AUSTRALIAN PRODUCT INFORMATION – SMOFKABIVEN LOW OSMO (AMINO ACIDS 2.5%, ELECTROLYTES 0.4%, LIPIDS 3.5% and GLUCOSE 6.8%)

1. NAME OF THE MEDICINE

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

The active ingredients are:

AMINO ACIDS 2.5%: Alanine, Arginine, Glycine, Histidine, Isoleucine, Leucine, Lysine acetate, Methionine, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine.

ELECTROLYTES 0.4%: Calcium chloride dihydrate, Sodium glycerophosphate hydrate, Magnesium sulfate heptahydrate, Potassium chloride, Sodium acetate trihydrate, Zinc sulfate heptahydrate.

LIPIDS 3.5%: Soya oil, Fish oil - rich in Omega-3 acids, Medium-chain triglycerides, Olive oil.

GLUCOSE 6.8%: Glucose monohydrate.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

	850 mL[1]	**1400 mL**	**1950 mL**	**2500 mL[1]**	**Per 1000 mL**
Amino acid solution 10% with electrolytes	213 mL	350 mL	488 mL	625 mL	250 mL
Glucose 11.8%	489 mL	805 mL	1121 mL	1438 mL	575 mL
Lipid emulsion 20%	149 mL	245 mL	341 mL	438 mL	175 mL

This corresponds to the following total compositions:

Active ingredients	**850 mL**	**1400 mL**	**1950 mL**	**2500 mL**	**Per 1000 mL**
Alanine	3.0 g	4.9 g	6.8 g	8.8 g	3.5 g
Arginine	2.6 g	4.2 g	5.9 g	7.5 g	3.0 g
Glycine	2.3 g	3.9 g	5.4 g	6.9 g	2.8 g
Histidine	0.64 g	1.1 g	1.5 g	1.9 g	0.75 g
Isoleucine	1.1 g	1.8 g	2.4 g	3.1 g	1.3 g
Leucine	1.6 g	2.6 g	3.6 g	4.6 g	1.9 g
Lysine acetate *corresponding to* Lysine	1.4 g	2.3 g	3.2 g	4.1 g	1.7 g
Methionine	0.92 g	1.5 g	2.1 g	2.7 g	1.1 g
Phenylalanine	1.1 g	1.8 g	2.5 g	3.2 g	1.3 g
Proline	2.4 g	3.9 g	5.5 g	7.0 g	2.8 g
Serine	1.4 g	2.3 g	3.2 g	4.1 g	1.6 g
Taurine	0.21 g	0.35 g	0.49 g	0.63 g	0.25 g
Threonine	0.94 g	1.5 g	2.1 g	2.8 g	1.1 g
Tryptophan	0.43 g	0.70 g	0.98 g	1.3 g	0.50 g

[1] The total volume for bags is shown as the sum of the non-rounded chamber volumes

Active ingredients	**850 mL**	**1400 mL**	**1950 mL**	**2500 mL**	**Per 1000 mL**
Tyrosine	0.085 g	0.14 g	0.20 g	0.25 g	0.10 g
Valine	1.3 g	2.2 g	3.0 g	3.9 g	1.6 g
Calcium chloride dihydrate *corresponding to* Calcium chloride	0.12 g	0.20 g	0.27 g	0.35 g	0.14 g
Sodium glycerophosphate (hydrate) *corresponding to* Sodium glycerophosphate	0.89 g	1.5 g	2.0 g	2.6 g	1.0 g
Magnesium sulphate heptahydrate *corresponding to* Magnesium sulphate	0.26 g	0.42 g	0.59 g	0.75 g	0.30 g
Potassium chloride	0.95 g	1.6 g	2.2 g	2.8 g	1.1 g
Sodium acetate trihydrate *corresponding to* Sodium acetate	0.72 g	1.2 g	1.7 g	2.1 g	0.85 g
Zinc sulphate heptahydrate *corresponding to* Zinc sulphate	0.0027 g	0.0045 g	0.0063 g	0.0081 g	0.0032 g
Glucose monohydrate *corresponding to* Glucose (anhydrous)	58 g	95 g	132 g	170 g	68 g
Soya-bean oil, refined	8.9 g	15 g	20 g	26 g	11 g
Medium-chain triglycerides	8.9 g	15 g	20 g	26 g	11 g
Olive oil, refined	7.5 g	12 g	17 g	22 g	8.8 g
Fish oil, rich in omega-3-acids	4.5 g	7.4 g	10 g	13 g	5.3 g

