOFlipid and has a particle size and biological properties similar to those of endogenous chylomicrons. The different constituents of SMOFlipid, i.e. soybean oil, medium-chain triglycerides, olive oil, and fish oil have their own pharmacodynamic properties. The energy content (9 kcal/g) is the same for all fatty acids.

Soybean oil has a high content of essential fatty acids (linoleic acid and alpha linolenic acid). The omega-6 fatty acid linoleic acid is the most abundant. The ratio of omega-6/omega-3 fatty acid in SMOFlipid 20% is approximately 2.5:1.

Medium-chain fatty acids are rapidly oxidized.

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 characterized 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 prostaglandins, thromboxanes and leukotrienes, thereby modulating inflammation.

Vitamin E protects unsaturated fatty acids against lipid peroxidation.

The amino acids are utilized for tissue protein synthesis and any surplus is channeled to a number of metabolic pathways. Studies have shown a thermogenic effect of amino acid infusion.

Dextrose contributes to maintain or replete the normal nutritional status through provision of energy.

Pharmacokinetics

The ingredients of SmofKabiven and SmofKabiven extra Nitrogen (amino acids, with electrolytes, lipids, dextrose) are distributed, metabolized and eliminated in the same manner as if they had been administered individually. The bioavailability of intravenously infused substances such as SmofKabiven and SmofKabiven extra Nitrogen is 100%.

The individual triglycerides in SmofKabiven and SmofKabiven extra Nitrogen have different clearance rates. Clearance is fastest for medium chain triglycerides (MCT). Fish oil in a mixture with LCT has the same clearance rate as LCT alone.

The principal pharmacokinetic property of the infused amino acids and electrolytes is that the intravenously infused amino acids directly reach the systemic circulation.

Depending on the nutritional state, dextrose can be rapidly metabolized to carbon dioxide and water, stored in the liver and muscles as glycogen, or converted to fat in the adipose tissue.

Special Populations and Conditions

Pharmacokinetic data have not been obtained in special patient populations or conditions.

Pediatrics: Exploratory studies with the lipid compound have been conducted but confirmatory pivotal studies have not been provided. No pediatric studies with SmofKabiven or SmofKabiven extra Nitrogen have been performed.

Geriatrics: The metabolism of SmofKabiven and SmofKabiven extra Nitrogen does not appear to be affected in elderly.

Gender: There are no differences between the genders regarding the metabolism of SmofKabiven and SmofKabiven extra Nitrogen.

Hepatic Insufficiency: Overdosing of energy regardless of origin (glucose or lipids) may cause steatosis and result in further hepatic impairment.

Renal Insufficiency: As SmofKabiven and SmofKabiven extra Nitrogen add to circulatory volume, it is important to have an adequate renal function. In case of renal failure, it is recommended to have access to renal replacement therapy due to the risk of fluid overload.

STORAGE AND STABILITY

Shelf life of the products in overwrap: 24 months

Store below 25 °C. Do not freeze.

Do not use SmofKabiven and SmofKabiven extra Nitrogen after expiry date printed on the container.

Store bags in overwrap.

For use once the overwrap is removed.

Do not use if package is damaged. Use only if the amino acid and dextrose solutions are clear and colourless or slightly yellow and the lipid emulsion is white, opaque, and homogenous. The contents of the three separate chambers must be mixed before use, and before any additions are made via the additive port.

Once the bag is activated, ensure the vertical seals between chambers are broken at least from the bend in the seals and down to the ports. Then, the bag should be inverted several times to ensure a homogenous mixture which does not show any evidence of phase separation. The upper sections of the vertical seals above the bend and the horizontal seal may remain closed.

Only administration sets and administration lines made of DEHP-free material should be used.
For single use only. Any unused emulsion must be discarded.

Shelf life after mixing

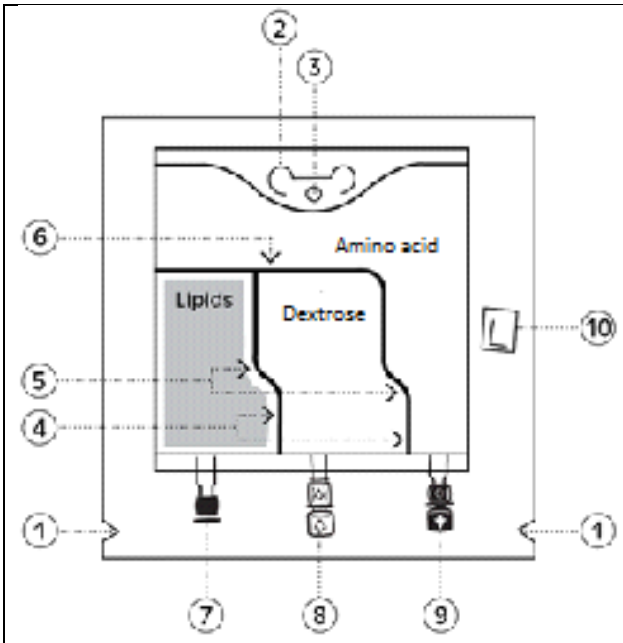
Chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 36 hours at 25 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user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

Shelf life after mixing with additives

Compatibility for different additives and the storage time of the different admixtures will be available upon request. From a microbiological point of view, the product should be used immediately after mixing and 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 °C to 8 °C. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

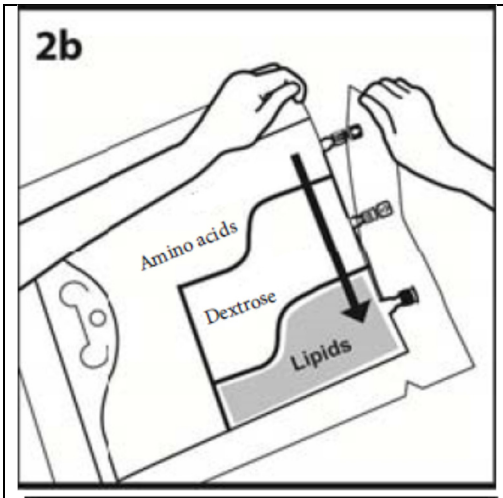
Before administering the product in plastic bag to the patient, review these directions:

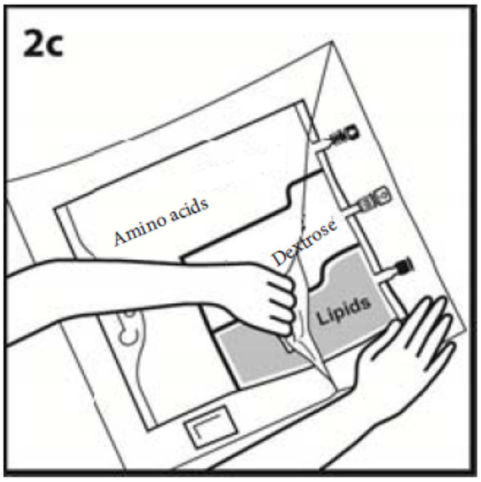
<table>
<tr>
<td> 
</td>
<td>The Bag

1. Overwrap Notch
2. Handle
3. Hole (For hanging the bag)
4. Vertical Seals (Must break to activate)
5. Bends in Vertical Seals
6. Horizontal Seal (May remain unopened)
7. Blind Port (NEVER use this port)
8. WHITE Additive Port
9. BLUE Infusion Port
10. Oxygen Absorber (Present between bag and inside overwrap-position may vary)</td>
</tr>
<tr>
<td></td>
<td>1. INSPECT BAG PRIOR TO ACTIVATION.

SmofKabiven and SmofKabiven extra Nitrogen are 3 chambered bags:
- One chamber is WHITE.
- Two chambers are CLEAR.

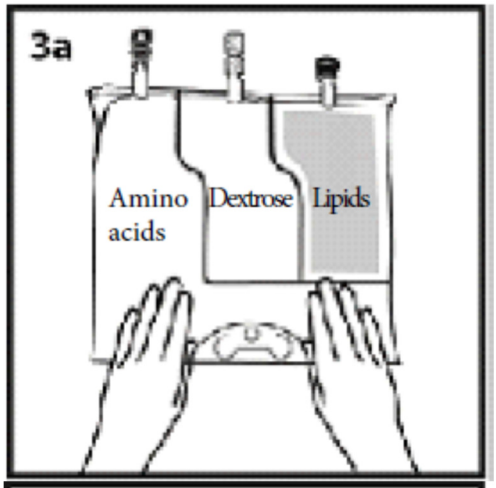
a) Discard bag if:
- More than one chamber is WHITE.
- Solution is YELLOW.
- Seals are already BROKEN.
- Visible particles are present</td>
</tr>
</table>

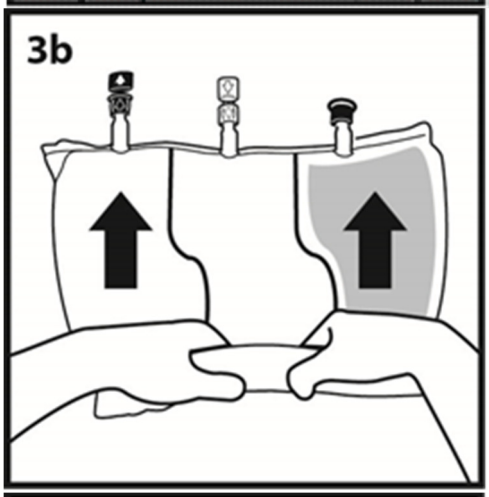


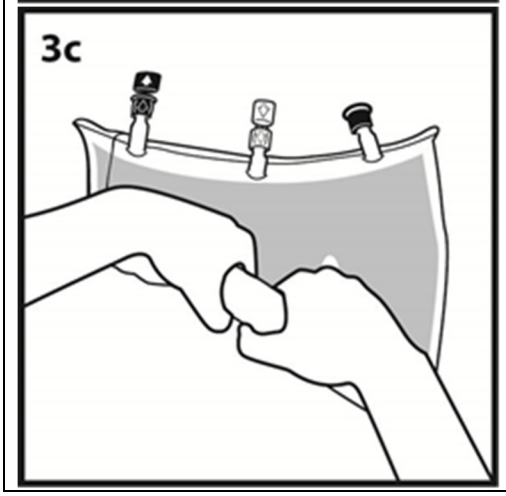


2. REMOVE OVERWRAP.

a) Place bag on a clean, flat surface.
b) Tear from Overwrap Notch, located close to the ports.
c) Tear long sides open to access the inner bag.
d) Discard Overwrap and Oxygen Absorber.







