NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SmofKabiven® (Infusion, emulsion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SmofKabiven is a three chamber bag system of amino acid solution with electrolytes, glucose solution and lipid emulsion for intravenous infusion.

Each bag contains the following partial volumes depending on the four pack sizes.

	986 mL	**1477 mL**	**1970 mL**	**2463 mL**	**Per 1000 mL**
Amino acid solution with electrolytes (mL)	500	750	1000	1250	508
Glucose 42% (mL)	298	446	595	744	302
Lipid emulsion (mL)	188	281	375	469	190

This corresponds to the following total compositions:

Active ingredients (g)	**986 mL**	**1477mL**	**1970 mL**	**2463 mL**	**Per 1000 mL**
Alanine	7.0	10.5	14.0	17.5	7.1
Arginine	6.0	9.0	12.0	15.0	6.1
Glycine	5.5	8.2	11.0	13.8	5.6
Histidine	1.5	2.2	3.0	3.7	1.5
Isoleucine	2.5	3.8	5.0	6.2	2.5
Leucine	3.7	5.6	7.4	9.4	3.8
Lysine (as acetate)	3.3	5.0	6.6	8.4	3.4
Methionine	2.2	3.2	4.3	5.4	2.2
Phenylalanine	2.6	3.8	5.1	6.4	2.6
Proline	5.6	8.4	11.2	14.0	5.7
Serine	3.2	4.9	6.5	8.1	3.3
Taurine	0.50	0.75	1.0	1.2	0.50
Threonine	2.2	3.3	4.4	5.4	2.2
Tryptophan	1.0	1.5	2.0	2.5	1.0
Tyrosine	0.20	0.30	0.40	0.49	0.20
Valine	3.1	4.6	6.2	7.6	3.1
Calcium chloride (as dihydrate)	0.28	0.42	0.56	0.69	0.28
Sodium glycerophosphate (as hydrate)	2.1	3.1	4.2	5.2	2.1
Magnesium sulfate (as heptahydrate)	0.60	0.90	1.2	1.5	0.61
Potassium chloride	2.2	3.4	4.5	5.7	2.3
Sodium acetate (as trihydrate)	1.7	2.6	3.4	4.2	1.7
Zinc sulfate (as heptahydrate)	0.0065	0.0097	0.013	0.016	0.0066
Glucose (as monohydrate)	125	187	250	313	127
Soya oil	11.3	16.9	22.5	28.1	11.4
Medium chain triglycerides	11.3	16.9	22.5	28.1	11.4
Olive oil	9.4	14.1	18.8	23.4	9.5
Rich in omega-3 fish oil	5.6	8.4	11.3	14.0	5.7

Corresponding to:

	986 mL	1477 mL	1970 mL	2463 mL	Per 1000 mL
• Amino acids (g)	50	75	100	125	51
• Nitrogen (g)	8	12	16	20	8
• Lipids (g)	38	56	75	94	38
• Carbohydrates – Glucose (anhydrous) (g)	125	187	250	313	127
• Electrolytes (mmol)					
- sodium	40	60	80	100	41
- potassium	30	45	60	74	30
- magnesium	5.0	7.5	10	12	5.1
- calcium	2.5	3.8	5.0	6.2	2.5
- phosphate[1]	12	19	25	31	13
- zinc	0.04	0.06	0.08	0.1	0.04
- sulfate	5.0	7.5	10	13	5.1
- chloride	35	52	70	89	36
- acetate	104	157	209	261	106
• Energy content					
- total (approx.)	1100 kcal 4600 kJ	1600 kcal 6700 kJ	2200 kcal 9200 kJ	2700 kcal 11300 kJ	
- non protein (approx.)	900 kcal 3800 kJ	1300 kcal 5400 kJ	1800kcal 7500 kJ	2200 kcal 9200 kJ	

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

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Infusion, emulsion.