Corresponding to:

	850 mL	**1400 mL**	**1950 mL**	**2500 mL**	**Per 1000 mL**
Amino acids	21.3 g	35.0 g	48.8 g	62.6 g	25.0 g
Nitrogen	3.41 g	5.60 g	7.81 g	10.0 g	4.00 g
Electrolytes					
- sodium	17 mmol	28 mmol	39 mmol	50 mmol	20 mmol
- potassium	13 mmol	21 mmol	29 mmol	38 mmol	15 mmol
- magnesium	2.1 mmol	3.5 mmol	4.9 mmol	6.3 mmol	2.5 mmol
- calcium	1.1 mmol	1.8 mmol	2.5 mmol	3.1 mmol	1.3 mmol
- phosphate[1]	6.4 mmol	10 mmol	15 mmol	19 mmol	7.5 mmol
- zinc	0.017 mmol	0.028 mmol	0.039 mmol	0.050 mmol	0.020 mmol
- sulfate	2.2 mmol	3.5 mmol	4.9 mmol	6.3 mmol	2.5 mmol
- chloride	15 mmol	25 mmol	34 mmol	44 mmol	18 mmol
- acetate	44 mmol	73 mmol	100 mmol	130 mmol	52 mmol
Carbohydrates					
- Glucose (anhydrous)	57.8 g	95.1 g	132 g	170 g	68.0 g

	850 mL	1400 mL	1950 mL	2500 mL	Per 1000 mL
Lipids	29.8 g	49.0 g	68.2 g	87.6 g	35.0 g
Energy content					
- total (approx.)	600 kcal/ 2.5 MJ	1000 kcal/ 4.2 MJ	1400 kcal/ 5.9 MJ	1800 kcal/ 7.5 MJ	723 kcal/ 3.03 MJ
- non-protein (approx.)	530 kcal/ 2.22 MJ	872 kcal/ 3.65 MJ	1215 kcal/ 5.08 MJ	1559 kcal/ 6.52 MJ	623 kcal/ 2.61 MJ
- glucose (approx.)[2]	246 kcal 1.03MJ	404 kcal 1.69 MJ	563 kcal 2.35 MJ	724 kcal 3.03 MJ	
- lipid (approx.)[3]	284 kcal 1.19 MJ	468 kcal 1.96 MJ	652 kcal 2.73 MJ	835 kcal 3.49 MJ	
- glucose/lipid ratio	46/54	46/54	46/54	46/54	
- protein[4] (g)/energy (kcal) ratio	1/29	1/29	1/29	1/29	

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

[2] Includes calories from glycerol

[3] Includes calories from egg lecithin (phospholipids)

[4] In the form of amino acids

Excipients with known effect: Egg lecithin

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Emulsion for intravenous infusion.

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

Osmolality: Approx. 870 mOsmol/kg water
Osmolarity: Approx. 750 mOsmol/L
pH (after mixing): Approx. 5.6

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Dosage (dose and interval)

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 Special warnings and precautions for use.

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).

As part of routine assessment, the clinician should assess the dosage infused and make adjustment if long term use is being considered especially regarding zinc levels.

Additives
SmofKabiven Low Osmo may not cover sufficiently the total nutrient requirements of paediatric patients and in such cases macro- and/or micronutrients should be provided in addition, as appropriate and at the discretion of the physician.
Trace elements, vitamins and possibly electrolytes (taking into account the electrolytes already present in SmofKabiven Low Osmo) should be added to SmofKabiven Low Osmo according to the patient's need.

The contents of the three separate chambers have to be mixed before any additions are made via the additive port.

Any additions should be made aseptically.

ADULTS
The requirements are 0.10-0.15 g nitrogen/kg bw/day (0.6-0.9 g amino acids/kg bw/day) in the normal nutritional state or in conditions with mild catabolic stress. In patients with moderate to high metabolic stress with or without malnutrition, the requirements are in the range of 0.15-0.25 g nitrogen/kg bw/day (0.9-1.6 g amino acids/kg bw/day). In some very special conditions (e.g. burns or marked anabolism) the nitrogen need may be even higher.

