1 NAME OF THE MEDICINE

Alanine, arginine, glycine, histidine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMINOVEN is a clear, colourless to slightly yellow solution. Each litre contains:

Aminoven	10%
Alanine (g)	14.0
Arginine (g)	12.0
Glycine (g)	11.0
Histidine (g)	3.0
Isoleucine (g)	5.0
Leucine (g)	7.4
Lysine (g)	6.6
Methionine (g)	4.3
Phenylalanine (g)	5.1
Proline (g)	11.2
Serine (g)	6.5
Taurine (g)	1.0
Threonine (g)	4.4
Tryptophan (g)	2.0
Tyrosine (g)	0.4
Valine (g)	6.2
Total amino acids (g)	100
Total Nitrogen (g)	16.2
Total energy (kJ) (kcal)	1680 (400)
pH	5.5–6.3
Titratable acidity (mmol NaOH/L)	22
Osmolality (mOsm/kg water)	1070

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

3 PHARMACEUTICAL FORM

Injection, intravenous infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

To supply amino acids as part of a composite admixture of total parenteral nutrition.

4.2 Dose and method of administration

Dosage depends on the severity of the catabolic state and amino acid requirement. A daily dose of 1.0–1.5 g amino acids/kg body weight/day is commonly used but recommendations from current professional nutritional guidelines should be consulted.

Clinical trial data on duration of therapy are limited to up to 7 days of administration in post-operative patients.

Adults

Dosage

10–20 mL of Aminoven 10% per kg body weight (equivalent to 1.0–2.0 g amino acids per kg body weight/day), e.g. corresponding to 700–1400 mL Aminoven 10% at 70 kg body weight/day.

Maximum infusion rate

1.0 mL of Aminoven 10% per kg body weight per hour (equivalent to 0.1 g amino acids per kg body weight an hour).

Maximum daily dose

20 mL of Aminoven 10% per kg body weight (equivalent to 2.0 g amino acids per kg body weight/day) corresponding to 1400 mL Aminoven 10% or 140 g amino acids at 70 kg body weight.

Children and adolescents (2–18 years)

Dosage

The dose should be adjusted to hydration status, biological development and body weight. A dose of 10–20 mL/kg/day equivalent to 1.0–2.0 g amino acid/kg/day should meet the needs of most paediatric patients.

Maximum infusion rate

Same as for adults, see information above.

Maximum daily dose

Same as for adults, see information above.

Method of administration

For administration via a central vein as a continuous infusion.

Instructions for Use/Handling

Use in one patient on one occasion only. Contains no antimicrobial preservative. Any unused solution should be discarded. (Please also refer to Section 4.4 Special warnings and precautions for use).

Additives

Additions should be performed aseptically immediately before the start of the infusion. Discard any residual contents.

All steps of admixing must be performed under strictly aseptic conditions, e.g. using laminar air flow technique, by professionally trained personnel according to individual hospital policy.

Compatibility with Aminoven 10% 1000 mL has been documented for up to the following concentrations:

- 10% Fat emulsion (1000 mL Intralipid 10%)
- 20% Fat emulsion (500 mL Intralipid 20%)
- 30% Fat emulsion (500 mL Intralipid 30%)
- Fat soluble vitamins (10 mL Vitalipid N Adult)
- Water soluble vitamins (1 vial Soluvit N)
- Glucose 20% to 50% (1000 mL)

- 150 mmol Na^+
- 5 mmol Ca^{2+}
- 150 mmol K^+
- 5 mmol Mg^{2+}
- 286 mmol Cl^-
- 15 mmol phosphate (organic)
- 0.2 µmol Chromium
- 20 µmol Copper
- 20 µmol Iron
- 5 µmol Manganese
- 1 µmol Iodine
- 50 µmol Fluoride
- 0.2 µmol Molybdenum
- 0.4 µmol Selenium
- 100 µmol Zinc

Recommended admixing sequence

1. Add trace elements and phosphate-free electrolyte solutions to Aminoven.
2. Add phosphate-containing electrolytes to the glucose solution.
3. Transfer the solutions produced in steps 1 and 2 into the ethylvinylacetate (EVA) bag.
4. Reconstitute Soluvit N with Vitalipid N and add to Intralipid.
5. Transfer Intralipid/vitamin mixture to the EVA bag.
6. Mix the contents of the bag by gentle agitation.

Note: Glucose solutions should not be added directly to Intralipid, but should be mixed with Aminoven first. Electrolytes should never be added directly to Intralipid, but should be diluted in Aminoven and glucose solution before being mixed with the emulsion. If creaming is observed on addition of electrolytes, invert or shake the emulsion before usage. Do not use if inversion or gently shaking does not result in an even mixture. Precipitation of calcium phosphate is possible if both calcium and phosphate ions are added. When a mixture must be stored in the refrigerator for up to 24 hours before use, the vitamins and trace elements should be added just prior to administration.

The use of EVA bags for compounding should follow the manufacturer's instructions under strictly aseptic conditions.

Shelf life after first opening

Aminoven should be used with sterile transfer equipment immediately after opening.

Shelf life after mixing with other components

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2 to 8°C for not more than 24 hours.