3. ACTIVATE BAG.

a) Place bag on a clean, flat surface with text side up and ports pointing away from you.

b) Roll tightly from top of bag down toward ports.

c) Apply pressure until both Vertical Seals break and entire contents are white. It may take up to 5 seconds of continued pressure to break Vertical Seals.

NOTE: Both Vertical Seals must be broken from bends to ports. Upper section of Vertical Seals and Horizontal Seal may remain unbroken.

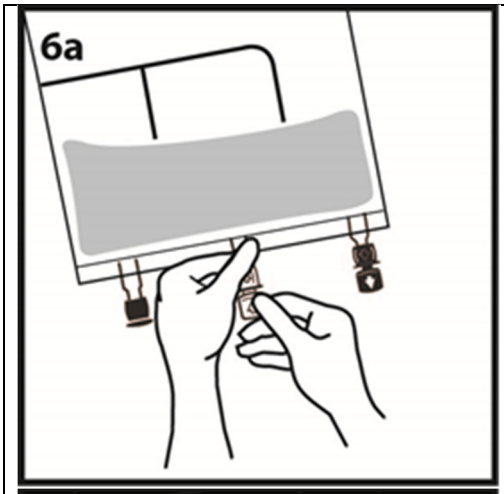
d) After both Vertical Seals are broken, mix contents thoroughly by inverting the bag at least three times to ensure a homogenous mixture.

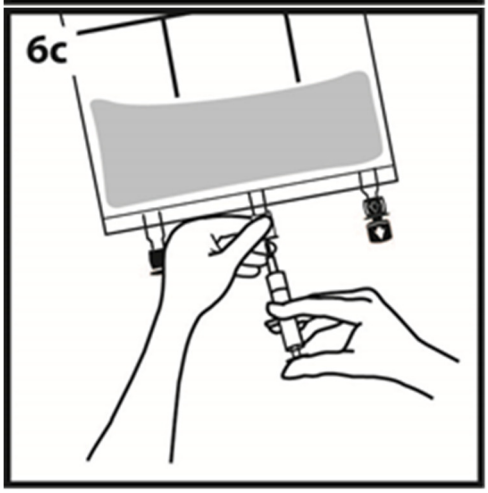
4. INSPECT BAG TO CONFIRM ACTIVATION.

- An activated bag has both Vertical Seals broken from bends to ports and entire contents are white.

5. IDENTIFY CORRECT PORT.

- Additive port is **WHITE** with arrow pointing toward bag.
- Infusion port is **BLUE** with arrow pointing away from bag.





6. MAKE ADDITIONS (if prescribed).

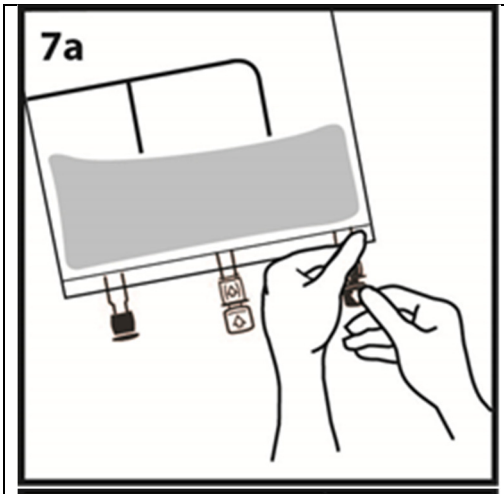
WARNING: Ensure additives are compatible.

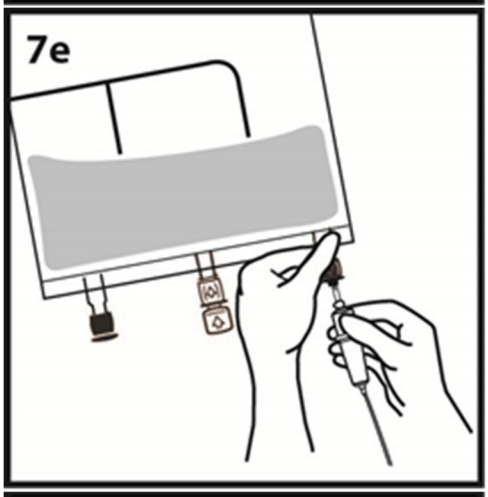
To provide total parenteral nutrition, trace elements, vitamins, and possibly electrolytes (taking into account the electrolytes already present in SmofKabiven and SmofKabiven extra Nitrogen) should be added according to the patient's requirements.

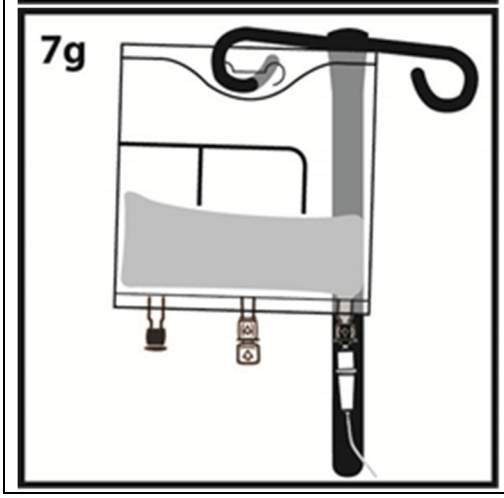
Additives should be thoroughly mixed with components.

a) **Immediately before injecting additives, break off WHITE Additive Port cap with the arrow pointing toward the bag.**
b) Hold base of Additive Port horizontally.
c) **Insert needle horizontally through the center of Additive Port's septum and inject additives.**
d) Repeat as necessary using aseptic technique.
e) Mix thoroughly after each addition.

<u>NOTE</u>: The membrane of Additive Port is sterile at first use. Use aseptic technique for subsequent additions. The septum can be pierced up to 10 times with the recommended needle size 18 – 23 G 1½ inches (40 mm).







7. SPIKE AND HANG BAG.

a) **Immediately before inserting the infusion set, break off BLUE Infusion Port cap with the arrow pointing away from the bag.**
b) Use a non-vented infusion set or close the air-inlet on a vented set. It is recommended to use a 1.2 µm in-line filter.
c) Close the roller clamp of the infusion set.
d) Hold the base of Infusion Port.
e) **Insert spike through Infusion Port by rotating your wrist slightly until the spike is inserted.**
f) Lift and hold the bag with both hands.
g) **Hang the bag by Hole below Handle.**

<u>NOTE</u>: The membrane of Infusion Port is sterile at first use. Use infusion sets (according to ISO Number 8536-4) with an external spike diameter of 5.5 – 5.7 mm.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion w/v (5.1% & 0.7% / 12.7% / 3.8%); w/v] and SmofKabiven extra Nitrogen [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v] consist of three chamber bag systems. Each bag contains the following partial volumes depending on the pack sizes.

Table 6 - Partial Volumes of Amino Acids with Electrolytes, Dextrose and Lipid Emulsion for SmofKabiven

	986 mL	**1477 mL**	**1970 mL**	**2463 mL**	**Per 100 mL**
Amino acid solution with electrolytes (mL)	500	750	1000	1250	50.8
Dextrose 42% (mL)	298	446	595	744	30.2
Lipid emulsion (mL)	188	281	375	469	19.0

Table 7 - Partial Volumes of Amino Acids with Electrolytes, Dextrose and Lipid Emulsion for SmofKabiven extra Nitrogen

	506 mL	**1012 mL**	**1518 mL**	**2025 mL**	**2531 mL**	**Per 100 mL**
Amino acid solution with electrolytes (mL)	331	662	993	1325	1656	65.4
Dextrose 42% (mL)	102	204	306	408	510	20.2
Lipid emulsion (mL)	73	146	219	292	365	14.4

This corresponds to the following total compositions:

Table 8 – Contents of Mixed Products

Composition		SmofKabiven	SmofKabiven extra Nitrogen
Lipids (g/100 mL)		3.8	2.9
Dextrose anhydrous (g/100 mL)		12.7	8.5
Amino acids (g/100 mL)		5.1	6.5
Total Nitrogen (g/100 mL)		0.8	1.1
Lipids mg/100 mL	Soybean oil, refined	1140 mg	870 mg
	Medium chain triglycerides	1140 mg	870 mg
	Olive oil, refined	950 mg	720 mg
	Fish oil, rich in omega-3-acids	570 mg	430 mg
	Total g/100 mg mixed emulsion	3.8 g	2.9 g
Essential amino acids (mg/100 mL)	Lysine (as acetate)	340	430
	Phenylalanine	260	330
	Leucine	380	480
	Valine	310	410
	Threonine	220	290
	Methionine	220	280
	Isoleucine	250	330
	Tryptophan	100	130
Nonessential amino acids (mg/100 mL)	Alanine	710	920
	Arginine	610	790
	Glycine	560	720
	Proline	570	730
	Histidine	150	200
	Serine	330	430
	Taurine	50	65
	Tyrosine	20	26
Electrolytes (mg/100mL)	Sodium acetate trihydrate	170	160
	Potassium chloride	230	230
	Sodium glycerophosphate anhydrous	210	230
	Magnesium sulfate heptahydrate	61	61
	Calcium chloride dihydrate	28	28
	Zinc sulfate heptahydrate	0.66	0.66
Electrolytes (mmol/100 mL)	Sodium	4.1	4.1
	Potassium	3.0	3.1
	Magnesium	0.51	0.51
	Calcium	0.25	0.26
	Phosphate[1]	1.3	1.3
	Zinc	0.004	0.004
	Sulfate	0.51	0.51
	Chloride	3.6	3.6
	Acetate	10.6	12.5
Calorie content	From non-protein (approx.) (kcal/L)	912	627
	From non-protein (approx.) (MJ/L)	3.8	2.6
	Total (approx.) (kcal/L)	1115	889
	Total (approx.) (MJ/L)	4.7	3.7