Dosage:
The dosage range of 20-40 mL SmofKabiven Low Osmo/kg bw/day corresponds to 0.08-0.16 g nitrogen/kg bw/day (0.5-1.0 g amino acids/kg bw/day) and 14-29 kcal/kg bw/day of total energy (12-25 kcal/kg bw/day of non-protein energy). This covers the need of the majority of the patients. In obese patients the dose should be based on the estimated ideal weight.

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

The infusion rate should not exceed 3.7 mL/kg bw/h (corresponding to 0.25 g glucose, 0.09 g amino acids, and 0.13 g lipids/kg bw/h). 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 40 mL/kg bw/day.

The recommended maximum daily dose of 40 mL/kg bw/day will provide 1.0 g amino acids/kg bw/day (corresponding to 0.16 g nitrogen/kg bw/day), 2.7 g glucose/kg bw/day, 1.4 g lipids/kg bw/day and a total energy content of 29 kcal/kg bw/day (corresponding to 25 kcal/kg·bw/day of non-protein energy).

Duration:
Peripheral administration of SmofKabiven Low Osmo in adults is suitable for a limited period (days to a couple of weeks).

PAEDIATRIC POPULATION
Children (2-11 years)

Dosage:
The dose up to 40 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 4.0 mL/kg bw/h (corresponding to 0.10 g amino acids/kg/h, 0.27 g/glucose/kg/h and 0.14 g lipids/kg/h). At the recommended maximum infusion rate, do not use an infusion period longer than 10 hours, 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 40 mL/kg bw/day.

The recommended maximum daily dose of 40 mL/kg bw/day will provide 1 g amino acids/kg bw/day (corresponding to 0.16 g nitrogen/kg bw/day), 2.7 g glucose/kg bw/day, 1.4 g lipids/kg bw/day and a total energy content of 29 kcal/kg bw/day (corresponding to 25 kcal/kg bw/day of non-protein energy).

In previously well-nourished children without significant fluid restrictions aged 2 years or older and expected to be in need of PN, the product can be used to maintain body composition during a limited period of time.

Duration:
Peripheral administration of SmofKabiven Low Osmo in children is suitable for a limited period (days to a couple of weeks).

Adolescents (12-17 years)

In adolescents, SmofKabiven Low Osmo can be used as in adults.

Method of administration

Intravenous use, infusion into a peripheral or central vein.

The use in paediatric patients should be supported by monitoring following the most current expert nutrition support guidelines prepared by the treating hospital or by expert groups such as the American Society of Parenteral and Enteral Nutrition (ASPEN) or the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical

Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR).

For instructions on preparation of the medicinal product before administration, see section 6.4 Special precautions for storage.

Compatibility

Compatibility data are available with the named branded products Addaven, Vitalipid N Adult, Soluvit N (lyophilized) and Glycophos in defined amounts and generics of sodium or potassium electrolytes in defined concentrations. When making electrolyte additions, the amounts already present in the bag should be taken into account to meet the clinical needs of the patient. Generated data supports additions to the activated bag according to the summary table below.

	Volume
SmofKabiven Low Osmo bag size	850 mL, 1400 mL, 1950 mL and 2500 mL
Additive	
Addaven	0 - 10 mL
Soluvit N (lyophilized)	0 - 1 vial
Vitalipid N Adult	0 - 10 mL
	Electrolyte range*
Sodium	≤ 150 mmol/L
Potassium	≤ 150 mmol/L
Phosphate (Inorganic or Glycophos)	≤ 15 mmol/L

* Including amounts present in the bag

Note: This table is intended to indicate compatibility. It is not a dosing guideline.

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 List of excipients.
- Severe hyperlipidaemia
- Severe liver insufficiency
- Severe blood coagulation disorders
- Congenital errors of amino acid metabolism
- Severe renal insufficiency without access to haemofiltration 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)
- Neonates and infants under 2 years of age

4.4 Special warnings and precautions for use

Identified precautions

The capacity to eliminate lipids 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, see section 4.8 Adverse effects (undesirable effects).