4.3 Contraindications

As for all amino acid solutions the administration of Aminoven is contraindicated in the following conditions: disturbances of amino acid metabolism, metabolic acidosis, renal insufficiency without haemodialysis or haemofiltration treatment, advanced liver insufficiency, fluid overload, shock, hypoxia, decompensated heart failure.

The administration of Aminoven 10% is contraindicated in children less than 2 years of age. For children under 2 years, paediatric amino acid preparations should be used, which are formulated to meet their different metabolic needs. No clinical studies have been conducted with Aminoven 10% solution in the paediatric population.

4.4 Special warnings and precautions for use

Aminoven is to be used as part of a comprehensive Total Parenteral Nutrition (TPN) regimen that takes into account the needs of the individual patient: the need for and capacity to tolerate a given dose of TPN depends on the metabolic state of the patient and his/her organ function.

It is necessary to assess vital signs (e.g. well-being, blood pressure, breathing, etc) during TPN. Serum electrolytes, fluid balance and renal function should be properly monitored during administration. Laboratory tests for monitoring should include blood and urine glucose, serum proteins, kidney and liver function tests, serum electrolytes, haemogram, serum and urine osmolarities, and blood urea. Triglycerides should be checked if lipids are administered simultaneously. Aminoven 10% itself has no effect on the triglyceride levels.

Care should be exercised in the administration of large volume infusion fluids to patients with cardiac insufficiency to avoid risk of development of pulmonary oedema.

In cases of hypokalaemia and/or hyponatraemia adequate amounts of potassium and/or sodium should be supplied simultaneously.

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

Aminoven 10% should always be a part of a TPN regimen and therefore some general precautions would need to be considered. TPN without any oral or enteral concomitant intake of nutrients may lead to jaundice due to cholestasis. This may be reversed by administration of small amounts of oral/enteral intake compatible with tolerability of the gut. This will also have a positive effect on the gut function in general. Jaundice may also appear during TPN without any proven cholestasis and reduction of energy will most of the time reverse this condition if TPN is the real cause. Infusion with a high content of glucose with or without simultaneous administration of lipids results in lipogenesis and fat deposition in the liver. The same can be seen when too much lipids are administered.

All TPN regimens are hypertonic which will result in development of thrombophlebitis as a result of duration of time of infusion (and osmolarity). Central venous catheters may result in central complications like thrombosis with a potential risk of embolism. Extravasation of TPN-admixtures may cause tissue damage. The severity of the damage is dependent on the osmolarity of the fluid, the amount extravasated before stopping the infusion, and the location of extravasation. Areas with a thin subcutaneous layer between the skin and an underlying bone are more vulnerable. Dilution of the extravasated area by using infiltration with physiological saline can be considered but are almost never needed.

TPN should not be administered in patients with septic shock. It is recommended to withhold TPN in the early stage of septicaemia and establish the cause of the condition. If TPN is indicated during a stable and chronic state of sepsis, special attention must be taken to vital signs and a more frequent laboratory monitoring should be done.

There have been no reported allergic reactions from Aminoven 10%, however other components of TPN may cause hypersensitivity.

Aminoven 10% is in the vast majority of cases administered simultaneously with other nutrients. If the amino acid solution as a part of TPN by any reason is given separately in a sequential way, it can result in nausea if the infusion is given too fast. If nausea appears, the infusion should be stopped or slowed down. (Please also refer to Section 4.9 Overdose).

Use in hepatic impairment

See Section 4.3 Contraindications.

Use in renal impairment

See Section 4.3 Contraindications.

Use in the elderly

No specific studies have been performed.

Paediatric use

No specific studies have been performed.

Effects on laboratory tests

No specific studies have been performed.

4.5 Interaction with other medicines and other forms of interaction

No interactions are shown to date.

For incompatibility information, see Section 6.2 Incompatibilities.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No specific studies have been performed.

Use in pregnancy

No specific studies have been performed. However, clinical experiences with similar parenteral amino acid solutions have shown no evidence of risk during pregnancy. The risk/benefit relationship should be considered before administering Aminoven during pregnancy.

Use in lactation

No specific studies have been performed. However, clinical experiences with similar parenteral amino acid solutions have shown no evidence of risk during breastfeeding. The risk/benefit relationship should be considered before administering Aminoven during breastfeeding.

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 have been reported from the use of Aminoven as a component of parenteral nutrition (PN) in clinical trials. The following tables list the adverse events reported in several PN clinical studies involving Aminoven 10% and 15%.

Table 1: Clinical study AS CS 01 FR (central vein infusion)

	Treatment Group							
	Aminoven 10% n = 16				Nutrilamine 16[1] n = 14			
	n related[2]	% related	n non-related[3]	% non-related	n related	% related	n non-related	% non-related
Gastrointestinal disorders								
GI haemorrhage	–	–	–	–	–	–	1	7.1
Rectal bleeding	–	–	–	–	–	–	1	7.1
Diarrhoea	–	–	–	–	–	–	1	7.1
Vomiting	–	–	–	–	–	–	1	7.1
Liver disorders								
Alkaline phosphatase elevations	1	6.3	–	–	1	7.1	–	–
Resistance mechanism disorders								
Sepsis	–	–	2	12.5	–	–	–	–
Metabolic disorders								
Hyperglycaemia + osmotic polyurea	1	6.3	–	–	–	–	–	–
CNS disorders								
Agitation	–	–	1	6.3	–	–	–	–
Myocardial disorders								
Angina pectoris	–	–	–	–	–	–	1	7.5
Urinary system disorders								
Urinary infection	–	–	1	6.3	–	–	–	–

1 Comparator amino acid product not available in Australia.
2 Related could be expanded as dubious, possible, likely or very likely.
3 Non-related could be expanded as likely excluded or non-assessable.