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

Table 9 - Contents of Mixed Product per Pack of SmofKabiven

Composition		986 mL	1477 mL	1970 mL	2463 mL
Amino acids (g)		50	75	100	125
Nitrogen (g)		8	12	16	20
Lipids (g)		38	56	75	94
Dextrose (anhydrous) (g)		125	187	250	313
Essential amino acids (g)	Lysine (as acetate)	3.3	5.0	6.6	8.4
	Phenylalanine	2.6	3.8	5.1	6.4
	Leucine	3.7	5.6	7.4	9.4
	Valine	3.1	4.6	6.2	7.6
	Threonine	2.2	3.3	4.4	5.4
	Methionine	2.2	3.2	4.3	5.4
	Isoleucine	2.5	3.8	5.0	6.2
	Tryptophan	1.0	1.5	2.0	2.5
Nonessential amino acids (g)	Alanine	7.0	10.5	14.0	17.5
	Arginine	6.0	9.0	12.0	15.0
	Glycine	5.5	8.2	11.0	13.8
	Proline	5.6	8.4	11.2	14.0
	Histidine	1.5	2.2	3.0	3.7
	Serine	3.2	4.9	6.5	8.1
	Taurine	0.5	0.75	1.0	1.2
	Tyrosine	0.20	0.30	0.40	0.49
Lipids (g)	Soybean oil, refined	11.3	16.9	22.5	28.1
	Triglycerides, medium chain	11.3	16.9	22.5	28.1
	Olive oil, refined	9.4	14.1	18.8	23.4
	Fish oil	5.6	8.4	11.3	14.0
Electrolytes (g)	Sodium acetate trihydrate	1.7	2.6	3.4	4.2
	Potassium chloride	2.2	3.4	4.5	5.7
	Sodium glycerophosphate (as hydrate)	2.1	3.1	4.2	5.2
	Magnesium sulfate heptahydrate	0.60	0.90	1.2	1.5
	Calcium chloride dihydrate	0.28	0.42	0.56	0.69
	Zinc sulfate heptahydrate	0.0065	0.0097	0.013	0.016
Electrolytes (mmol)	Sodium	40	60	80	100
	Potassium	30	45	60	74
	Magnesium	5.0	7.5	10	12
	Calcium	2.5	3.8	5.0	6.2
	Phosphate[1]	12	19	25	31
	Zinc	0.04	0.06	0.08	0.1
	Sulfate	5.0	7.5	10	13
	Chloride	35	52	70	89
	Acetate	104	157	209	261
Calorie content	Total (kcal)	1100	1600	2200	2700
	Total (MJ)	4.6	6.7	9.2	11.3
	From non-protein (kcal)	900	1300	1800	2200
	From non-protein (MJ)	3.8	5.4	7.5	9.2
pH		approx. 5.6			
Osmolarity (mOsm/L)		approx. 1500			
Osmolality (mOsm/kg water)		approx. 1800			

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

Table 10 - Contents of Mixed Product per Pack of SmofKabiven extra Nitrogen

Composition		506 mL	1012 mL	1518 mL	2025 mL	2531 mL
Amino acids (g)		33	66	99	133	166
Nitrogen (g)		5	11	16	21	27
Lipids (g)		15	29	44	58	73
Dextrose (anhydrous) (g)		43	86	129	171	214
Essential amino acids (g)	Lysine (as acetate)	2.2	4.4	6.6	8.7	11
	Phenylalanine	1.7	3.4	5.1	6.8	8.4
	Leucine	2.4	4.9	7.3	9.8	12
	Valine	2.1	4.1	6.2	8.2	10
	Threonine	1.5	2.9	4.4	5.8	7.3
	Methionine	1.4	2.8	4.3	5.7	7.1
	Isoleucine	1.7	3.3	5.0	6.6	8.3
	Tryptophan	0.66	1.3	2.0	2.7	3.3
Nonessential amino acids (g)	Alanine	4.6	9.3	14	19	23
	Arginine	4.0	7.9	12	16	20
	Glycine	3.6	7.3	11	15	18
	Proline	3.7	7.4	11	15	19
	Histidine	1.0	2.0	3.0	4.0	5.0
	Serine	2.2	4.3	6.5	8.6	11
	Taurine	0.33	0.66	1.0	1.3	1.7
	Tyrosine	0.13	0.26	0.40	0.53	0.66
Lipids (g)	Soybean oil, refined	4.4	8.8	13	18	22
	Triglycerides, medium chain	4.4	8.8	13	18	22
	Olive oil, refined	3.7	7.3	11	15	18
	Fish oil	2.2	4.4	6.6	8.8	11
Electrolytes (g)	Sodium acetate trihydrate	0.82	1.6	2.5	3.3	4.1
	Potassium chloride	1.2	2.3	3.5	4.6	5.8
	Sodium glycerophosphate (as hydrate)	1.2	2.3	3.5	4.6	5.8
	Magnesium sulfate heptahydrate	0.31	0.62	0.92	1.2	1.5
	Calcium chloride dihydrate	0.14	0.29	0.43	0.58	0.72
	Zinc sulfate heptahydrate	0.0033	0.0066	0.010	0.013	0.017
Electrolytes (mmol)	Sodium	21	41	62	83	103
	Potassium	16	31	46	62	77
	Magnesium	2.6	5.2	7.7	10	13
	Calcium	1.3	2.6	3.9	5.2	6.5
	Phosphate[1]	6.4	13	19	26	32
	Zinc	0.02	0.04	0.06	0.08	0.1
	Sulfate	2.6	5.2	7.8	10	13
	Chloride	18	36	54	72	90
	Acetate	63	126	189	253	316
Calorie content	Total (kcal)	450	900	1350	1800	2250
	Total (MJ)	1.9	3.8	5.6	7.5	9.4
	From non-protein (kcal)	317	635	952	1270	1590
	From non-protein (MJ)	1.3	2.7	4.0	5.3	6.6
pH		approx. 5.6				
Osmolarity (mOsm/L)		approx. 1300				
Osmolality (mOsm/kg water)		approx. 1600				

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

Excipients are:

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 injection

Product Container

The container consists of a multi-chamber inner bag and an overwrap. The inner bag is partitioned into three chambers to keep the components separated until the bag is activated by the user. An oxygen absorber is placed between the inner bag and the overwrap. The inner bag is made of a multilayer polymer film that 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:

SmofKabiven:
986 mL bag: 1 carton with 4 bags
1477 mL bag: 1 carton with 4 bags
1970 mL bag: 1 carton with 4 bags
2463 mL bag: 1 carton with 3 bags

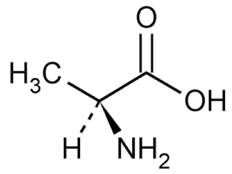
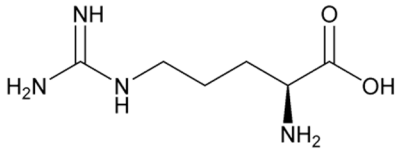
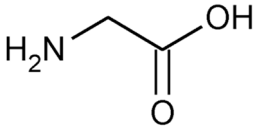
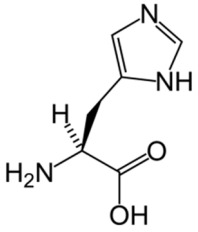
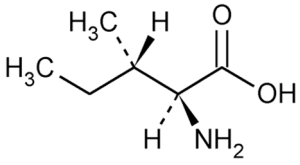
SmofKabiven extra Nitrogen:
506 mL bag: 1 carton with 6 bags
1012 mL bag: 1 carton with 4 bags
1518 mL bag: 1 carton with 4 bags
2025 mL bag: 1 carton with 4 bags
2531 mL bag: 1 carton with 3 bags

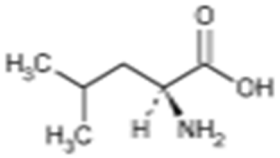
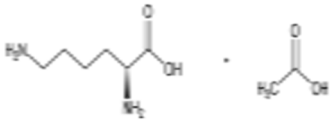
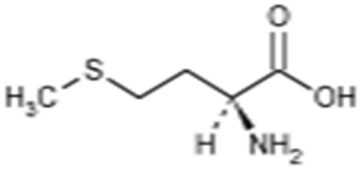
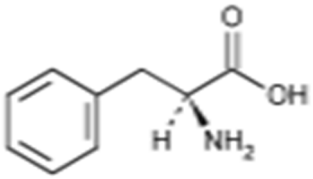
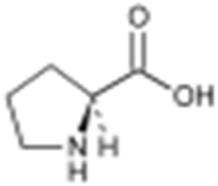
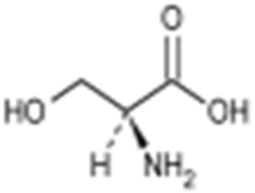
PART II: SCIENTIFIC INFORMATION