SmofKabiven Low Osmo 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 and egg lecithin, which may rarely cause allergic reactions. This also applies to corn (maize) and corn that may be contained in the medicine as small amounts of impurities. 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.

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

Since an increased risk of infection is associated with the use of any peripheral or central vein, strict aseptic precautions should be taken to avoid any contamination during catheter insertion and manipulation.

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

Blood cell count and coagulation should be monitored when lipids are given for a longer period.

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

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

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

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

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 Low Osmo 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 Low Osmo 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 cause acute folate deficiency; folic acid should therefore be given daily.

Vitamin B complex deficiency may occur with glucose administration.

Thrombophlebitis may occur if peripheral veins are used for infusions. The catheter insertion site should be evaluated daily for local signs of phlebitis.

SmofKabiven Low Osmo is a preparation of complex composition. It is, therefore, strongly advisable not to add other solutions if compatibility is not proven (see section 4.2).

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.

Use in hepatic impairment

SmofKabiven Low Osmo is contraindicated in severe liver insufficiency.

SmofKabiven Low Osmo should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with impaired liver function.

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 Parenteral nutrition in general and may have the potential to reverse PNALD in children with short bowel syndrome.

Use in renal impairment

SmofKabiven Low Osmo is contraindicated in severe renal insufficiency without access to hemofiltration or dialysis.

SmofKabiven should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with renal failure.

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

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 lipid metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridemia, even at the recommended infusion rate, and in association with a sudden change in the patient’s clinical condition, such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipemia, fever, lipid infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the lipid 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 Low Osmo 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.

Use in the elderly

No data available.

Paediatric use

Due to composition of the amino acid solution in SmofKabiven Low Osmo it is not suitable for the use in neonates and infants below 2 years of age. There is at present no clinical trial conducted on the use of SmofKabiven Low Osmo in children and adolescents (age 2 to 16/18 years).

Effects on laboratory tests

The lipid content of SmofKabiven Low Osmo may interfere with certain laboratory measurements (e.g. bilirubin, lactate anhydrogenase, 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.

4.5 Interaction with other medicines and other forms of 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.

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 Low Osmo 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

Effects on fertility

The potential effects of SmofKabiven Low Osmo on fertility and general reproductive performance have not been determined in animal studies.

Use in pregnancy

SmofKabiven Low Osmo is exempt from pregnancy categorisation. There are no adequate and well-controlled studies in pregnant women with SmofKabiven Low Osmo or its individual components; therefore, the safety of SmofKabiven Low Osmo in pregnant women is not known.

No animal studies have been conducted with the combined lipid components of SmofKabiven Low Osmo 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 Low Osmo during the period of organogenesis. SmofKabiven Low Osmo should not be used during pregnancy unless the expected therapeutic benefit clearly outweighs the potential risk to the foetus.

Use in lactation

It is not known whether SmofKabiven Low Osmo 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 Low Osmo. SmofKabiven Low Osmo should be used during lactation only if clearly needed.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

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

Table 1. **Adverse events with at least possible relationship to the study drug in the study 03-3CB7-001**

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 7 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) occurring in more than 2 patients in SMOFlipid 20% group versus comparator pooled groups.

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 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)	-

* Drug-related adverse events include those with relationship reported as being dubious, possible, likely, or very likely

Adverse Events in Table 4 are based on general assessment of trials and clinical experience of the product SmofKabiven.

Table 4: Adverse Event Summary from clinical trials and clinical experience

	Very Common *≥ 1/10*	***Common*** *≥ 1/100 to < 1/10*	***Uncommon*** *≥ 1/1,000 to < 1/100*	***Rare*** *≥ 1/10,000 to < 1/1,000*
Cardiac disorders				Tachycardia
Respiratory, thoracic & mediastinal disorders				Dyspnoea

	Very Common *≥ 1/10*	***Common*** *≥ 1/100 to < 1/10*	***Uncommon*** *≥ 1/1,000 to < 1/100*	***Rare*** *≥ 1/10,000 to < 1/1,000*
Gastrointestinal disorders			Lack of appetite, nausea, vomiting	
Metabolism & nutrition disorders			Elevated plasma levels of liver enzymes	
Vascular disorders				Hypotension, hypertension
General disorders & administration site conditions	Within a few days, vein irritation, phlebitis or thrombophlebitis may occur.	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 Low Osmo should be performed.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

See section 4.6 Special warnings and precautions for use “Fat overload syndrome”, “Excess of amino acid infusion” and “Excess of glucose infusion”.