Table 2: Clinical study AS CS 02 FR (central vein infusion)

	Treatment Group							
	Aminoven 15% n = 16				Vintene[1] (control) n = 16			
	n related[2]	% related	n non-related[3]	% non-related	n related	% related	n non-related	% non-related
Metabolic disorders								
Hyperglycaemia	1	6.3	–	–	1	6.3	–	–
Hyperglycaemia + osmotic polyurea	–	–	–	–	2	12.5	–	–
Hypophosphoraemia	1	6.3	–	–	–	–	–	–
Respiratory disorders								
Nosocomial pulmonary infections	–	–	1	6.3	–	–	1	6.3
Hypoxia	–	–	–	–	–	–	1	6.3
Gastrointestinal disorders								
Peritonitis	–	–	1	6.3	–	–	–	–
Sigmoiditis	–	–	–	–	–	–	1	6.3
Diarrhoea	–	–	1	6.3	–	–	–	–

	Treatment Group							
	Aminoven 15% n = 16				Vintene[1] (control) n = 16			
	n related[2]	% related	n non-related[3]	% non-related	n related	% related	n non-related	% non-related
Liver disorders								
SGOT, SGPT elevations	–	–	1	6.3	–	–	–	–
Icterus	–	–	–	–	1	6.3	–	–
Urinary system disorders								
Renal insufficiency	–	–	1	6.3	–	–	1	6.3
Resistance mechanism disorders								
Multiple organ failure	–	–	1	6.3	–	–	–	–
Sepsis	–	–	–	–	–	–	1	6.3
Platelets & bleeding disorders								
Thrombopenia aggravation	–	–	1	6.3	–	–	–	–
Skin disorders								
Rash erythematous	–	–	–	–	–	–	1	6.3
Endocrine disorders								
Parotitis	–	–	–	–	–	–	1	6.3

1 Comparator amino acid product not available in Australia.
2 Related could be expanded as dubious, possible, likely or very likely.
3 Non-related could be expanded as likely excluded or non-assessable.

Aminoven 15% is first registered in January 1999 and from that time on until the recent PSUR dated July 2006, seventeen serious adverse reactions have been reported, which occurred in an ongoing clinical study investigating intradialytic parenteral nutrition in patients suffering from terminal renal insufficiency and malnutrition (study code: 24332-IDPN). Sixteen of these serious adverse reactions have been assessed as not or unlikely related. One serious adverse reaction (metabolic and nutrition disorders, metabolic disorder) has been assessed as possible related to PN. Underlying diabetes was the major predisposing factor.

Table 3: Clinical study 00-3CB4-001 (central vein infusion)

System Organ Class/ Preferred Term	Treatment Group							
	3CB Structo EL[1] n = 19				Kabiven G 19%[2] (control) n = 19			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Metabolism and nutrition disorders								
Hyperglycaemia NOS	3	15.8	–	–	2	10.5	–	–
Hyperkalaemia	1	5.3	–	–	–	–	1	5.3
Appetite decreased NOS	–	–	1	5.3	–	–	–	–
Hypertriglyceridaemia	–	–	–	–	1	5.3	–	–
Hypokalaemia	–	–	–	–	–	–	1	5.3
Hypomagnesaemia	–	–	1	5.3	–	–	–	–
Hypophosphataemia	1	5.3	–	–	–	–	–	–

System Organ Class/ Preferred Term	Treatment Group							
	3CB Structo EL[1] n = 19				Kabiven G 19%[2] (control) n = 19			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Surgical and medical procedures								
Intestinal adhesion lysis	–	–	1	5.3	–	–	2	10.5
Gastroenterostomy	–	–	1	5.3	–	–	1	5.3
Choledochoentero-stomy	–	–	–	–	–	–	1	5.3
Colectomy partial	–	–	–	–	–	–	1	5.3
Pancreatectomy	–	–	–	–	–	–	1	5.3
Pancreaticoduodenec-tomy	–	–	1	5.3	–	–	–	–
Panproctocolectomy	–	–	1	5.3	–	–	–	–
Small intestinal resection	–	–	–	–	–	–	1	5.3
Splenectomy	–	–	–	–	–	–	1	5.3
Gastrointestinal disorders								
Dyspepsia	–	–	2	10.5	–	–	3	15.8
Nausea	–	–	–	–	–	–	2	10.5
Vomiting NOS	–	–	–	–	–	–	2	10.5
Constipation	–	–	1	5.3	–	–	–	–
Diarrhoea NOS	–	–	–	–	–	–	1	5.3
Pancreatitis aggravated	–	–	1	5.3	–	–	–	–
Infections and infestations								
Lower respiratory tract infection NOS	–	–	2	10.5	–	–	2	10.5
Catheter related infection	2	10.5	–	–	1	5.3	–	–
General disorders and administration site conditions								
Pyrexia	1	5.3	2	10.5	1	5.3	–	–
Oedema lower limb	–	–	–	–	–	–	1	5.3
Cardiac disorders								
Atrial fibrillation	–	–	1	5.3	–	–	–	–
Left ventricular failure	–	–	1	5.3	–	–	–	–
Supraventricular tachycardia	–	–	–	–	–	–	1	5.3
Injury, poisoning and procedural complications								
Anaemia postoperative	–	–	2	10.5	–	–	1	5.3
Blood and lymphatic system disorders								
Anaemia NOS	–	–	2	10.5	–	–	–	–
Respiratory, thoracic and mediastinal disorders								
Atelectasis	–	–	1	5.3	–	–	–	–
Pleural effusion	–	–	1	5.3	–	–	–	–
Pneumonia NOS	–	–	1	5.3	–	–	–	–
Pneumothorax NOS	–	–	1	5.3	–	–	–	–
Respiratory failure (excl neonatal)	–	–	1	5.3	–	–	–	–