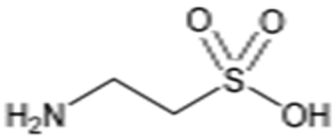
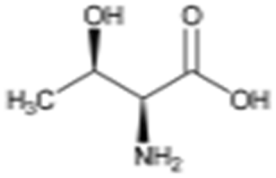
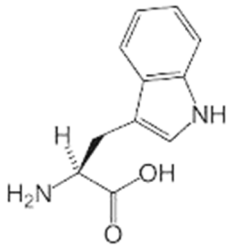
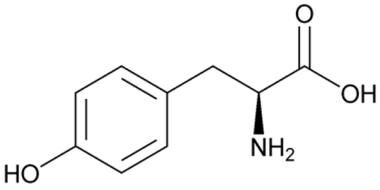
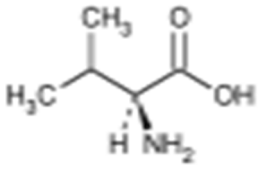
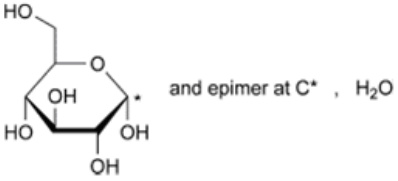
PHARMACEUTICAL INFORMATION

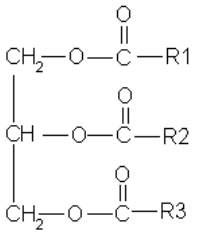
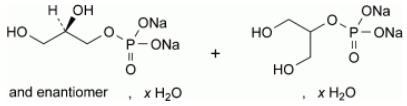
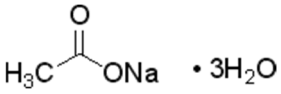
Drug Substance

SmofKabiven [Amino acids with electrolytes, dextrose and lipid injectable emulsion (5.1% & 0.7% / 12.7% / 3.8%); w/v] and SmofKabiven extra Nitrogen [Amino acids with electrolytes, dextrose and lipid injectable emulsion (6.5% & 0.7% / 8.5% / 2.9%); w/v]

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical properties
L-Alanine (S)-2-aminopropionic acid	$C_3H_7NO_2$ 89.09		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in alcohol.
L-Arginine (2S)-2-amino-5-guanidinopentanoic acid	$C_6H_{14}N_4O_2$ 174.20		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in alcohol.
Glycine Aminoacetic acid	$C_2H_5NO_2$ 75.07		White or almost white crystalline powder, freely soluble in water, very slightly soluble in alcohol.
L-Histidine (S)-2-amino-1H-imidazole-4-propionic acid	$C_6H_9N_3O_2$ 155.15		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol (96%).
L-Isoleucine (2S, 3S)-2-amino-3-methylpentanoic acid	$C_6H_{13}NO_2$ 131.17		White or almost white crystalline powder or flakes, sparingly soluble in water, slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical properties
L-Leucine (2S)-2-amino-4-methylpentanoic acid	$C_6H_{13}NO_2$ 131.17		White or almost white crystalline powder or shiny flakes, sparingly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Lysine Acetate (2S)-2,6-diaminohexanoic acid monoacetate	$C_6H_{14}N_2O_2 \cdot C2H_4O_2$ 206.24		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in ethanol (96%).
L-Methionine (2S)-2-amino-4-(methylsulfanyl) butanoic acid	$C_5H_{11}NO_2S$ 149.21		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol.
L-Phenylalanine (2S)-2-amino-3-phenylpropanoic acid	$C_9H_{11}NO_2$ 165.19		White or almost white crystalline powder or shiny, white flakes, sparingly soluble in water, very slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Proline (S)-2-pyrrolidinecarboxylic acid	$C_5H_9NO_2$ 115.13		White or almost white crystalline powder or colourless crystals, very soluble in water, freely soluble in alcohol.
L-Serine (S)-2-amino-3-hydroxypropionic acid	$C_3H_7NO_3$ 105.09		White or almost white crystalline powder or colourless crystals, freely soluble in water, practically insoluble in alcohol.

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical properties
Taurine 2-aminoethane sulfonic acid	$C_2H_7NO_3S$ 125.15		White or almost white crystalline powder or colourless crystals, freely soluble in water
L-Threonine (2S, 3R)-2-amino-3-hydroxybutanoic acid	$C_4H_9NO_3$ 119.12		White crystalline powder or colourless crystals, soluble in water, practically insoluble in ethanol.
L-Tryptophan (2S)-2-amino-3-(indol-3-yl) propanoic acid	$C_{11}H_{12}N_2O_2$ 204.23		White or almost white crystalline or amorphous powder, sparingly soluble in water, slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Tyrosine (S)-2-amino-3-(4-hydroxyphenyl) propionic acid	$C_9H_{11}NO_3$ 181.19		White crystalline powder or colourless crystals, very slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Valine (S)-2-amino-3-methylbutanoic acid	$C_5H_{11}NO_2$ 117.15		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol.
Dextrose D-glucose monohydrate	$C_6H_{12}O_6 \cdot H_2O$ 198.2		White crystalline powder with a sweet taste, freely soluble in water, sparingly soluble in alcohol.

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical properties
Soybean oil	Triacylglycerol (triglyceride) with fatty acid chains mainly C16:0, C18:0, C18:1, C18:2, C18:3	 R_1, R_2, R_3 represents the chain of the fatty acids linked to the glycerol backbone.	Liquid at room temperature. Practically insoluble in water, very soluble in acetone and in heptane while slightly soluble in ethanol.
Medium chain triglycerides (MCT)	Triacylglycerol (triglyceride) with fatty acid chains mainly C8:0, C10:0		
Olive Oil	Triacylglycerol (triglyceride) with fatty acid chains mainly C16:0, C18:1, C18:2		
Fish Oil	Triacylglycerol (triglyceride) fatty acids mainly C20:5, C22:6		
Sodium glycerophosphate	$C_3H_7Na_2O_6P$ 216.04	 and enantiomer , x H_2O , x H_2O	White crystalline powder or crystals, freely soluble in water, practically insoluble in acetone and in alcohol.
Sodium acetate trihydrate	C2H3NaO2·3H 2O 136.08		Colourless crystals, very soluble in water, soluble in alcohol.
Potassium chloride	KCl 74.55		White or almost white crystalline powder or colourless crystals, freely soluble in water, practically insoluble in anhydrous alcohol.
Magnesium sulphate heptahydrate	$MgSO_4$ $7H_2O$ 246.48		White crystalline powder, hygroscopic, very soluble in water, slightly soluble in alcohol, glycerol, insoluble in acetone.

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical properties
Calcium chloride dihydrate	$CaCl_2 \cdot 2H_2O$ 147.01		White crystalline powder, hygroscopic, freely soluble in water, soluble in alcohol.
Zinc sulphate heptahydrate	$ZnSO_4 \cdot 7H_2O$ 287.55		White or almost white, crystalline powder or colourless, transparent crystals, efflorescent, very soluble in water, practically insoluble in ethanol

CLINICAL TRIALS

Study demographics and trial design

One phase 3 open-label, randomised, active-controlled, parallel-group study (03-3CB7-001) was conducted in patients after major intestinal tract surgery requiring parenteral nutrition. The aim was to evaluate safety and tolerance of SmofKabiven compared to another three-chamber bag product, Kabiven (containing a soybean oil emulsion, amino acids and dextrose) available in US and Europe. A total of 53 patients (age range 35-82 years; 17 females) received 15 to 30 mL SmofKabiven or comparator/kg bw/day by central intravenous infusion for five to seven days. Safety parameters were adverse events, blood laboratory, and vital signs.

A phase 3 open-label, randomised, active-controlled, parallel-group study (03-3CB8-001) was performed in patients requiring parenteral nutrition to evaluate safety and tolerance of SmofKabiven Peripheral compared to another peripheral three-chamber bag product available in Europe. A total of 52 patients (age range 20-84 years; 36 females) received up to 40 mL SmofKabiven Peripheral or comparator/kg bw/day into peripheral veins for 5 to 7 days. Safety parameters were adverse events, blood laboratory, vital signs and local tolerance.

Table 11 - Summary of patient demographics for clinical trials on SmofKabiven

Study No.	Trial design	Dosage (g lipids/kg bw/h)	Route of administration	Duration (days)	Study subjects (n)	Age range (years)
03-3CB7-001 Safety	open-label, randomized, active-controlled, parallel-group	Day 1: 0.6 Days 2-4: 0.9–1.2 Days 5-7: 0.6-1.2	Intravenous	5-7	53	≥18
03-3CB8-001 Safety	open-label, randomized, active-controlled, parallel-group	max 1.1 for test product and 1.4 for reference product	Intravenous	5-7	52	≥18
bw: body weight; n: number;						

Study results

The study 03-3CB7-001 provided good evidence that SmofKabiven is well tolerated and safe. Based on the overall number of patients with AEs, safety and tolerability was comparable in both groups. Reported AEs were mild in 14/26 patients in the SmofKabiven group and 17/27 patients in the control group or moderate in 19/26 patients in the SmofKabiven group and 10/27 patients in the control group, respectively. Of these 17 patients in the SmofKabiven group and 11 patients in the control group experienced AEs possibly or probably related to the study drug. Serious AEs (SAEs) occurred in 5 subjects in the SmofKabiven group and in 2 subjects in the control group. No drug related SAE was observed. No clinically significant changes in vital signs were recorded. Eight patients in the SmofKabiven group and 5 in the control group were withdrawn due to an AE.