If symptoms of overdose of lipids 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 haemodiafiltration may be considered.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Soya oil has a high content of essential fatty acids. Of the essential fatty acids, the omega-6 fatty acid linoleic acid is the most abundant (approx. 55-60% of the lipid component). Alpha-linolenic acid, an omega-3 fatty acid, constitutes about 8% of the lipid component.

Medium-chain fatty acids are rapidly oxidised.

Olive oil mainly provides energy in the form of mono-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 leukotrienes.

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.

Clinical trials

A randomised clinical trial had been conducted with SMOFKabiven, which is a product with the same qualitative composition as SmofKabiven Low Osmo.

In the clinical trial 03-3CB7-001, 53 subjects who had undergone major intestinal surgery were randomised to receive either SMOFKabiven (n=26) or Kabiven G19% (n=27) for 5 – 7 days as TPN. The majority of subjects received at least five study infusions: 19 (73.1%) of the SMOFKabiven group and 18 (66.7%) of the Kabiven G19% group. Twenty five (96.2%) of the SMOFKabiven group and 23 (85.2%) of the Kabiven G19% group experienced at least one adverse event (AE). The most frequent AEs were gastrointestinal (nausea, flatulence and vomiting) and hypertension. Most events were mild to moderate in severity, with 17 subjects in the SMOFKabiven group and 11 subjects in the Kabiven G19% group experiencing AEs which were considered to be possibly or probably related to the study drug. Serious AEs (SAEs) occurred in five subjects in the SMOFKabiven group and two subjects in the Kabiven G19% group. All SAEs were judged to be unrelated to the study medication;

being considered related to concomitant medication and the abdominal surgery the subjects had undergone. No clinically significant changes in vital signs were recorded. No drug related serious AE was observed in the study. The majority of reported AEs were mild with 14/26 in the SMOFKabiven group and 17/27 in the control group or moderate 19/26 and 10/27 respectively. Four patients in each group experienced at least one severe AE, however an unlikely relationship to the study drugs were found in the majority of patients in each group. One patient in the study group experienced an AE probably related to the study drug (nausea). A higher number of subjects experienced AEs that were possibly study drug related in the SMOFKabiven group with symptoms like nausea, vomiting and flatulence, which also are common postoperative symptoms after major abdominal surgery.

5.2 Pharmacokinetic properties

Absorption

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.

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.

Distribution

No data available.

Metabolism

Amino acids and electrolytes
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.

Excretion

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

5.3 Preclinical safety data

Genotoxicity

The genotoxic potential of SmofKabiven Low Osmo has not been assessed. The lipid component of SmofKabiven Low Osmo, 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 Low Osmo.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Glycerol
- Egg lecithin
- dl-alpha-tocopherol
- Sodium oleate
- Sodium hydroxide (pH adjuster)
- Glacial acetic acid (pH adjuster)
- Hydrochloric acid (pH adjuster)
- Water for injections

6.2 Incompatibilities

For incompatibilities, refer to section 4.5 – Interactions with other medicines and other forms of interactions. SmofKabiven Low Osmo may only be mixed with other medicinal products for which compatibility has been documented – see section 4.2 Dose and method of administration, “Compatibility”.

6.3 Shelf life

Shelf life of the medicinal product as packaged for sale

2 years.

Shelf life after mixing the contents of the three chambers

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

Store below 25°C. Do not freeze. Store in overpouch.

Instructions for use

Do not use if package is damaged. Use only if the amino acid and glucose solutions are clear and colourless or slightly yellow and the lipid emulsion is white and homogenous. The contents of the

three separate chambers have to be mixed before use, and before any additions are made via the additive port, please refer to Section 4.2 Dose and method of administration, Additives.

After separation of the peelable seals the bag should be inverted on a number of occasions to ensure a homogenous mixture, which does not show any evidence of phase separation. Please also refer to Appendix “SPECIAL HANDLING INSTRUCTIONS” for further handling instructions.

For single use in one patient 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.

6.5 Nature and contents of container

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, Biofine.