System Organ Class/ Preferred Term	Treatment Group							
	3CB Structo EL[1] n = 19				Kabiven G 19%[2] (control) n = 19			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Investigations								
Biopsy intestine	–	–	–	–	–	–	1	5.3
Nervous system disorders								
Headache NOS	–	–	1	5.3	–	–	–	–

1 3CB Structo EL is a three chamber bag containing Aminoven 10% with electrolytes as amino acid and electrolyte source, a 20% fat emulsion and glucose 42%. It is not available in Australia.
2 Kabiven G19% is a three chamber bag containing Vamin 18 Novum as amino acid and electrolyte source, Intralipid 20% as fat source and Glucose 19%.
3 Related comprised possibly related.
4 Non-related comprised unlikely related.
NOS = Not Otherwise Specified.

Since 3CB Structo EL's first registration in January 2003, only one unlabeled serious adverse reaction (cardiac disorders, palpitation) has been spontaneously reported in the PSURs which has been assessed as possible related to PN by the reporter and probably related to PN by the company.

Table 4: Clinical study 00-3CB4-001 (peripheral vein infusion)

System Organ Class/ Preferred Term	Treatment Group							
	3CB StructoPeri EL[1] n = 20				Kabiven G 11%[2] (control) n = 21			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Investigations								
Alanine aminotransferase increased	1	5.0	–	–	2	9.5	–	–
Blood glucose increased	–	–	–	–	2	9.5	–	–
Blood phosphate decreased	2	10.0	–	–	–	–	–	–
Blood potassium decreased	–	–	2	10.0	–	–	–	–
Blood triglycerides increased	–	–	–	–	2	9.5	–	–
Gammaglutamyltransferase increased	1	5.0	–	–	1	4.8	–	–
Blood alkaline phosphatase NOS increased	–	–	–	–	1	4.8	–	–
Blood bilirubin increased	–	–	–	–	1	4.8	–	–
Metabolism and nutrition disorders								
Hyperglycaemia NOS	2	10.0	–	–	3	14.3	–	–
Hypokalaemia	–	–	1	5.0	–	–	1	4.8
Fluid overload	1	5.0	–	–	–	–	–	–
Hyperkalaemia	–	–	–	–	1	4.8	–	–

System Organ Class/ Preferred Term	Treatment Group							
	3CB StructoPeri EL[1] n = 20				Kabiven G 11%[2] (control) n = 21			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Hypertriglyceridaemia	1	5.0	–	–	–	–	–	–
Gastrointestinal disorders								
Abdominal pain aggravated	–	–	1	5.0	–	–	–	–
Constipation	–	–	1	5.0	–	–	–	–
Vomiting NOS	–	–	–	–	–	–	1	4.8
Vascular disorders								
Abdominal aortic aneurysm haemorrhage	–	–	1	5.0	–	–	–	–
Phlebitis NOS	–	–	–	–	1	4.8	–	–
Wound haemorrhage	–	–	1	5.0	–	–	–	–
Blood and lymphatic system disorders								
Anaemia NOS	–	–	–	–	–	–	1	4.8
Hepatobiliary disorders								
Jaundice NOS	–	–	–	–	1	4.8	–	–
Infections and infestations								
Oral candidiasis	–	–	1	5.0	–	–	–	–
Injury, poisoning and procedural complications								
Anastomotic leak	–	–	–	–	–	–	1	4.8
Respiratory, thoracic and mediastinal disorders								
Cough	–	–	1	5.0	–	–	–	–
Dyspnoea NOS	–	–	1	5.0	–	–	–	–

1 3CB StructoPeri EL is a three chamber bag containing Aminoven 10% with electrolytes as amino acid and electrolyte source, a 20% fat emulsion and glucose 13%.
2 Kabiven G11% is a three chamber bag containing Vamin 18 Novum as amino acid and electrolyte source, Intralipid 20% as fat source and Glucose 11%.
3 Related comprised probably or possibly related.
4 Non-related comprised unlikely related.
NOS = Not Otherwise Specified.

3CB StructoPeri EL was first registered in October 2003. From that time on no serious adverse reactions have reported in the PSURs.