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

Osmolality	approx. 1800 mOsm/kg water
Osmolarity	approx. 1500 mOsm/L
pH (after mixing)	approx. 5.6

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral nutrition for adult patients and children aged 2 years and above when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Dose and method of administration

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

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

The dose should be individualised to the patient's clinical condition, body weight (bw), nutritional and energy requirements, adjusting dosage based upon additional oral/enteral intake. 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).

Adults
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.

Dosage:
The dosage range of 13-31 ml SmofKabiven/kg bw/day will provide 0.6-1.6 g amino acids/kg bw/day (corresponds to 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). This covers the need of the majority of the patients. In obese patients the dose should be based on the estimated ideal weight.

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

The infusion rate should not exceed 2.0 ml/kg bw/h (corresponding to 0.10 g amino acids, 0.25 g glucose and 0.08 g lipids/kg bw/h). The recommended infusion period is 14-24 hours.

Maximum daily dose:
The maximum daily dose varies with the clinical condition of the patient and may even change from day to day. The recommended maximum daily dose is 35 ml/kg bw/day.

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

Paediatric population
Children (2-11 years)
Dosage:
The dose up to 35 ml/kg bw/day should be regularly adjusted to the requirements of the paediatric patient that varies more than in adult patients.

Infusion rate:
The recommended maximum infusion rate is 2.4 ml/kg bw/h (corresponding to 0.12 g amino acids/kg/h, 0.30 g/glucose/kg/h and 0.09 g lipids/kg/h). At the recommended maximum infusion rate, do not use an infusion period longer than 14 hours 30 minutes, except in exceptional cases and with careful monitoring.

The recommended infusion period is 12-24 hours.

Maximum daily dose:
The maximum daily dose varies with the clinical condition of the patient and may even change from day to day. The recommended maximum daily dose is 35 ml/kg bw/day.

The recommended maximum daily dose of 35 ml/kg bw/day will provide 1.8 g amino acids/kg bw/day (corresponding to 0.28 g nitrogen/kg bw/day), 4.5 g glucose/kg bw/day, 1.33 g lipids/kg

bw/day and a total energy content of 39 kcal/kg bw/day (corresponding to 31 kcal/kg bw/day of non-protein energy).

Adolescents (12-16/18 years)
In adolescents, SmofKabiven can be used as in adults.

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

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

For instructions on preparation of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to fish-, egg-, soya- or peanut protein or corn (maize) and corn products or to any of the active substances or excipients listed in section 6.1
- Severe hyperlipidaemia
- Severe liver insufficiency
- Severe blood coagulation disorders
- Congenital errors of amino acid metabolism
- Severe renal insufficiency without access to hemofiltration or dialysis
- Acute shock
- Uncontrolled hyperglycaemia
- Pathologically elevated serum levels of any of the included electrolytes
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, and decompensated cardiac insufficiency
- Haemophagocytotic 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)
- Infants and children under 2 years of age

4.4 Special warnings and precautions for use
The capacity to eliminate fat is individual and should therefore be monitored according to the routines of the clinician. This is in general done by checking the triglyceride levels. The concentration of triglycerides in serum should not exceed 3 mmol/L during infusion. An overdose may lead to fat overload syndrome. (Please also refer to "Fat overload syndrome").

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

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

To avoid risks associated with too rapid infusion rates, it is recommended to use a continuous and well-controlled infusion, if possible by using an appropriate infusion pump as per each hospital setting needs, e.g. a volumetric pump.

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.

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

SmofKabiven should be given with caution to patients with a tendency towards electrolyte retention. Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be discontinued.

The monitoring of serum glucose, electrolytes and osmolarity as well as fluid balance, acid-base status and liver enzyme tests is recommended.

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

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

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

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

The infusion should be stopped immediately at any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea).

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

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

SmofKabiven should not be given simultaneously with blood in the same infusion set due to the risk of pseudo-agglutination.

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

Amino acid solutions may precipitate acute folate deficiency; folic acid should therefore be given daily.

Vitamin B complex deficiency may occur with glucose administration.