The Biofine inner bag film consists of poly(propylene-co-ethylene), synthetic rubber poly[styreneblock-(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[styreneblock-(butylene-co-ethylene)] (SEBS) equipped with synthetic polyisoprene (latex-free) stoppers.

The blind port, which is only used during manufacturing, is made of polypropylene equipped with a synthetic polyisoprene (latex-free) stopper.

Pack sizes*

- 1 x 850 mL, 5 x 850 mL AUST R 329432
- 1 x 1400 mL, 4 x 1400 mL AUST R 329617
- 1 x 1950 mL, 4 x 1950 mL AUST R 329618
- 1 x 2500 mL, 3 x 2500 mL AUST R 329619

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicinal product or waste material should be disposed in accordance with local requirements.

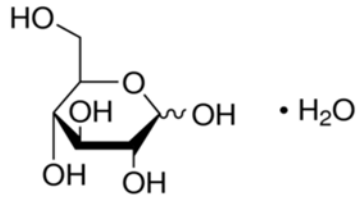
6.7 Physicochemical properties

Chemical structure

Chemical structures are included for the glucose and the electrolyte components only.

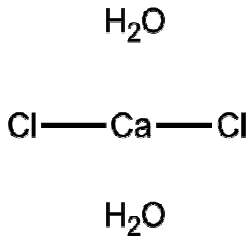
The amino acid and the lipid components are large molecules and therefore structures for these are not included.

Glucose monohydrate



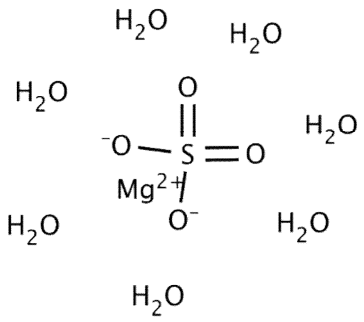
Empirical formula: 198.17 g/mol
Molecular weight: $C_6H_{12}O_6 \cdot H_2O$

Calcium chloride dihydrate



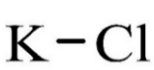
Empirical formula: $CaCl_2 \cdot 2H_2O$
Molecular weight: 147.01 g/mol

Magnesium sulfate heptahydrate



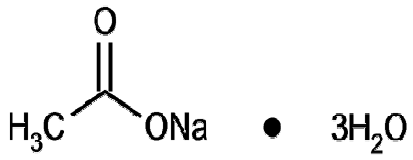
Empirical formula: $MgSO_4 \cdot 7H_2O$
Molecular weight: 246.47 g/mol

Potassium chloride



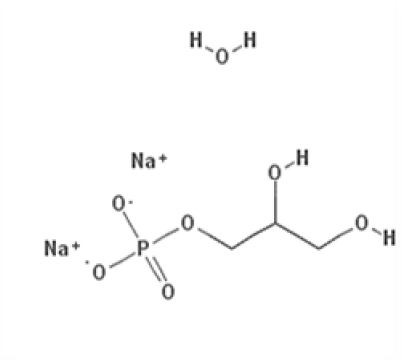
Empirical formula: KCl
Molecular weight: 74.55 g/mol

Sodium acetate trihydrate



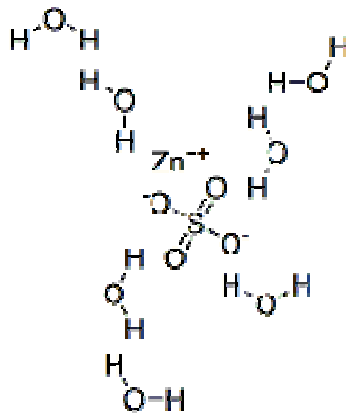
Empirical formula: $C_2H_9NaO_5$
Molecular weight: 136.08 g/mol

Sodium glycerophosphate hydrate



Empirical formula: $C_3H_7Na_2O_6P$
Molecular weight: 216.04 g/mol

Zinc sulfate heptahydrate



Empirical formula: $ZnSO_4 \cdot 7H_2O$
Molecular weight: 287.58 g/mol

CAS number

ACTIVE SUBSTANCE	CAS NUMBER
Amino Acids	
Alanine	56-41-7
Arginine	74-79-3
Glycine	56-40-6
Histidine	71-00-1