In study 03-3CB8-001 the majority of patients reported mild or moderate AEs. One of 27 patients in the SmofKabiven Peripheral and 1/25 patients in the comparator group experienced non-related, fatal SAEs. No drug-related SAE was observed in the study. Possible relationship to the study medication was reported for AEs in 1/27 and 2/25 patients after SmofKabiven Peripheral (thrombophlebitis) and comparator treatment (thrombophlebitis and anemia), respectively. One of 27 patients in the SmofKabiven Peripheral group was withdrawn from the study due to an AE (thrombophlebitis). Differences in clinical laboratory measurements between treatment groups and changes between baseline (Study Day 1) and examination after the last study medication were minor in both groups. There were no differences between groups regarding pulse rate, blood pressure, or body temperature. The incidence of local intolerance was higher in the SmofKabiven Peripheral than in the comparator group and was of low to moderate intensity. Evaluation of overall safety and tolerability of both treatments showed a lower number of AEs or pathological clinical laboratory values in the SmofKabiven Peripheral group than in the comparator group.

In addition, studies with individual components contained in SmofKabiven have been carried out as described below:

Lipid Emulsion (SMOFlipid 20%)

Study demographics and trial design

The trial design and patient demographic data for the company sponsored studies investigating SMOFlipid 20% in adult patients are summarised in Table 12 below.

Five clinical studies investigated SMOFlipid 20% versus soybean oil emulsion in 22 healthy adult volunteers and 281 adult patients (total of 303 adults). Of these, 73 patients were treated in a long-term study over 4-week treatment duration. Efficacy was studied in addition to safety in one study. For details of pharmacokinetic studies refer to DETAILED PHARMACOLOGY.

Table 12 - Summary of patient demographics for clinical trials on SMOFlipid 20%

Study No.	Trial design	Dosage (g lipids/kg bw/h)	Route of administration	Duration	Study subjects(n)	Age (Range)
Healthy volunteers						
FE-SM-01-BE Pharmaco-kinetics (5.3.3.1.1)	open-label, randomized, active-controlled, crossover	0.15	Intravenous	4 h	10	18-45
FE-SM-02-DE Pharmaco-kinetics (5.3.3.1.2)	double-blind, randomized, active-controlled, crossover	0.125	Intravenous	6 h	12	18-45
Adult patients						
FE-SM-03-DE Efficacy/Safety (5.3.5.1.1.A)	double-blind, randomized, active-controlled, parallel-group	1.5	Intravenous	5 d	249	≥18
FE-SM-04-CH Safety (SMOFlipid 5.3.5.1.2.A)	double-blind, randomized, active-controlled, parallel-group	up to max 2	Intravenous	10-14 d	32	≥18
05-SMOF-006 Safety (SMOFlipid 5.3.5.1.5.A)	double-blind, randomized, active-controlled, parallel-group	max 1-2	Intravenous	4 weeks	73	18-85

d: day: h: hour

Study results

In two randomised, two-period crossover studies in healthy volunteers, the elimination of triglycerides appeared to be faster for SMOFlipid 20% compared to a standard soybean oil emulsion.

Three randomised, double-blind clinical phase III studies FE-SM-03-DE, FE-SM-04-CH and 05-SMOF-006 were performed. In FE-SM-04-CH and 05-SMOF-006, safety was investigated and considered comparable in SMOFlipid 20% and the comparator soybean oil emulsions, given in the same dose (20%). Study 05-SMOF-006 performed with 73 patients requiring long-term parenteral nutrition during 4 weeks showed a reduction of the ratio of ω-6/ω-3-fatty acids in red blood cell phospholipids and plasma lipoproteins.

Study FE-SM-03-DE investigated the safety and efficacy of SMOFlipid 20% (compared with a soy bean oil emulsion) in 249 postsurgical patients. SMOFlipid 20% was well-tolerated and safe. Both treatment groups showed similar serum triglyceride concentrations during 5 days study treatment. Due to the different composition of the lipid emulsion, patients receiving SMOFlipid 20% had higher mean concentrations of the ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and lower mean concentrations of the ω-6 fatty acid linoleic acid than patients receiving soybean oil emulsion in plasma, platelet phospholipids, and leukocyte phospholipids. The ω-3/ω-6 ratio was significantly increased in the SMOFlipid 20% group compared to the soybean oil emulsion group.

Amino Acids (Aminoven 10%)

Study demographics and trial design

The trial design and patient demographics in this company sponsored study on Aminoven 10% are summarised in Table 13 below. One phase 3 clinical study on Aminoven was performed in 30 critically-ill patients who required parenteral nutrition for 5 to 7 days to evaluate efficacy and safety of Aminoven 10% compared to an isonitrogenous amino acid solution.

Table 13 - Summary of patient demographics for clinical with Aminoven 10%

Study No.	Trial design	Dosage (g lipids/kg bw/d)	Route of administration	Duration (days)	Study subjects (n)	Age range (years)
AS-CR-01-FR* Efficacy/Safety	open, randomized, active-controlled, parallel-group	1.5	Intravenous	5-7	30	≥18

* Test product: Cosmosteril 10% is synonymous with Aminoven 10%.

Study results

Similar results in both treatment groups were shown for the primary efficacy endpoint cumulative nitrogen balance. There were no significant differences with regard to the evolution of nutritional markers such as transthyretin (pre-albumin), retinol binding protein, C-reactive protein, and urinary 3-methylhistidine/creatinine ratio between the groups. The number of AEs was comparable between the treatment groups. Administration of Aminoven 10% was not associated with clinically relevant or unexpected AEs, neither by nature nor by incidence. The results of the study showed that both amino acid solutions were well tolerated.

Dextrose 42%

Glucose in varying concentrations is well established as the optimal carbohydrate source for parenteral nutrition.

DETAILED PHARMACOLOGY

No pharmacology studies have been performed using SmofKabiven or SmofKabiven extra Nitrogen. The clinical pharmacology of the individual constituents of SmofKabiven and SmofKabiven extra Nitrogen is described below.

The bioavailability of intravenously infused substances is by definition 100%.

Lipid emulsion (SMOFlipid 20%)

Pharmacokinetics

Two phase 1 pharmacokinetic studies using a randomised two-period crossover design performed in healthy adult men examined the intravascular metabolism of SMOFlipid 20% (study FE-SM-01-BE) and the elimination of triglycerides as well as the pharmacokinetics of other lipid parameters after administration of SMOFlipid 20% (study FE-SM-02-DE). The comparator in both studies was a soybean oil emulsion.

Both studies indicated that SMOFlipid 20% was well metabolized intravascularly and showed advantages over a soybean oil emulsion. Specifically, the less marked increase in triglycerides during infusion of SMOFlipid 20% and the faster elimination after stopping the infusion (i.e. shorter half-life) compared to a soybean oil emulsion are of potential benefit, particularly for patients with a limited triglyceride elimination capacity.

Pharmacodynamics

The pharmacodynamic functions of lipid emulsions are the provision of energy and essential fatty acids linoleic acid and α-linolenic acid. SMOFlipid 20% comprises 4 different lipid components, soybean oil 6%, MCT 6%, olive oil 5%, and fish oil 3% as a source of energy with high caloric density and as source of essential fatty acids from fish oil.

The pharmacodynamic properties of SMOFlipid 20% have not been systematically examined in clinical trials because the individual lipid components have been examined for many years. The pharmacodynamic effect of SMOFlipid 20% is expected to result from the combined effects of the individual components.

Soybean oil
Soybean oil is the main source of essential fatty acids in SMOFlipid 20%. Both linoleic and α-linolenic acids are long-chain fatty acids (LCFA; >12 carbon atoms) as well as polyunsaturated fatty acids (PUFAs). PUFAs are important constituents of all cell membrane phospholipids and serve as precursors for the synthesis of lipid mediators called eicosanoids (e.g. prostaglandins and leukotrienes)[1]. An excess of either ω-6 or ω-3 PUFA in parenteral lipid emulsions may be immunosuppressive. The more balanced the ω-6 to ω-3 ratio, the less immunosuppressive effects of the lipid emulsion were observed in a rat heart allotransplantation model [2]. According to clinical and experimental data, it has been suggested that the most favorable ω-6/ω-3 ratio is in the range of 2:1 to 4:1 [1, 2, 3, 4, 5, 6]. The ratio of ω-6/ω-3 fatty acids in SMOFlipid 20% is approximately 2.5:1.

Medium-chain triglycerides (MCT)
MCT are more rapidly cleared from the blood stream than long-chain triglycerides (LCT), and MCFA are more rapidly oxidized compared to LCFA [7, 8], thus providing the body with a form of immediately available energy. MCFA are not stored in fat tissue and do not accumulate in the liver [9, 10]. Intravenous MCT administration has not been associated with steatosis or hepatic dysfunction [11, 12]. Hepatic metabolism of MCFAs results in stimulation of synthesis of ketone bodies which can be used as an energy source but eventually result in acidosis [13, 14, 15, 16, 17, 18]. Therefore, it is important not to include an excessive quantity of MCT in a lipid emulsion. An emulsion containing as much as 75% MCT (and 25% LCT) has been tested in critically ill patients without observing any harmful effects [19, 20]. The amount of MCT (30%) in SMOFlipid 20% is considered safe as it is lower than in the physical mixtures of MCT/LCT already commercially available in Europe. Replacing a part of LCT by MCT in SMOFlipid 20% reduces the total amount of PUFAs, and thus reduces the risk of lipid peroxidation and the associated requirements for antioxidants [21].

Olive oil
SMOFlipid 20% contains 50 g/L olive oil which includes LCT rich in monounsaturated fatty acid (MUFA). Olive oil is rich in the immunologically inert MUFA oleic acid (C18:1ω9) and mainly provides energy.

MUFAs are less prone to lipid peroxidation than PUFAs due to fewer double bonds in the carbon chains.