Table 5: Clinical study 00-3CB7-001 (central vein infusion)

System Organ Class/ Preferred Term	Treatment Group							
	3CB SMOF EL[1] n = 26				Kabiven G 19%[2] (control) n = 27			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Gastrointestinal disorders								
Nausea	5	19.2	–	–	7	25.9	1	3.7
Flatulence	4	15.4	3	11.5	1	3.7	3	11.1
Vomiting NOS	7	26.9	–	–	2	7.4	1	3.7
Dyspepsia	–	–	5	19.2	–	–	1	3.7

System Organ Class/ Preferred Term	Treatment Group							
	3CB SMOF EL[1] n = 26				Kabiven G 19%[2] (control) n = 27			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Abdominal pain NOS	–	–	1	3.8	1	3.7	1	3.7
Peritonitis	–	–	2	7.7	–	–	–	–
Abdominal distension	–	–	1	3.8	–	–	–	–
Abdominal pain upper	–	–	–	–	–	–	1	3.7
Diarrhoea NOS	–	–	–	–	–	–	1	3.7
Epigastric discomfort	–	–	1	3.8	–	–	–	–
Gastrointestinal motility disorder NOS	–	–	–	–	–	–	1	3.7
Ileus paralytic	–	–	1	3.8	–	–	–	–
Peritoneal disorder NOS	–	–	–	–	–	–	1	3.7
Subileus	–	–	1	3.8	–	–	–	–
Vascular disorders								
Hypertension NOS	1	3.8	2	7.7	–	–	7	25.9
General disorders and administration site conditions								
Pyrexia	–	–	3	11.5	–	–	2	7.4
Oedema NOS	1	3.8	–	–	–	–	1	3.7
Catheter related complication	–	–	–	–	–	–	1	3.7
Inflammation NOS	–	–	–	–	–	–	1	3.7
Intermittant pyrexia	–	–	–	–	–	–	1	3.7
Pain NOS	–	–	1	3.8	–	–	–	–
Rigors	–	–	–	–	–	–	1	3.7
Metabolism and nutrition disorders								
Hypokalaemia NOS	–	–	2	7.7	–	–	2	7.4
Hyperglycaemia NOS	1	3.8	1	3.8	–	–	–	–
Musculoskeletal and connective tissue disorders								
Shoulder blade pain	–	–	1	3.8	–	–	1	3.7
Arthralgia	–	–	1	3.8	–	–	–	–
Back pain	–	–	1	3.8	–	–	–	–
Bone pain	–	–	–	–	–	–	1	3.7
Fistula NOS	–	–	1	3.8	–	–	–	–
Pain in extremity	–	–	1	3.8	–	–	–	–
Skin and subcutaneous tissue disorders								
Pruritus	–	–	3	11.5	–	–	1	3.7
Exanthem	–	–	–	–	–	–	1	3.7
Sweating increased	–	–	1	3.8	–	–	–	–
Injury, poisoning and procedural complications								
Failure to anastomose	–	–	1	3.8	–	–	1	3.7
Pancreatic anastomotic leak	–	–	1	3.8	–	–	–	–
Post procedural bile leak	–	–	1	3.8	–	–	–	–
Postoperative fever	–	–			–	–	1	3.7
Suture related complication	–	–	1	3.8	–	–	–	–

System Organ Class/ Preferred Term	Treatment Group							
	3CB SMOF EL[1] n = 26				Kabiven G 19%[2] (control) n = 27			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Renal and urinary disorders								
Oliguria	–	–	1	3.8			3	11.1
Dysuria	–	–	–	–	–	–	1	3.7
Nervous system disorders								
Sensory disturbance NOS	–	–	–	–	–	–	2	7.4
Dizziness	–	–	–	–	–	–	1	3.7
Headache	–	–	–	–	–	–	1	3.7
Infections and infestations								
Catheter related infection	–	–	2	7.7	–	–	–	–
Pneumonia NOS	–	–	1	3.8	–	–	–	–
Septic shock	–	–	1	3.8	–	–	–	–
Staphylococcal infection	–	–	1	3.8	–	–	–	–
Respiratory, thoracic and mediastinal disorders								
Respiratory failure	–	–	2	7.7	–	–	–	–
Hiccups	–	–	–	–	–	–	1	3.7
Hypoxia	–	–	1	3.8	–	–	–	–
Tachypnoea	–	–	1	3.8	–	–	–	–
Psychiatric disorders								
Depression	–	–	1	3.8	–	–	–	–
Insomnia	–	–	–	–	–	–	1	3.7
Blood and lymphatic system disorders								
Coagulopathy	–	–	–	–	–	–	1	3.7
Hepatobiliary disorders								
Cholangitis NOS	–	–	–	–	–	–	1	3.7
Neoplasms benign, malignant and unspecified incl. cysts								
Tumour haemorrhage	–	–	–	–	–	–	1	3.7
Reproductive system and breast disorders								
Scrotal oedema	–	–	1	3.8	–	–	–	–

1 3CB SMOF EL is a three chamber bag containing Aminoven 10% with electrolytes as amino acid and electrolyte source, a 20% fat emulsion and glucose 42%.
2 Kabiven G19% is a three chamber bag containing Vamin 18 Novum as amino acid and electrolyte source, Intralipid 20% as fat source and Glucose 19%.
3 Related comprised probable or possible related.
4 Non-related comprised unlikely related.
NOS = Not Otherwise Specified.