Review of current available literature associated with Parenteral Nutrition Associated Liver Dysfunction (PNALD) shows emerging evidence indicating that fish oil-based lipid emulsions improve liver function within the scope of PN in general and may have the potential to reverse PNALD in children with short bowel syndrome.

Excessive exposure to light and UV light should be avoided as peroxide formation may occur.

Genotoxicity
The genotoxic potential of SmofKabiven has not been assessed. The lipid component of SmofKabiven, SMOFlipid, was not mutagenic or clastogenic in a battery of genotoxicity studies, including the Ames bacterial mutagenicity assay, a mammalian mutagenicity assay, a chromosome aberration assay in human peripheral lymphocytes, and an *in vivo* rat micronucleus assay.

Carcinogenicity
No carcinogenicity studies have been conducted with the combined components of SmofKabiven.

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

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

Fat overload syndrome
Impaired capacity to eliminate triglycerides can lead to "Fat overload syndrome" which may be caused by overdose. Patients should be monitored for possible signs of metabolic overload. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient's clinical condition, such as renal function impairment or infection. Fat overload syndrome is characterised by hyperlipidaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopaenia, thrombocytopaenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued. Should signs of a fat overload syndrome occur, the infusion of SmofKabiven should be discontinued.

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

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

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

Heparin given in clinical doses causes a transient release of lipoprotein lipase into the circulation. This may result initially in increased plasma lipolysis followed by a transient decrease in triglyceride clearance.

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

4.6 Fertility, pregnancy and lactation
Fertility
The potential effects of SmofKabiven on fertility and general reproductive performance have not been determined in animal studies.

Pregnancy
There are no adequate and well-controlled studies in pregnant women with SmofKabiven or its individual components; therefore the safety of SmofKabiven in pregnant women is not known.

No animal studies have been conducted with the combined lipid components of SmofKabiven to evaluate effects on reproduction. Embryotoxicity and increased incidences of foetal skeletal variations have been observed in rabbits that had received medium chain fatty acid-containing lipids similar to those in SmofKabiven during the period of organogenesis. SmofKabiven should not be used during pregnancy unless the expected therapeutic benefit clearly outweighs the potential risk to the foetus.

Breast-feeding
It is not known whether SmofKabiven can enter maternal milk. As zinc is excreted in milk, there is a theoretical risk of zinc-induced copper deficiency in the infant at high doses of SmofKabiven. SmofKabiven should be used during lactation only if clearly needed.

4.7 Effects on ability to drive and use machines
No effects on the ability to drive and use machines are to be expected.

4.8 Undesirable effects
Adverse events with at least possible relationship to the study drug observed in the study 03-3CB7-001 are presented in Table 1 below.

Table 1. Adverse events with at least possible relationship to the study drug in the study 03-3CB7-007

Adverse events sorted according to the relationship to study drug n(%) of patients		Treatment group	
		SmofKabiven (n=26)	Comparator (n=27)
Probable	Subjects with remarks	1 (3.8)	-
	Nausea	1 (3.8)	-
Possible	Subjects with remarks	16 (61.5)	11 (40.7)
	Nausea	4 (15.4)	7 (25.9)
	Vomiting NOS	7 (26.9)	2 (7.4)
	Flatulence	4 (15.4)	1 (3.7)
	Abdominal Pain NOS	-	1 (3.7)
	Hyperglycaemia NOS	1 (3.8)	-
	Hypertension NOS	1 (3.8)	-
	Oedema NOS	1 (3.8)	-

NOS: Not otherwise specified. The study was performed in patients with mainly gastric or colon cancers and existing gastrointestinal disorders and elevated CRP in all subjects before inclusion in the study.

Drug-related adverse events have been reported from clinical studies with the separate components of SmofKabiven, SMOFlipid 20% and Aminoven 10%.

Table 2 below lists the common drug-related Treatment-Emergent Adverse Events (TEAEs) in SMOFlipid 20% and comparator pooled groups (i.e those occurring in more than 2 patients of any pooled group) observed in 7 clinical trials.