Fish oil
Fish oil is characterized by a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both of which belong to the PUFA ω-3 LCFA family. DHA and EPA are important structural and functional components of cell membranes, and EPA is also a precursor of eicosanoids such as prostaglandins, thromboxanes, and leukotrienes, which exhibit a lower inflammatory potential than those derived from ω-6 PUFA arachidonic acid (AA).

Administration of ω-3 fatty acids is followed by an increased ω-3/ω-6 fatty acid ratio in the cell membranes. SMOFlipid contains 15% fish oil. After 5 days post-operative total parenteral nutrition with SMOFlipid, ω-3 fatty acids as well as ω-3/ω-6 fatty acid ratio were significantly

increased in plasma phospholipids and also in leukocytes and platelets compared to a soybean oil emulsion treatment. As a consequence, the EPA/AA ratio was increased resulting in a significantly higher leukotriene B5 (LTB5) release of neutrophils after stimulation versus the control group. Leukotriene B4 (derived from AA) remained similar in both groups leading to a significantly increased LTB5/LTB4 ratio in the SMOFlipid group only [22].

Amino acids (Aminoven 10%)

Pharmacokinetics

The amino acids in Aminoven 10% enter the plasma pool of corresponding free amino acids. From the intravascular space, amino acids distribute to the interstitial fluid and into the intracellular space. Plasma and intracellular free amino acid concentrations are endogenously regulated within narrow ranges, depending on age, nutritional status, and pathological condition of the patient.

Balanced amino acid solutions such as Aminoven 10% do not significantly alter the physiological amino acid pool when infused at a constant and slow infusion rate.

Characteristic changes in the physiological plasma amino acid pool occur when the regulative function of essential organs like liver and kidneys are seriously impaired. In such cases special formulated amino acid solutions may be recommended for restoring homeostasis.

Only a small proportion of the infused amino acids is eliminated by the kidneys. For the majority of amino acids plasma half-lives between 10 and 30 minutes have been reported.

Pharmacodynamics

The amino acids contained in Aminoven 10% are all naturally occurring physiological compounds. Amino acid solutions provide the building blocks for protein synthesis and are a source of energy. Furthermore, amino acids serve as precursors of various biochemical pathways and are important signalling molecules mediating multiple cellular communication processes. The individual amino acids show different pharmacodynamic properties.

Dextrose (Glucose 42%)

Pharmacokinetics

Depending on the nutritional state, dextrose can be rapidly metabolized in carbon dioxide and water, stored in the liver and muscles as glycogen, or converted to fat in adipose tissue.

Pharmacodynamics

Dextrose is the main source of energy for the body and contributes to glucose metabolism.

MICROBIOLOGY

Not Applicable

TOXICOLOGY

Studies performed with SmofKabiven
A local tolerance study in rabbits and an in vitro hemocompatibility study have been performed with SmofKabiven[23,24]. Both studies showed good local tolerance and no signs of incompatibility.

Further preclinical studies with SmofKabiven have not been performed. However, preclinical data for SMOFlipid as well as amino acid and dextrose solutions of various concentrations and sodium glycerophosphate reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

The following toxicological studies have been performed with SMOFlipid.

Type of study	Species	SMOFlipid Doses g TG/kg bw/day	Observations and conclusions
Single-Dose Toxicity			
	Rat	9, 18, 36,	No significant toxicity associated with SMOFlipid up to a dose level of 18 g TG/kg bw (90 mL/kg bw). At 36 g TG/kg bw. toxic signs were observed due to the excessive administration of fluid volume [25]
Repeat-Dose Toxicity			
26-day	Rat	12, 15, 18	Two continuous intravenous infusion (24 hours/day) studies with SMOFlipid® 20% in rats at doses up to 18 and 9 g TG/kg bw/day and initially scheduled for 42 days and 8 weeks had to be terminated after 26 and 30 days, respectively, due to high mortality in the treated groups. A combination of the physical nature of the test material, the flow rate and 24 hour/day continuous exposure were not compatible with the intended duration of infusion. It was concluded that subchronic or chronic 24-hour a day continuous intravenous infusion of total parenteral nutrition products in the rat model is not feasible. There was no difference between SMOFlipid® 20% and Intralipid® 20% as the reference product. [26, 27]
30-day	Rat	3, 6, 9*	

Type of study	Species	SMOFlipid Doses g TG/kg bw/day	Observations and conclusions
4-week	Dog	9*	Good tolerance was demonstrated. An adjustment to the intravenous supply of energy was indicated by a dose-related reduction in food intake over time. A dose- and time-related reduction in lymphocytes and thrombocytes was found after high doses, i.e., 9 and 6 g TG/kg bw/day, respectively. Serum cholesterol and phospholipids were increased approx. in proportion to the molar dose of TG and reversed completely within 4 weeks of recovery. Significant morphological changes were fatty changes in hepatocytes (fat in the centriacinar region); lungs (foci of granulomatous pneumonia) and kidney (interstitial nephritis). At the end of the 4-week recovery period all afore described drug substance-related changes had subsided [28, 29].
13-week	Dog	3, 6**	
Genotoxicity			
In vitro			
Bacterial gene mutation	*S. typhimurium*	Up to 40 mg/plate	No mutagenic effects were observed [30, 31, 32]
Chromosomal aberration	Human lymphocytes	Up to 5 mg/mL	
HPRT-test	V79 cells	Up to 10 mg/mL	
In vivo			
Bone marrow cytogenetic test	Rat	10	No mutagenic effect was observed [33]
Local Tolerance			
	Rabbit (iv,ia,pv,sc,im) Dog		*SMOFlipid 20%* revealed good local compliance in rabbits after intravenous infusion and following intra-arterial, paravenous and subcutaneous administration. Moderate local changes which had disappeared after 14 days were observed after intramuscular administration [34]. In the 4-week and 13-week repeat dose toxicity intravenous infusion studies in peripheral veins with *SMOFlipid 20%*, a similar slight to moderate reaction, mainly characterized by induration and swelling, was seen at the infusion sites in dogs in the test, reference, and control groups at similar incidence and severity. The vascular changes were consistent with the anticipated response to repeated venipuncture[28-29] The osmolality of *SMOFlipid 20%* is approximately 380 mOsm/kg water and similar that of human serum (281-297 mOsm/kg water).

*Reference Soybean oil emulsion
**Reference: 0.9% NaCl solution

No reproductive toxicity studies have been performed with SMOFlipid. However, studies have been performed with the individual components of SMOFlipid (LCT, MCT, olive oil, and fish oil) without revealing any toxic potential.
Safety pharmacology studies have not been performed with SMOFlipid. However, SMOFlipid repeat dose toxicity studies did not reveal any adverse effects on any organ system or function.

In toxicological studies performed with SMOFlipid no other effects than those expected after high doses of lipids were observed, based on single dose and repeat dose toxicity. No signs of genotoxic potential were detected in the respective studies. In a local tolerance study in rabbits, good local compliance was observed after intravenous infusion and following intra-arterial paravenous and subcutaneous administration. Moderate local changes observed after intramuscular administration disappeared after 14 days.

The following toxicological studies have been performed with Vamin or Novamine as a representative for Aminoven.

Type of study	Species	Vamin Novamine Doses g N/kg bw/day	Observations and conclusions
Safety Pharmacology			
	Cat	0.86	Study on cardiovascular, respiratory and metabolic functions after intravenous infusion of Vamin 18 EF showed no effects of biological/clinical significance in anesthetized cats [35].
Single-Dose Toxicity			
	Mouse	0.95	Vamin 18 EF was given to male mice at a dose of 50 mL/kg bw. for 7.5 hours without any symptoms of toxicity [36]
Repeat-Dose Toxicity			
4-week	Rat	3	Vamin 18 EF was infused for 20 h/day. The dose level was adequately high as they are in the order of 13.6 times the maximum recommend daily clinical dose of Vamin 18 Novum. Overall, the animals tolerated the solution very well [37].
4-week	Dog	0.42	In the 4-week study Vamin 14 was intravenously infused into alternate peripheral veins for 4 weeks. In the 13-week study Vamin 18 EF was administered by daily 12 h intravenous infusion into a central vein. In both studies, dogs tolerated the amino acid solutions well and did not show any treatment related clinical chemical or histopathological changes [38, 39].
13-week	Dog	0.94	

Type of study	Species	Vamin Novamine Doses g N/kg bw/day	Observations and conclusions
Genotoxicity			
In vitro			
Bacterial gene mutation	*S. typhimurium* *E. coli*	Up to 10 mg AA/plate	No mutagenic effects were observed for tested amino acid solution [40, 41].
Mouse lymphoma	L5178Y cells	Up to 10 mg AA/mL	
Reproductive and Developmental Toxicity			
Embryo-Fetal	Rabbit	0.54	A teratogenicity study in rabbits with Vamin 18 EF given intravenously on day 6-18 of pregnancy for 4 hours/day revealed no significant toxicity in dams or any embryotoxic or teratogenic effects [42].
Local Tolerance			
	Rabbit (iv,ia,pv,sc,im) Dog		Studies on Local Tolerance in the rabbit have been performed with *Aminomix Peripheral***. They revealed a good local compliance in rabbits after intravenous infusion and following intra-arterial, paravenous and subcutaneous administration [43]. In addition, the local tolerance of different *Vamin* solutions was thoroughly investigated in the respective repeated dose toxicity studies in rats and dogs both as part of the daily clinical observation and by histopathology at the end of the study. [37, 38,-39].
Other Toxicity Studies			
	Haemolysis (Human blood)		In vitro studies investigating hemocompatibility have been performed with *Aminomix Peripheral**. Incompatibility or hemolytic reactions were not observed [44].

* 2 chamber bag containing Glucose (63g per liter) and amino acids (35g per liter)

The following toxicological studies have been performed with Glycerophosphate:

Type of study	Species	Glycerophosphate Doses g /kg bw/day	Observations and conclusions
Safety Pharmacology			
	Cat	0.118	Study on cardiovascular functions after intravenous infusion of DP-Trauma 20% showed no effects of biological/clinical significance in anesthetized cats [35].