3CB SMOF EL is not yet registered. Therefore, no PSUR exists registering serious adverse reactions.

Table 6: Clinical study 00-3CB8-001 (peripheral vein infusion)

System Organ Class/ Preferred Term	Treatment Group							
	3CB SMOF Peri EL[1] n = 27				Kabiven G 11%[2] (control) n = 25			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Gastrointestinal disorders								
Abdominal pain	–	–	4	14.8	–	–	1	4.0
Nausea	–	–	1	3.7	–	–	2	8.0
Constipation	–	–	2	7.4	–	–	–	–
Flatulence	–	–	1	3.7	–	–	–	–
Vomiting	–	–	1	3.7	–	–	–	–
Diarrhoea	–	–	–	–	–	–	1	4.0
Pancreatitis	–	–	–	–	–	–	1	4.0
Metabolism and nutrition disorders								
Hypokalaemia	–	–	–	–	–	–	3	12
Hypoalbuminaemia	–	–	–	–	–	–	1	4.0
Hypomagnesaemia	–	–	–	–	–	–	1	4.0
Hyponatraemia	–	–	–	–	–	–	1	4.0
Nervous system disorders								
Headache	–	–	1	3.7	–	–	2	8.0
Dizziness	–	–	1	3.7	–	–	–	–
Vascular disorders								
Thrombophlebitis	1	3.7	–	–	1	4.0	–	–
Haemorrhage	–	–	1	3.7	–	–	–	–
Hypotension	–	–	–	–	–	–	1	4.0
Infections and infestations								
Sepsis	–	–	1	3.7	–	–	1	4.0
Liver abscess	–	–	1	3.7	–	–	–	–
Pneumonia	–	–	–	–	–	–	1	4.0
Staphylococcal infection	–	–	–	–	–	–	1	4.0
Skin and subcutaneous tissue disorders								
Pruritus	–	–	–	–	–	–	2	8.0
Exanthem	–	–	–	–	–	–	1	4.0
Skin lesion	–	–	–	–	–	–	1	4.0
General disorders and administration site conditions								
Pyrexia	–	–	–	–	–	–	2	8.0
Multi-organ failure	–	–	–	–	–	–	1	4.0
Psychiatric disorders								
Insomnia	–	–	–	–	–	–	2	8.0
Anxiety	–	–	1	3.7	–	–	–	–
Respiratory, thoracic and mediastinal disorders								
Dyspnoea excerbated	–	–	1	3.7	–	–	–	–
Dyspnoea	–	–	–	–	–	–	1	4.0
Oesophagobronchial fistula	–	–	–	–	–	–	1	4.0
Blood and lymphatic system disorders								
Anaemia	–	–	1	3.7	1	4.0	–	–
Cardiac disorders								
Angina pectoris	–	–	1	3.7	–	–	–	–

System Organ Class/ Preferred Term	Treatment Group							
	3CB SMOF Peri EL[1] n = 27				Kabiven G 11%[2] (control) n = 25			
	n related[3]	% related	n non-related[4]	% non-related	n related	% related	n non-related	% non-related
Left ventricular failure	–	–	1	3.7	–	–	–	–
Investigations								
Hepatic enzyme increased	–	–	1	3.7	–	–	–	–
Ammonia increased	–	–	–	–	1	4.0	–	–
Musculoskeletal and connective tissue disorders								
Muscle spasms	–	–	1	3.7	–	–	–	–
Arthralgia	–	–	–	–	–	–	1	4.0
Hepatobiliary disorders								
Hepatic necrosis	–	–	1	3.7	–	–	–	–

1 3CB SMOF Peri EL is a three chamber bag containing Aminoven 10% with electrolytes as amino acid and electrolyte source, a 20% fat emulsion and glucose 13%.
2 Kabiven G11% is a three chamber bag containing Vamin 18 Novum as amino acid and electrolyte source, Intralipid 20% as fat source and Glucose 11%.
3 Related comprised possible related.
4 Non-related comprised unlikely related.

3CB SMOF Peri EL is not yet registered. Therefore, no PSUR exists registering serious adverse reactions.

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 www.tga.gov.au/reporting-problems.

4.9 Overdose

As with other amino acid solutions, shivering, vomiting, nausea, and increased renal amino acid losses can occur when Aminoven is given in overdose or if the infusion rate is exceeded. Infusion should be stopped immediately in this case. It may be possible to continue with a reduced dosage.

A too rapid infusion can cause fluid overload and electrolyte disturbances. Beside control of electrolytes, it is recommended to monitor acid-base balance, creatinine and urea in blood. The tolerability of amino acid infusion is dependent on the patient's condition; liver and renal functions. This means that even at a dose of 1.0 to 1.5 g amino acids/kg body weight/day can result in overdose for patients during certain conditions. The infusion should not exceed 2.0 g amino acids/kg body weight/day in adults.