Table 2. Drug-related TEAEs in SMOFlipid 20% and comparator pooled groups observed in 7 clinical trials

Drug-related TEAEs n(%) of patients	Treatment group	
	SMOFlipid 20% pooled (n=282)	Comparator pooled (n=276)
Number of patients with at least 1 drug-related TEAE	45 (16.0)	43 (15.6)
Nausea	12 (4.3)	13 (4.7)
Vomiting	12 (4.3)	6 (2.2)
Blood triglycerides increased	6 (2.1)	3 (1.1)
Hyperglycaemia	5 (1.8)	3 (1.1)
Hyperbilirubinaemia	4 (1.4)	5 (1.8)
Flatulence	4 (1.4)	1 (0.4)
Liver function test abnormal	2 (0.7)	3 (1.1)
Hypertriglyceridaemia	2 (0.7)	3 (1.1)
Gamma-glutamyltransferase increased	1 (0.4)	3 (1.1)

Table 3 below lists the drug-related adverse events reported in the clinical study AS CS 01 FR with Aminoven 10%.

Table 3. Drug-related Adverse Events observed in the clinical study AS CS 01 FR

Drug-related AEs n(%) of patients	Treatment group	
	Aminoven 10% (n=16)	Comparator (n=14)
Alkaline phosphatase elevations	1 (6.3)	1 (7.1)
Hyperglycaemia + osmotic polyurea	1 (6.3)	-

* Related could be expanded as dubious, possible, likely or very likely

Adverse Events provided below in Table 4 are based on general assessment of trials and clinical experience of the product SmofKabiven. This table is also provided in the European SmPC.

Table 4. SmofKabiven Adverse Events from trials and clinical experience

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

Should these side-effects occur the risk-benefits assessment of continuing infusion of SmofKabiven should be performed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions.
https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose
Please also refer to sections "Fat overload syndrome", "Excess of amino acid infusion" and "Excess of glucose infusion".

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

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

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

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

For information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Solutions for parenteral nutrition.
ATC code: B05BA10

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

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

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

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

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

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

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

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

5.2 Pharmacokinetic properties
Lipid emulsion
The individual triglycerides in SMOFlipid have different clearance rates.

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

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

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

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

5.3 Preclinical safety data
Preclinical safety studies with SmofKabiven have not been performed. However, preclinical data for SMOFlipid as well as amino acid and glucose solutions of various concentrations and sodium glycerophosphate reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. No teratogenic effects or other embryotoxic injuries could be observed in rabbits with amino acid solutions and are not to be expected from fat emulsions and sodium glycerophosphate when giving at the recommended doses as substitution therapy.Nutritional products (amino acid solutions, fat emulsions, and sodium glycerophosphate) used in replacement therapy at physiological levels are not expected to be embryotoxic, teratogenic, or to influence reproductive performance or fertility.

In a test on guinea pigs (maximisation test) fish oil emulsion showed moderate dermal sensitisation. A systemic antigenicity test gave no indication of evidence of anaphylactic potential of fish oil.

In a local tolerance study in rabbits with SMOFlipid a slight, transient inflammation after intra-arterial, paravenous or subcutaneous administration was observed. After intra-muscular administration a moderate transient inflammation and tissue necrosis were seen in some animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Glycerol
Egg lecithin
all-*rac*-α-Tocopherol
Nitrogen
Sodium hydroxide (pH adjuster)
Sodium oleate
Acetic acid, glacial (pH adjuster)
Hydrochloric acid (pH adjuster)
Water for injections

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

6.3 Shelf life
Shelf life of the medicinal product as packaged for sale
2 years

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

Shelf life after mixing with additives
From a microbiological point of view, the product should be used immediately when additions have been made. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage
Do not store above 25°C. Do not freeze. Store in overpouch.

Shelf life after mixing: See section 6.3.
Shelf life after mixing with additives: See section 6.3.

