AUSTRALIAN PRODUCT INFORMATION - SMOFKABIVEN® ELECTROLYTE FREE (AMINO ACIDS 5.1%, LIPIDS 3.8%, GLUCOSE 12.7%)

1 NAME OF MEDICINE

Amino Acids 5.1%
Alanine, Arginine, Glycine, Histidine, Isoleucine, Leucine, Lysine acetate, Methionine, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine

Lipids 3.8%
Soya oil
Fish oil - rich in Omega-3 acids
Medium chain triglycerides
Olive oil

Glucose 12.7%
Glucose monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
SmofKabiven is a three chamber bag system of amino acid solution, 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 (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 acetate *corresponding to* Lysine	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
Glucose monohydrate *corresponding to* Glucose (anhydrous)	125	187	250	313	127

Active ingredients (g)	986 mL	1477mL	1970 mL	2463 mL	Per 1000 mL
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
Fish oil - rich in Omega-3 acids	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
• Acetate (mmol) [1]	73	110	147	183	74.5
• Phosphate (mmol) [2]	2.8	4.2	5.6	6.9	2.8
• 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	
- glucose (approx.)[3]	520 kcal 2200 kJ	770 kcal 3200 kJ	1040 kcal 4400 kJ	1290 kcal 5400 kJ	
- lipid (approx.)[4]	380 kcal 1600 kJ	530 kcal 2200 kJ	760 kcal 3200 kJ	910 kcal 3800 kJ	
- glucose/lipid ratio	58/42	58/42	58/42	58/42	
- protein (g)[5]/energy (kcal) ratio	1.5/32	1.5/32	1.5/32	1.5/32	

[1] Contribution from both the lipid emulsion and the amino acid solution.
[2] Contribution from lipid emulsion
[3] Include calories from glycerol
[4] Include calories from egg lecithin (phospholipids)
[5] 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 solution and free from particles.

The lipid emulsion is white and homogenous.

Osmolality: approx. 1600 mOsm/kg water
Osmolarity: approx. 1300 mOsm/L
pH (after mixing): approx. 5.6

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

Dosage (dose and interval)

The appearance of the product after mixing the three chambers is a white, homogenous emulsion.

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

The dose should be individualised with regard to the patient's clinical condition and body weight (bw).

The nitrogen requirements for maintenance of body protein mass depend on the patient's condition (e.g. nutritional state and degree of catabolic stress or anabolism).

Additives

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

Infusion rate

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

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

Maximum daily dose

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

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

Paediatric population
SmofKabiven Electrolyte Free is not recommended for use in children, see section 4.4 Special warnings and precautions for use.

Method of administration
Intravenous, infusion into a central vein.

The four different package sizes of SmofKabiven Electrolyte Free are intended for patients with high, moderately increased or basal nutritional requirements. To provide total parenteral nutrition, trace elements, vitamins and possibly electrolytes should be added to SmofKabiven Electrolyte Free according to the patient's need.

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, Vamin 18EF, Glycophos, Vitalipid N Adult/Infant and Soluvit N in defined amounts and generics of 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:

	Maximal total contents
SmofKabiven Electrolyte Free bag size	986 mL
Additive	**Volume**
Vamin 18 EF	0 - 330 mL
Addaven	0 - 10 mL
Soluvit N	0 - 1 vial
Vitalipid N Adult or Vitalipid N Infant	0 - 10 mL
Electrolyte limits[1]	**Amount per bag**
Sodium	≤ 150 mmol
Potassium	≤ 150 mmol
Calcium	≤ 5 mmol
Magnesium	≤ 5 mmol
Phosphate inorganic[2]	≤ 15 mmol
Zinc	≤ 0.2 mmol
Selenium	≤ 1 µmol

[1] Includes amounts from all products. Electrolyte additions may be scaled up for other bag sizes.

[2] The same limits are valid when additions of organic phosphate (i.e. Glycophos) are used.

Note: This table is intended to present 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
- 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
- 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)

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 Electrolyte Free 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 corn (maize) and corn products which may rarely cause allergic reactions. Cross allergic reaction has been observed between soybean 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.

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.

SmofKabiven Electrolyte Free is almost free of electrolytes for patients with special and/or limited electrolyte requirements. If required, sodium, potassium, calcium, magnesium and additional amounts of phosphate may be added governed by the clinical condition of the patient and by frequent monitoring of serum levels.

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

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.

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 Electrolyte Free 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.

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.

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 Electrolyte Free should be discontinued.

Excess of amino acid infusion
As with other amino acid solutions, the amino acid content in SmofKabiven Electrolyte Free 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 hepatic impairment
No data available.

Use in renal impairment
No data available.

Use in the elderly
No data available.

Paediatric use
Due to the composition of the amino acid solution in SmofKabiven Electrolyte Free it is not suitable for use in neonates and infants below 2 years of age. There is at present no experience on the use of SmofKabiven Electrolyte Free in children (age 2 years to 11 years).

Effects on laboratory tests
The fat content of SmofKabiven Electrolyte Free 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.

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 Electrolyte Free 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 Electrolyte Free on fertility and general reproductive performance have not been determined in animal studies.

Use in pregnancy (Category B3)
There are no adequate and well-controlled studies in pregnant women with SmofKabiven Electrolyte Free or its individual components; therefore, the safety of SmofKabiven Electrolyte Free in pregnant women is not known.

No animal studies have been conducted with the combined lipid components of SmofKabiven Electrolyte Free 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 Electrolyte Free 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 Electrolyte Free can enter maternal milk. Therefore, SmofKabiven Electrolyte Free 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 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 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)	-

* Drug-related adverse events include those with relationship reported as being 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 Electrolyte Free.