ACTIVE SUBSTANCE	CAS NUMBER
Isoleucine	73-32-5
Leucine	61-90-5
Lysine acetate	57282-49-2
Methionine	63-683
Phenylalanine	63-91-2
Proline	147-85-3
Serine	56-45-1
Taurine	107-35-7
Threonine	72-19-5
Tryptophan	73-22-3
Tyrosine	60-18-4
Valine	72-18-4
Electrolytes	
Calcium chloride dihydrate	10035-04-8
Magnesium sulfate heptahydrate	10034-99-8
Potassium chloride	7447-40-7
Sodium acetate trihydrate	6131-90-4
Sodium glycerophosphate hydrate	1334-74-3
Zinc sulfate heptahydrate	7446-20-0
Lipids	
Soya oil	8001-22-7
Fish oil - rich in Omega-3 acids	8016-13-5
Medium-chain triglycerides	73398-61-5, 65381-09-1
Olive oil	8001-25-0
Glucose	
Glucose monohydrate	5996-10-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Not Scheduled.

8. SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai, NSW 2080
Australia
Telephone: (02) 9391 5555

9. DATE OF FIRST APPROVAL

27 August 2020.

10. DATE OF REVISION

31 January 2022.

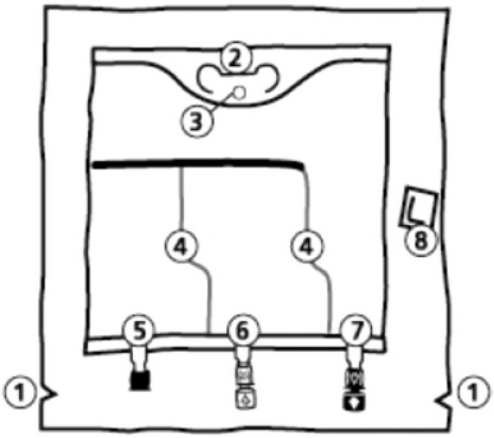
Summary table of changes:

Section changed	Summary of new information
2	Added energy values
4.2	Changed ‘sterile’ to ‘aseptic’ conditions.
6.4	Moved ‘Instructions for use’ to this section.
6.6	Moved ‘Instructions for use’ to section 6.4

APPENDIX: SPECIAL HANDLING INSTRUCTIONS

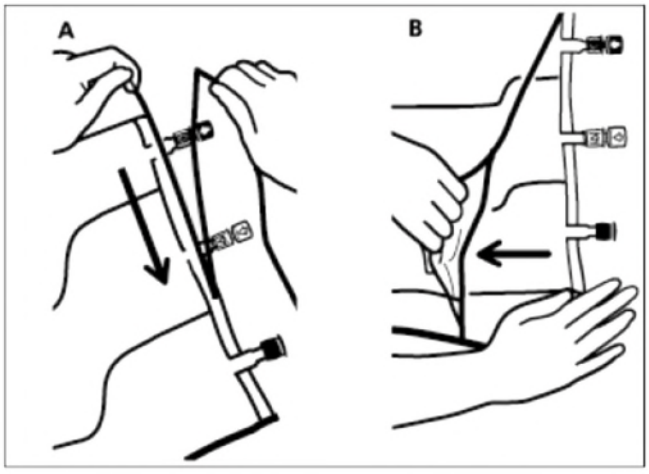
The bag

850 mL, 1400 mL, 1950 mL, 2500 mL



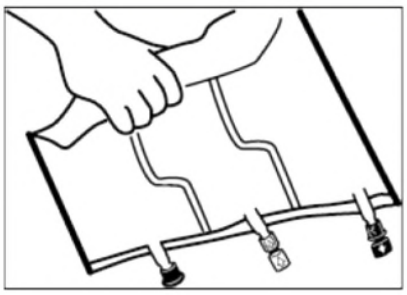
- Notches in the overpouch
- Handle
- Hole for hanging the bag
- Peelable seals
- Blind port (only used during manufacturing)
- Additive port
- Infusion port
- Oxygen absorber