6.5 Nature and contents of container
Store below 25°C. Do not freeze. Store in overpouch.

The container consists of a multi-chamber inner bag and an overpouch. The inner bag is separated into three chambers by peelable seals. An oxygen absorber is placed between the inner bag and the overpouch. The inner bag is made of a multilayer polymer film – Excel or Biofine. The Excel innerbag film consists of three layers. The inner layer consists of poly(propylene/ethylene) copolymer and styrene/ethylene/butylene/styrene thermoplastic elastomer (SEBS). The middle layer consists of SEBS and the outer layer consists of copolyester-ether. The infusion port is equipped with a polyolefine cap. The additive port is equipped with a synthetic polyisoprene (latex-free) stopper**.**

The Biofine inner bag film consists of poly(propylene-co-ethylene), synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) and synthetic rubber poly(styrene-block-isoprene) (SIS). The infusion and additive ports are made of polypropylene and synthetic rubber 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.

<u>Pack sizes</u>
(Excel Bags)
1 x 986 mL, 4 x 986 mL
1 x 1477 mL, 4 x 1477 mL
1 x 1970 mL, 2 x 1970 mL
1 x 2463 mL, 2 x 2463 mL

(Biofine Bags)
1 x 986 mL, 4 x 986 mL
1 x 1477 mL, 4 x 1477 mL
1 x 1970 mL, 4 x 1970 mL
1 x 2463 mL, 3 x 2463 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

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

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

Compatibility

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

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

Excessive exposure to light and UV light should be avoided as peroxide formation may occur.

Any additions should be made aseptically.

7. MEDICINE SCHEDULE

General Sale Medicine

8. SPONSOR

Fresenius Kabi New Zealand Limited
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9. DATE OF FIRST APPROVAL

17 January 2013

10. DATE OF REVISION OF THE TEXT

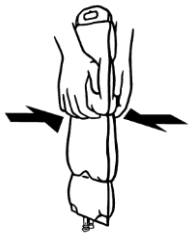
18 July 2017

SPECIAL HANDLING INSTRUCTIONS

Diagram 1 – Excel bag

1. To remove the cover wrap hold the bag upright and tear from the notch along the upper edge, then simply tear open the long side, pull off the plastic covering and discard it along with the oxygen absorber

2.



To mix the contents of the bag, place your fingertips on the upper compartment just on the seal as shown on the picture.

3 a.

Grip the sides of the upper chamber with your fingertips and your thumbs and gently roll your knuckles together until the seal breaks.

3 b.

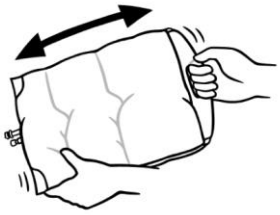
<u>Alternative technique:</u>

Put the bag, either with or without the cover wrap on a flat surface. Roll up the bag against the surface by using the handle until the seals are opened. Mix thoroughly by inverting the bag.

4.

The remaining section of seal may now be gently teased apart.

5.



To peel open the lower seal, use the same technique as described above. Mix thoroughly by gently inverting the bag end-over-end several times.

6

Before injecting additives swab the additive port with disinfectant.

7.

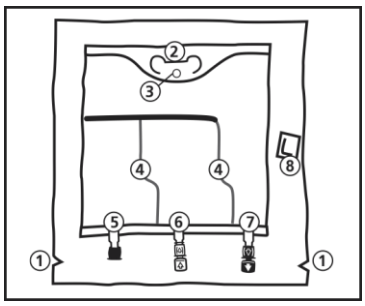
Support the base of the additive port. Fully insert the needle and inject the additives (with known compatibility) through the centre of the injection site. Mix thoroughly between each addition by inverting the bag several times.

8.

Use a non-vented infusion set or close the air-inlet on a vented set. Remove the set port cover by pulling the ring upwards. Support the base of the infusion port. Insert the spike straight into the infusion port. Twist and push the spike through the diaphragm. The spike should be fully inserted to secure it in place.