There is no specific antidote for overdose. Emergency procedures should be general supportive measures, with particular attention to respiratory and cardiovascular systems.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

The amino acids contained in Aminoven are all naturally occurring physiological compounds. As with the amino acids derived from the ingestion and assimilation of food proteins, parenterally administered amino acids enter the body pool of free amino acids and all subsequent metabolic pathways.

Clinical trials

Study 00-3CB4-001

This was a phase III single centre, randomised, open, parallel groups, active controlled study undertaken to compare safety and tolerability (primary objectives) and efficacy (secondary objective) of 3CB Structo EL (test product; group A) to Kabiven G 19% (control product; group B) in adult patients who were unable to sustain an adequate oral or enteral food intake for up to 7 days, and who therefore required parenteral nutrition (PN). No formal hypotheses testing were planned. 3CB Structo EL is a three chamber bag containing (in 1970 mL) anhydrous glucose 250 g, Aminoven 10% with electrolytes providing 100 g amino acids, and Structolipid as fat emulsion providing 75 g lipids (structured triglycerides). Kabiven G 19% is a three chamber bag containing Vamin 18 Novum as amino acid and electrolyte source, Intralipid 20% as fat source and Glucose 19%. Dosage was based on body weight (BW). The products were infused via a central venous line. The intention to treat (ITT) data set (those patients who received at least one dose of study drug) comprised of 19 patients in each group (all Caucasian). The portion of males was higher in group B (63%) than in group A (47%). Mean age of group A or B was 67.8 (SD 13.7) or 56.6 (SD 16.1) years, corresponding mean weight was 65.4 (13.7) vs. 65.3 (18) kg.

The following tables show number of patients and infused volume of study drug during the study period as well as number of infusions:

Day	Group A (3CB Structo EL)		Group B (Kabiven G 19%)	
	No. of patients	Volume infused (mL)[1]	No. of patients	Volume infused (mL)[1]
1	18	1541 ± 274	16	1876 ± 540
2	19	1475 ± 327	18	1952 ± 528
3	19	1474 ± 354	18	1992 ± 517
4	16	1496 ± 307	18	1992 ± 517
5	16	1526 ± 254	18	1962 ± 516
6	14	1517 ± 272	16	1985 ± 521
7	14	1402 ± 351	13	2018 ± 473

1 Mean volume and standard deviation is given

No. of infusions	Group A	Group B
	No. of patients	No. of patients
2		1
3	3	
5	2	3
6	1	5
7	13	10

Mean administered volumes of 1496 or 1526 mL 3CB Structo EL (on days 4 or 5) corresponded to a mean supply of 76 or 77 g amino acids per day. Based on mean BW of 65.4 kg, mean supply of amino acids was 1.2 g/kg BW/day which is in accordance with recommended daily dose of 1–2 g per kg BW. Thirteen patients terminated the study prematurely (inclusive 3 patients that did not receive any study medication) 6 patients in group A and 7 patients in group B.

Safety and tolerance were assessed by adverse event (AE) profile, vital signs and laboratory safety variables in blood, plasma and serum. A total of 27 of the 38 patients experienced at least one AE during the study, 13/19 in group A and 14/19 in group B; AEs of severe intensity were reported for 5 patients in each group. The most frequently reported AEs were dyspepsia (n = 2 vs. n = 3), hyperglycaemia (n = 3 vs. n = 2), lower respiratory tract infection (n = 2 vs. n = 2) and pyrexia (n = 3 vs. n = 1). Two patients from group A experienced a serious adverse event (SAE), aggravated pancreatitis and respiratory failure, respectively in the follow-up period of the study but no SAE occurred in group B. Both patients did not recover from the event and died. These SAEs were not related to the study medication. In group A, 7/19 patients had AEs possibly related to study medication, compared to 4/19 in group B; most frequent events were catheter related infections (n = 2 vs. n = 1) and hyperglycaemia (n = 3 vs. n = 2), other events were pyrexia (n = 1 each group), hyperkalaemia (n = 1, group A), hypophosphatemia (n = 1, group A) and hypertriglyceridaemia (n = 1, group B). No difference between the treatment groups was considered clinically significant, for any safety laboratory or vital signs parameters.

Efficacy endpoints (secondary) were laboratory variables; no clinical efficacy assessments were performed. No statistical significant differences (student`s t-test, $p < 0.05$) in the plasma concentration of amino acids (LOCF minus period 1) between both treatment groups were determined for most amino acids with two exceptions. Histidine was significantly higher in group B ($p = 0.0089$) where the mean (SD) values were 26.5 (41.6) vs. -2.9 (20.6) µmol/L, respectively. For taurine a significant higher concentration ($p = 0.0373$) was found in group A where the mean (SD) values were 18.7 (48.6) vs. -6.7 (15.8) µmol/L. There is a 28% higher concentration of histidine in Kabiven G 19% compared to 3CB Structo EL and in addition a higher volume of Kabiven was administered. Taurine is present in 3CB Structo EL but not in Kabiven. No statistical significant differences between the groups were found in serum concentrations of other potential nutritional parameters like pre-albumin and IGF-1.