Type of study	Species	Glycerophosphate Doses g /kg bw/day	Observations and conclusions
Single-Dose Toxicity			
	Mouse	0.96	No toxic effects were observed in mice given 60 mL /kg of Na-GP intravenously [45].
	Rat	0.073	Intravenous administration of a single dose of 17 mL/kg of a glycerophosphate containing dipeptide amino acid solution was tolerated well [46].
		1-6	LD 50 was found to be 3800 to 3400 mg/kg, respectively, for alpha and beta glycerophosphate after intravenous administration to rats [47].
Repeat-Dose Toxicity			
4-week	Rat	0.409	In a 4-week toxicity study of DP-Trauma 20% a dipeptide/amino acid solution containing sodium glycerophosphate no adverse clinical signs and no clinical or morphological evidence of organ toxicity were observed in rats after daily infusion of 94.6 mL/kg over 20 hours [37].
2-week	Dog	1 bid	In a 2-week toxicity study of 1000 mg/kg sodium-beta glycerophosphate twice per day was well tolerated and did not cause any signs of toxicity. This corresponds to a dose which was 28.2 times the maximum human dose [47]
4-week	Dog	0.066	In a 4-week toxicity study of DP-Trauma 20% a dipeptide/amino acid solution containing sodium glycerophosphate, no adverse clinical signs and no clinical or morphological evidence of organ toxicity were observed in dogs after daily infusion of 15 mL/kg over 6 hours [48].
Genotoxicity			
In vitro			
Bacterial gene mutation	*S. typhimurium*	Up to 5 mg/plate	No mutagenic effects were observed [49, 50].
Mouse lymphoma	L5178Y cells	Up to 2.16 mg/mL	
In vivo			
Bone marrow micronucleus	Mouse	2160 mg/kg bw intravenous bolus	No mutagenic effect was observed[51].
Local Tolerance			
	Rabbit (iv,ia,pv,sc,im)		Studies on Local Tolerance in rabbits have been performed with *Aminomix Peripheral**. They revealed good local compliance in rabbits after intravenous infusion and following intra-arterial, paravenous and subcutaneous administration [43]

Type of study	Species	Glycerophosphate Doses g /kg bw/day	Observations and conclusions
	Dog		In addition, the local tolerance of different glycerophosphate containing amino acid solutions was thoroughly investigated in the respective repeated dose toxicity studies in dogs both as part of the daily clinical observation and by histopathology at the end of the study [47, 48]
Other Toxicity Studies			
	Haemolysis (Human blood)		In vitro studies on hemocompatibility have been performed with *Aminomix Peripheral**. They did not show any incompatibility reactions or hemolytic properties [44]

*2 chamber bag containing Glucose (63g per liter) and Amino acids (35g per liter)

No teratogenic effects or other embryotoxic injuries could be observed in rabbits with amino acid solutions and are not to be expected from lipid emulsions and sodium glycerophosphate when given at the recommended doses during parenteral nutrition. Nutritional products (amino acid solutions, lipid emulsions, and sodium glycerophosphate) used during parenteral nutrition to maintain normal levels are not expected to be embryotoxic, teratogenic, or to influence reproductive performance or fertility.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

SmofKabiven®
Amino acids with electrolytes, dextrose and lipid injectable emulsion
5.1% & 0.7% / 12.7% / 3.8%; w/v

SmofKabiven® extra Nitrogen
Amino acids with electrolytes, dextrose and lipid injectable emulsion
6.5% & 0.7% / 8.5% / 2.9%; w/v

Read this carefully before you start taking **SmofKabiven** or **SmofKabiven extra Nitrogen** and each time you get a refill. This leaflet is a summary and will not tell you everything about SmofKabiven and SmofKabiven extra Nitrogen. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about SmofKabiven and SmofKabiven extra Nitrogen.

What are SmofKabiven and SmofKabiven extra Nitrogen used for?

SmofKabiven and SmofKabiven extra Nitrogen infusions deliver nutrition directly into your blood, when normal eating is not possible or appropriate for you.

How do SmofKabiven and SmofKabiven extra Nitrogen work?

SmofKabiven and SmofKabiven extra Nitrogen contain a mixture of fats, sugar and amino acids (building blocks for proteins) with salts. These are used to provide energy and nutrients when other forms of feeding are not enough or possible.

Your healthcare professionals may add more salts, vitamins and minerals to SmofKabiven and SmofKabiven extra Nitrogen.

What are the ingredients in SmofKabiven and SmofKabiven extra Nitrogen?

Medicinal ingredients:

Each 100 mL of mixed product for **SmofKabiven** contains:

Amino acids (building blocks for proteins)
Alanine 710 mg, arginine 610 mg, glycine 560 mg, histidine 150 mg, isoleucine 250 mg, leucine 380 mg, lysine acetate 340 mg, methionine 220 mg, phenylalanine 260 mg, proline 570 mg, serine 330 mg, taurine 50 mg, threonine 220 mg, tryptophan 100 mg, tyrosine 20 mg and valine 310 mg.

Electrolytes (salts)
Sodium acetate trihydrate 170 mg, calcium chloride dihydrate 20 mg, potassium chloride 230 mg, sodium glycerophosphate anhydrous 210 mg, magnesium sulfate heptahydrate 61 mg and zinc sulfate heptahydrate 0.66 mg

Lipids (fats)
Soybean oil 1140 mg, medium-chain triglycerides 1140 mg, olive oil 950 mg and fish oil 570 mg

Dextrose (sugar)
As glucose monohydrate 12.7 g

Each 100 mL of mixed product for **SmofKabiven extra Nitrogen** contains:

Amino acids (building blocks for proteins)
Alanine 920 mg, arginine 790 mg, glycine 720 mg, histidine 200 mg, isoleucine 330 mg, leucine 480 mg, lysine acetate 430 mg, methionine 280 mg, phenylalanine 330 mg, proline 730 mg, serine 430 mg, taurine 65 mg, threonine 290 mg, tryptophan 130 mg, tyrosine 26 mg and valine 410 mg.

Electrolytes (salts)
Sodium acetate trihydrate 160 mg, calcium chloride dihydrate 28 mg, potassium chloride 230 mg, sodium

glycerophosphate anhydrous 230 mg, magnesium sulfate heptahydrate 61 mg and zinc sulfate heptahydrate 0.66 mg

Lipid (fats)
Soybean oil 870 mg, medium-chain triglycerides 870 mg, olive oil 720 mg and fish oil 430 mg

Dextrose (sugar)
As glucose monohydrate 8.5 g

Non-medicinal ingredients in SmofKabiven and SmofKabiven extra Nitrogen:
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 injection

SmofKabiven and SmofKabiven extra Nitrogen come in the following dosage forms:

SmofKabiven and SmofKabiven extra Nitrogen consist of three separate chambers:
- One chamber with a mixture of fats which is:
  - Like milk
  - Consistent
- One chamber with a solution of amino acids (building blocks for proteins) which is:
  - Clear
  - Colourless to slightly yellow
- One chamber with a sugar solution which is:
  - Clear
  - Colourless to slightly yellow

Before use, break the seals between the chambers to mix the components together. The mixture will be:
- Cloudy
- White
- Consistent

Do not use SmofKabiven and SmofKabiven extra Nitrogen if:

- You are allergic (hypersensitive) to fish, eggs, peanuts, soya or any of the ingredients in SmofKabiven and SmofKabiven extra Nitrogen (see **What are the ingredients in SmofKabiven and SmofKabiven extra Nitrogen**)
- You have very high amounts of fats in your blood (severe hyperlipidemia)
- Your liver does not work properly
- Your body cannot use amino acids properly since birth
- You have a severely reduced ability to stop bleeding
- Your kidneys do not work properly and you are not on any type of blood purification (dialysis or hemofiltration)
- You have such a drop in blood pressure that you could die (shock)
- Your blood sugar is out of control
- Your blood has high amounts of any of the salts included in SmofKabiven and SmofKabiven extra Nitrogen
- You have a disease affecting your blood and immune system, called hemophagocytotic syndrome
- You have water build-up in your lungs (acute pulmonary edema)
- You have excess water in your body (hyperhydration)
- You have acute heart failure
- You have an unstable medical condition

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SmofKabiven or SmofKabiven extra Nitrogen. Talk about any health conditions you may have, including if:

- You have high amounts of fats in your blood
- You have an allergy to soybean, fish or eggs, which may rarely cause allergic reactions. Soybean may also cause reactions in patients who are allergic to peanuts.
- You cannot use fats and amino acids (building blocks for proteins) properly because you have:
  - Kidney or liver problems
  - High levels of sugar in your blood (diabetes)
  - An inflamed pancreas (pancreatitis)
  - Low amounts of thyroid hormones (hypothyroidism)
  - A full-body infection (sepsis) that can lead to death
- You have heart problems
- You tend to retain high amounts of salts in your body
- You are pregnant or planning to become pregnant
- You are breast feeding or planning to breastfeed
- You are taking any other medications

Other warnings you should know about:
Severe allergic reaction: If you develop any symptoms of an allergic reaction while taking SmofKabiven or SmofKabiven extra Nitrogen stop the infusion and seek immediate medical help. Symptoms may include:
- Fever
- Shivering
- Sweating
- Headache
- Skin rashes
- Trouble breathing

Fat overload syndrome: This might happen if your body has problems using fats and you received too much SmofKabiven or SmofKabiven extra Nitrogen. It may also happen if there is a sudden change in your condition, such as kidney problems or an infection. Contact your healthcare professional immediately if you experience any of the following symptoms:
- Fever
- High levels of fats in your blood
- Yellowing of the skin and eyes
- A drop in the number of red blood cells
- Difficulty to stop bleeding
- A drop in the number of white blood cells and platelets
- Increase in the size of the liver and spleen
- Coma

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SmofKabiven and SmofKabiven extra Nitrogen:

- Blood-thinning substances
  Inform your doctor if you are taking any blood-thinning substances such as heparins or coumarins (warfarin) that help prevent blood clots.