Diagram 2 – Biofine bag

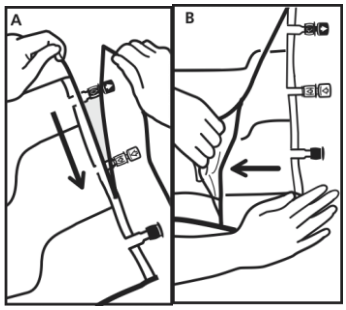
(1) Notches in the overpouch
(2) Handle
(3) Hole for hanging the bag
(4) Peelable seals
(5) Blind port (only used during manufacturing)
(6) Additive port
(7) Infusion port
(8) Oxygen absorber



1. Removal of overpouch

• (A) To remove overpouch, hold the bag horizontally and tear from the notch close to the ports along the upper edge.

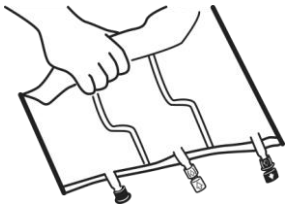
• (B) Then simply tear the long side, pull off the overpouch and discard it along with the oxygen absorber.



2. Mixing

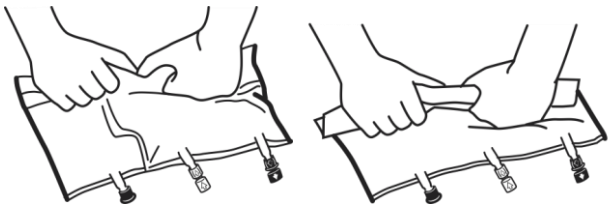
• Place the bag on a flat surface with text side up and ports pointing away.

• Starting from the right hand corner, roll the bag tightly and diagonally with the right hand.

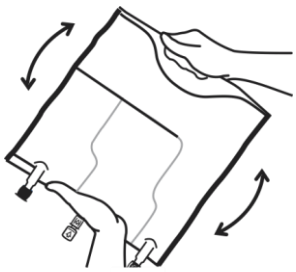


• Then applying a constant pressure with the left hand roll straight until the vertical seals are broken. The vertical peel seals open due to the pressure of the fluid. The peel seals can also be opened before removing the overpouch.

Please note: The liquids mix easily although the horizontal seal remains closed.



• Mix the contents of the three chambers by inverting the bag three times until the components are thoroughly mixed.



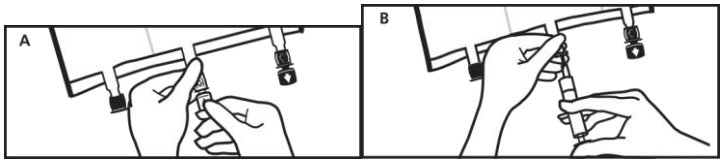
3. Finalising the preparation:

• (A) Place the bag on a flat surface with text side up again. Shortly before injecting the additives, break off the tamper-evident arrow flag from the white additive port.

Please note: The membrane in the additive port is sterile.

• (B) Hold the base of the additive port. Insert the needle, inject the additives (with known compatibility) through the centre of the injection site.

• Mix thoroughly between each addition by inverting the bag three times. Use syringes with needles of 18-23 gauge and a maximum length of 40 mm.



• (C) Shortly before inserting the infusion set, break off the tamper evident arrow flag from the blue infusion port.

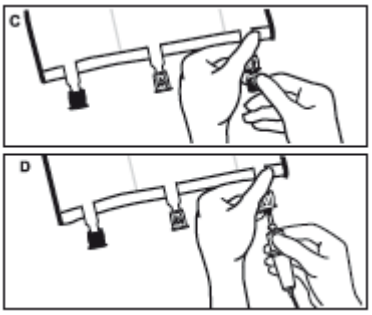
Please note: The membrane in the infusion port is sterile.

• (D) 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 up the bag

• Hang the bag up by the hole below the handle.