Table 4. Adverse Events Summary from clinical 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 Electrolyte Free should be performed.

Reporting 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

Please also refer to section 4.4 Special warnings and precautions for use for information on “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 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

Mechanism of action

Lipid emulsion

The lipid emulsion of SmofKabiven Electrolyte Free 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 (linoleic acid and alpha-linolenic acid). The omega-6 fatty acid linoleic acid is the most abundant.

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 prostaglandins, thromboxanes and leukotrienes.

Amino acids

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 has been conducted with SmofKabiven.

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
The pharmacokinetic properties of the infused amino acids are essentially the same as for amino acids supplied by ordinary food. Except the amino acids of dietary protein first enter the portal vein and then the systemic circulation, while intravenously infused amino acids directly 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
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 Electrolyte Free has not been assessed. The lipid component of SmofKabiven Electrolyte Free, 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 Electrolyte Free.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Only medicinal or nutrition solutions for which compatibility has been documented may be added to SmofKabiven Electrolyte Free. See section 4.2 Dose and method of administration, “Compatibility”.

6.3 Shelf life

Shelf Life before mixing

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 homogeneous. 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 homogeneous mixture, which does not show any evidence of phase separation. (Please also refer to Appendix “SPECIAL 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[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.

Pack sizes*

1 x 986 mL, 4 x 986 mL	AUST R 173891
1 x 1477 mL, 4 x 1477 mL	AUST R 180548
1 x 1970 mL, 4 x 1970 mL	AUST R 180549
1 x 2463 mL, 3 x 2463 mL	AUST R 180550

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

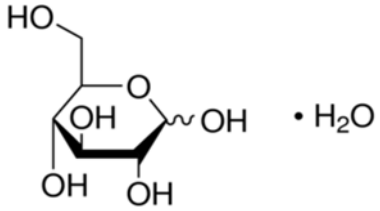
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

Chemical structure is only included for the glucose molecule 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: $C_6H_{12}O_6 \cdot H_2O$

CAS number

Active Substance	CAS number
Amino Acids 5.1%	
Alanine	56-41-7
Arginine	74-79-3
Glycine	56-40-6
Histidine	71-00-1
Isoleucine	73-32-5
Leucine	61-90-5
Lysine acetate	57282-49-2
Methionine	63-68-3
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
Lipids 3.8%	
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 12.7%	
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

09 Jan 2012

10 DATE OF REVISION OF THE TEXT

31 Jan 2022

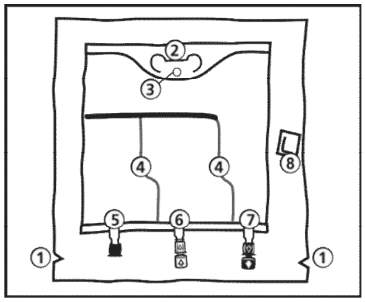
Summary table of changes

Section Changed	Summary of new information
2	Corrected the expression of active ingredients
4.2	Separate titles added for dosage, method of administration and compatibility. Added compatibility data from section 6.2
6.2	Compatibility data moved to section 4.2
6.4	Added statement about aseptic processing
8	Removed NZ sponsor details

APPENDIX: SPECIAL HANDLING INSTRUCTIONS

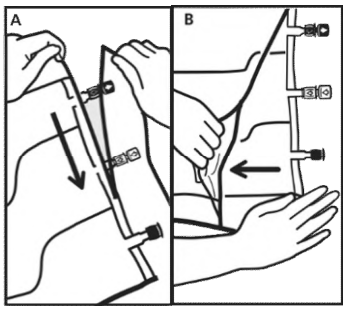
Biofine bag

(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



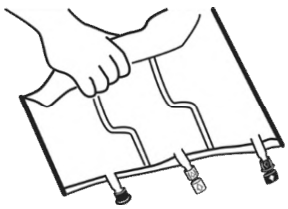
1. Removal of overpouch

- (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.

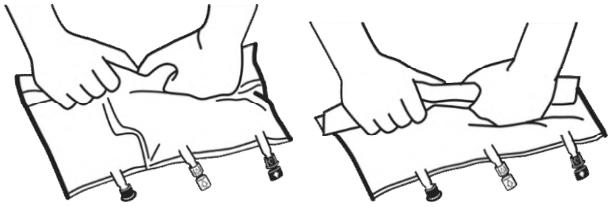


2. Mixing

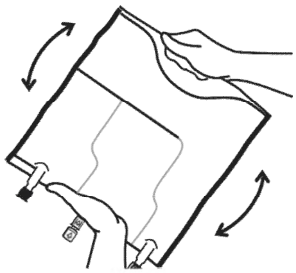
- Place the bag on a flat surface with text side up and ports pointing away.
- Starting from the right hand corner, roll the bag tightly and diagonally with the right hand.



- 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.

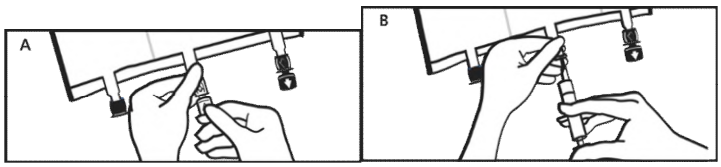


- Mix the contents of the three chambers by inverting the bag three times until the components are thoroughly mixed.

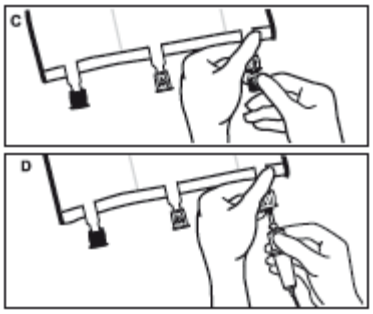


3. Finalising the preparation:

- (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.