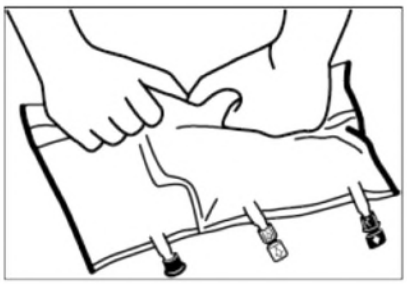
1. Removal of Overpouch

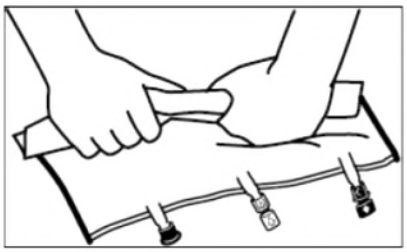


- To remove overpouch, hold the bag horizontally and tear from the notch close to the ports along the upper edge (A).
- Then simply tear the long side, pull off the overpouch and discard it along with the oxygen absorber (B).

2. Mixing

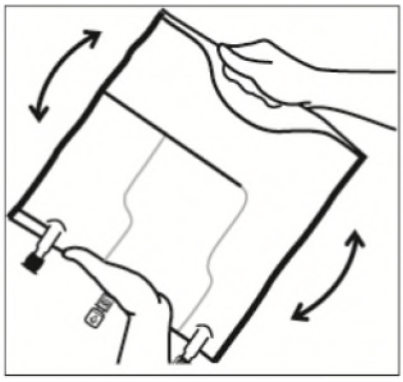






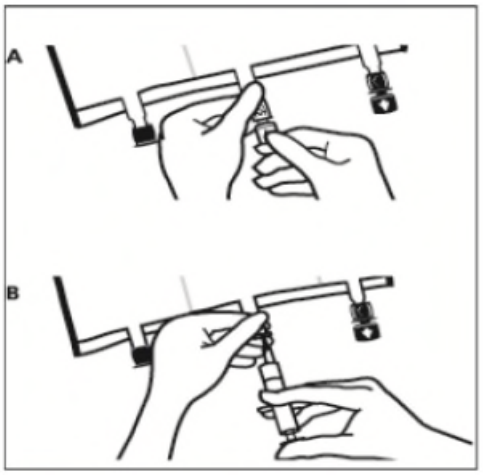
- Place the bag on a flat surface.
- Roll up the bag tightly from the handle side towards the ports, firstly with the right hand and then applying a constant pressure with the left hand until the vertical seals are broken. The vertical peel seals open due to the pressure of the fluid. The peel seals can also be opened before removing the 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.

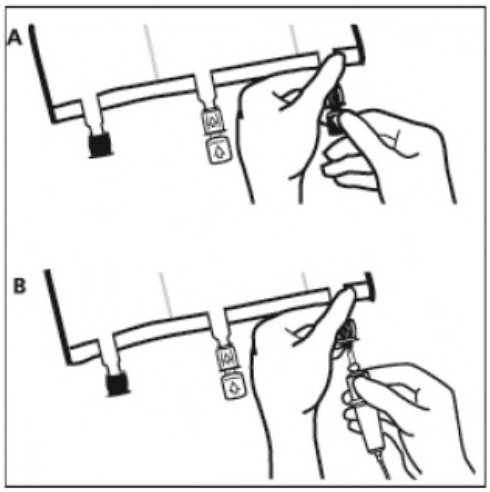
3. Finalising the Preparation



- Place the bag on a flat surface again. Shortly before injecting the 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.



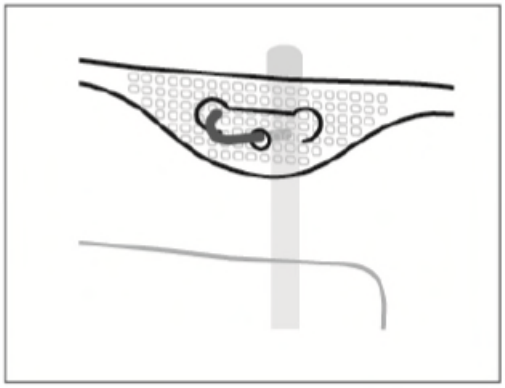
- Shortly before inserting the infusion set, break off the tamper evident arrow flag from the blue infusion port (A).

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. Hooking up the Bag



- Hook the bag up by the hole below the handle.