  Soybean oil has a natural content of vitamin K1 which promotes blood clotting. However, the amount of soybean oil in SmofKabiven and SmofKabiven extra Nitrogen is very low and not expected to significantly prevent the blood-thinning effect of coumarins.

- Laboratory tests
  SmofKabiven and SmofKabiven extra Nitrogen may interfere with certain laboratory tests. It is important to tell any doctor doing tests that you are using SmofKabiven or SmofKabiven extra Nitrogen.

How to take SmofKabiven and SmofKabiven extra Nitrogen:

- SmofKabiven and SmofKabiven extra Nitrogen can be given:
  - In a hospital
  - In a managed care facility
  - At home
    - under the supervision of a healthcare professional.
    - by yourself, after receiving training and with the agreement of your healthcare team.
- Additional nutrients may be added by pharmacy professionals.
- Use SmofKabiven and SmofKabiven extra Nitrogen only if the mixture is consistent and looks like milk.
- Use only if the bag is not damaged.
- Use germ-free (aseptic) procedures.
- The bag should only be used once.
- Throw away any unused product.

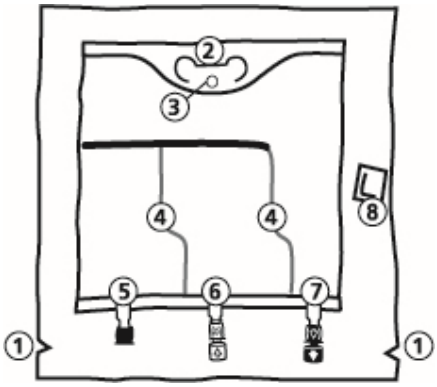
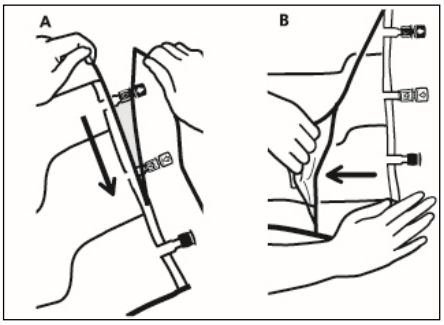
Usual adult dose:

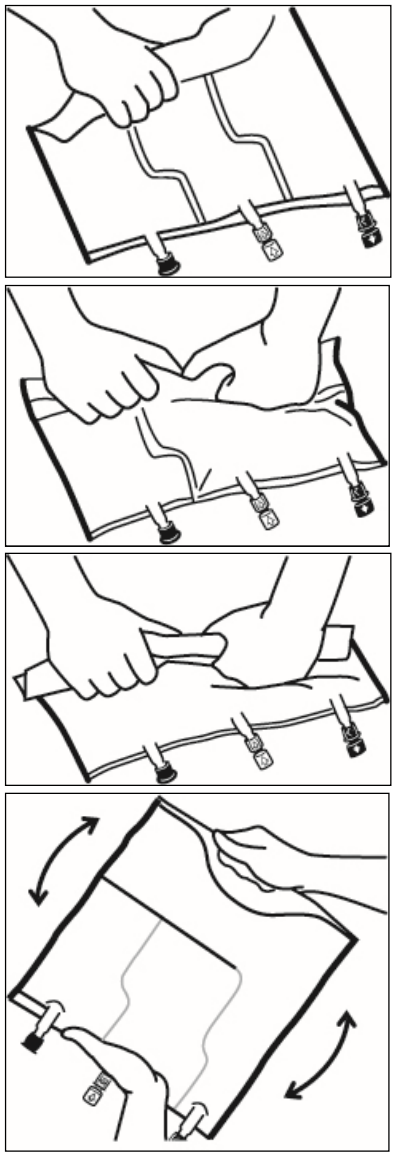
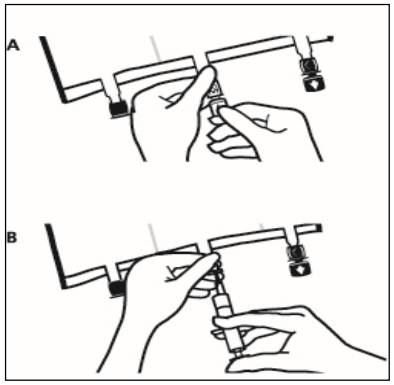
- You will receive your medicine by injection directly into your blood.
- Your healthcare professional will control how much and how fast SmofKabiven and SmofKabiven extra Nitrogen are given, based on your needs and medical condition.
- SmofKabiven and SmofKabiven extra Nitrogen should be given continuously, over 14 to 24 hours.
- Your doctor will monitor your condition and periodically test your blood and urine.

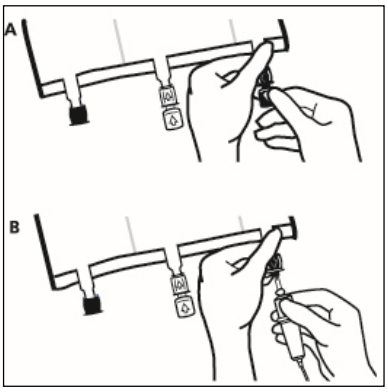
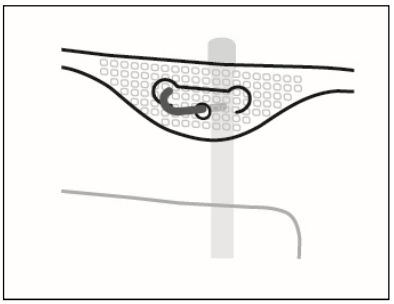
Instructions for use and handling

Before administering the product in the plastic bag to the patient, intravenously, review these directions:

These instructions are only intended as guidelines for product use. Please ask your healthcare professional for detailed instructions on handling.

The bag  	1. Notches in the overwrap 2. Handle 3. Hole for hanging the bag 4. Vertical seals 5. Blind port (only used during manufacturing) 6. WHITE Additive port 7. BLUE Infusion port 8. Oxygen absorber (present between bag and overwrap)
1 . Removal of overwrap  	• To remove overwrap, hold the bag horizontally and tear from the notch close to the ports along the upper edge (A). • Then simply tear the long side, pull off the overwrap and discard it along with the oxygen absorber (B).

2. Mixing 	• Place the bag on a clean, flat surface. The text side should be face up and the ports should be pointing away from you. • Roll up the bag tightly from the handle side towards the ports, first with the right hand and then applying a constant pressure with the left hand until the vertical seals are broken. The vertical peel seals open due to the pressure of the fluid. The peel seals can also be opened before removing the overwrap. **Please note:** The liquids mix easily even though the horizontal seal remains closed. • Mix the contents of the three chambers by inverting the bag three times until the components are thoroughly mixed. The entire contents of the bag will be white when mixed.
3. Finalising the preparation:  	• Place the bag on a clean, flat surface again. If injecting any additives, break off the tamper-evident arrow flag from the white additive port (A). **Please note:** The membrane in the additive port is sterile. • Hold the base of the additive port. Insert the needle, inject the additives (with known compatibility) through the centre of the injection site (B). • Mix thoroughly between each addition by inverting the bag three times. Use syringes with needles of 18-23 gauge and a length of max. 40 mm.

	• Immediately before inserting the infusion set, break off the tamper evident arrow flag from the blue infusion port (A). **Please note:** The membrane in the infusion port is sterile. • Use a non-vented infusion set or close the air-inlet on a vented set. • Hold the base of the infusion port. • Push the spike through the infusion port. The spike should be fully inserted to secure it in place. **Please note:** The inner part of the infusion port is sterile.
4. Hanging the bag 	• Hang the bag up by the hole below the handle.

<u>Overdose</u>:

If you think that the dose you have received was too high or was infused too quickly, inform your healthcare professional immediately. In case of overdose there is a risk of receiving too much fat. This is called "fat overload syndrome". In these cases, the infusion should be stopped or, if necessary, continued at a reduced dosage. See section "**Other warnings you should know about**" for more information.

If you have any further questions on the use of this product, ask your healthcare professional.

If you think you have taken too much SmofKabiven or SmofKabiven extra Nitrogen, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

<u>What are possible side effects from using SmofKabiven and SmofKabiven extra Nitrogen</u>?

These are not all the possible side effects you may feel when taking SmofKabiven and SmofKabiven extra Nitrogen. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Nausea
- Vomiting
- Chills

SmofKabiven and SmofKabiven extra Nitrogen can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Serious allergic reaction:** fever, shivering, skin rash, hives, redness, headache, or difficulty breathing			√
High blood pressure			√
Increased heart rate			√
Low blood pressure: dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.			√
Fat overload syndrome: fever, yellowing of the skin and eyes, coma			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store below 25 °C. Do not freeze.
Store bags in overwrap. Keep out of reach and sight of children.

Do not use SmofKabiven and SmofKabiven extra Nitrogen after the expiry date which is printed on the bag (YYYY-MM). The expiry date refers to the last day of the month.

Once the seals between the chambers have been broken and the product has been mixed, the product should be used immediately.

For patient comfort, SmofKabiven and SmofKabiven extra Nitrogen should be at room temperature before administration.

If you want more information about SmofKabiven or SmofKabiven extra Nitrogen:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication

Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp);
- the manufacturer's website (http://www.fresenius-kabi.ca), or by calling 1-877-821-7724 (toll-free-telephone).

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