Study 03-3CB7-001

This was a Phase III, single centre, open, randomized, active controlled study undertaken to compare safety and tolerance of 3CB SMOF EL (test product; group A) with Kabiven G 19% (reference product; group B) in post-operative, adult patients of major gastro-intestinal tract surgery requiring parenteral nutrition for at least 5 days. The study was not an efficacy study. 3CB SMOF EL is a three chamber bag containing (in 1970 mL) anhydrous glucose 250 g, Aminoven 10% with electrolytes providing 100 g amino acids and SMOFlipid providing 75 g lipids. SMOFlipid is a fat emulsion containing (in 1000 mL) soya-bean oil 60 g, medium chain triglycerides 60 g, olive oil 50 g and fish oil 30 g. Kabiven G 19% (see study 00-3CB4-001). Dosage was based on body weight (BW). The products were infused via a central venous line. The ITT analysis set comprised of 53 patients (26 in group A and 27 in group B; all Caucasian) who received at least one dose of study medication.

The following tables show number of patients and infused volume of study drug during the study period as well as number of infusions:

Day	Group A (3CB SMOF EL)		Group B (Kabiven G 19%)	
	No. of patients	Volume infused (mL)[1]	No. of patients	Volume infused (mL)[1]
1	26	990 ± 325	27	1081 ± 229
2	24	1485 ± 365	27	1596 ± 316
3	21	1550 ± 277	25	1557 ± 489
4	20	1755 ± 413	22	1805 ± 612
5	19	1509 ± 441	18	1735 ± 358
6	4	1415 ± 199	2	2160 ± 339
7	2	1230 ± 42	1	2430

1 Mean volume and standard deviation is given

No. of infusions	Group A	Group B
	No. of patients	No. of patients
1	2	
2	3	2
3	1	3
4	1	4
5	15	16
6	2	1
7	2	1

The portion of males was higher in group B (77.8%) than in group A (57.7%). Mean age of patients in group A or B was 57.7 (SD 12.6) or 63.0 (SD 10.1) years, corresponding mean weight was 72.4 (11.3) vs. 74.4 (10.2) kg. Mean administered volumes of 1550 or 1755 mL 3CB SMOF EL (on days 3 or 4) corresponded to a mean supply of 79 or 89 g amino acids per day. Based on a mean BW of 72.4kg, mean supply of amino acids was 1.1 or 1.2 g/kg BW/day which is in accordance with recommended daily dose of 1–2 g per kg BW. Seventeen patients terminated the study prematurely, 8 patients in group A, and 9 patients in group B.

Safety and tolerance were assessed by AE profile, vital signs and laboratory safety variables in blood, plasma and serum. No formal hypothesis testing was planned. 25/26 and 23/27 patients in group A and B, respectively, experienced at least one AE during the study; AEs of severe intensity were reported for 4 patients in each group. AEs concerned most frequently the gastrointestinal system, namely nausea (5/26 or 8/27 patients in group A or B), flatulence (7/26 vs. 4/27 patients), and vomiting NOS (not otherwise specified) (7/26 vs. 3/27 patients). SAEs occurred in 5/26 or 2/27 patients in group A or B. All SAEs were regarded as unlikely related to the study medication. SAEs in both groups consisted predominantly of post-operative complications due to insufficiency of sutures and anastomosis leading to paralytic ileus in one patient. Other patients suffered from local peritonitis, pancreatic fistula, a postprocedural bile leak, peritonism and a nosocomial pneumonia leading to respiratory insufficiency, respectively. In another patient who suffered from a haemorrhage, this event was a direct consequence of the metastatic pancreas carcinoma infiltrating the stomach. Possibly related AEs occurred in 16/26 or 11/27 patients in group A or B. This concerned mostly nausea (4/26 vs. 7/27 patients) and vomiting (7/26 vs. 2/27 patients). In one patient in group A, the AE nausea was regarded as probably related to the study drug. From day 1 to final examination, patients of group A compared to group B showed no noticeable differences regarding the means of the laboratory parameters and vital signs.

5.2 Pharmacokinetic properties

The amino acids in Aminoven enter the plasma pool of corresponding free amino acids. From the intravascular space, amino acids distribute to the interstitial fluid and, individually regulated for each single amino acid, into the intracellular space of different tissues as required.

Plasma and intracellular free amino acid concentrations are endogenously regulated within narrow ranges, depending on the age, nutritional status and pathological condition of the patient.

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

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 acid solutions may be recommended for restoring homeostasis.

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.

5.3 Preclinical safety data

Genotoxicity

No specific studies have been performed.

Carcinogenicity

No specific studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Glacial acetic acid
- Water for injections

6.2 Incompatibilities

Due to the increased risk of microbiological contamination and incompatibilities, amino acid solutions should not be mixed with other medicinal products. Should it become necessary to add other nutrients, please refer to Section 4.2 Dose and method of administration, Additives.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Do not freeze.

6.5 Nature and contents of container

Glass (type II, clear) bottle: 500 mL (AUST R 117659), 1000 mL (AUST R 117661).

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

The physicochemical properties of this medicine were not assessed as part of its registration.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled.

8 SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai NSW 2080

Telephone: (02) 9391 5555

9 DATE OF FIRST APPROVAL

22 October 2007

10 DATE OF REVISION

15 November 2019

Summary Table of Changes

Section changed	Summary of new information
n.a.	reformatted PI