Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for SMOFlipid 20%, Aminoven 10% (with or without electrolytes) and glucose 42%

Proprietary Product Name: SmofKabiven and SmofKabiven Electrolyte Free Emulsion

Sponsor: Fresenius Kabi Australia Pty Ltd

March 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New fixed combination
Decision:	Approved
Date of Decision:	20 December 2011
Active ingredient(s):	Lipids [Soya Oil, Medium Chain Triglycerides (MCT),Olive Oil, Fish Oil (Rich in Omega-3 Acids)], Glucose and Amino Acids [L-Alanine, L-Arginine, Glycine, L-Histidine, L-Isoleucine, L-Leucine, L-Lysine (as L-Lycine Acetate), L-Methionine, L-Phenylalanine, L-Proline, L-Serine, Taurine, L-Threonine, L-Tryptophan, L-Tyrosine & L-Valine] with or without Electrolytes [Calcium Chloride (as Dihydrate), Sodium Glycerophosphate (as Hydrate), Magnesium Sulfate (as Heptahydrate), Potassium Chloride, sodium acetate (as trihydrate), zinc sulfate (as Heptahydrate)]
Product Name(s):	SmofKabiven and SmofKabiven Electrolyte Free
Sponsor's Name and Address:	Fresenius Kabi Australia Pty Ltd Locked Bag 1074, Pymble BC, NSW 2073
Dose form(s):	Emulsion for intravenous (IV) Infusion
Strength(s):	Amino Acids 5.1% (with or without Electrolytes 0.7%), Lipids 3.8% & Glucose 12.7% ; Bag sizes: 986 mL, 1477 mL, 1970 mL and 2463 mL
Container(s):	3-Chamber Infusion Bag
Pack size(s):	1 or 4 bags (986 mL & 1477 mL), 1 or 2 bags (1970 mL and 2463 mL)
Approved Therapeutic use:	Parenteral nutrition for adult patients when oral or enteral nutrition is impossible, insufficient or contraindicated.
Route(s) of administration:	Intravenous (IV)
Dosage:	See Product Information (PI)
ARTG Number (s)	173890, 180543, 180546, 180547, 173891, 180548, 180549 and 180550

Product Background

This AusPAR describes the application by Fresenius Kabi Australia Pty Ltd to register new fixed combinations of the following previously approved active ingredients; Aminoven 10% (with or without electrolytes) as the amino acid solution and Glucose 42%. Whilst SMOFlipid 20% (AUST R 158359) and Aminoven 10% without electrolytes (AUST R 117659 & 117661) are already registered in Australia by Fresenius Kabi as single

component products, Aminoven 10% with electrolytes which does not exist as a single component product is not registered in Australia.

The proposed products are SMOFlipid 20%, Aminoven 10% with electrolytes and Glucose 42% (SmofKabiven) or SMOFlipid 20%, Aminoven 10% without electrolytes and Glucose 42% (SmofKabiven Electrolyte Free) emulsion for infusion.

The components of SmofKabiven or SmofKabiven Electrolyte Free are in detail:

- SMOFlipid 20% is comprised of the lipid components Soybean oil, Medium chain triglycerides (MCT), Olive oil and Fish oil.
  This composition of the different oils was chosen to:
  - - Provide sufficient amounts of essential fatty acids and energy
  - - Decrease the load of ω-6 polyunsaturated fatty acids, especially linoleic acid
  - - Provide the very long chain ω-3 fatty acids EPA and DHA and thereby decrease the ω6:ω-3 fatty acid ratio- Replace part of the polyunsaturated fatty acids by monounsaturated fatty acids (oleic acid)
  - - Include medium chain trigylcerides to provide additional rapidly available energy
- Aminoven 10% is an amino acid solution to provide a source of nitrogen and the essential amino acids.
- Glucose solution for the provision of energy.

Two such combination packs are currently registered in Australia. These are Kabiven G11% (for peripheral and central venous administration) and Kabiven G19% (for central venous administration). Kabiven G11% and G19% are a three-chamber combination packs consisting of Intralipid 20% as the lipid emulsion, Vamin 18 (with electrolytes) Novum as the amino acid solution and a Glucose solution.

While the patient's clinical condition may require individual balance of some of these elements, the numerous commercial solutions available to mix together (such as separate lipid emulsions, amino acid solutions, fat or water soluble vitamins) as well as combination packs of standard solutions (all-in-one admixtures) are often presented as multi-chamber bags to simplify the mixing and delivery of TPN.

The four different package sizes of each SmofKabiven and 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 (taking into account the electrolytes already present in SmofKabiven) should be added to SmofKabiven according to the patient's need.

Regulatory Status

The first registration of SmofKabiven and SmofKabiven EF was in Sweden (Reference Member State, via the Mutual Recognition Process (MRP)) on 21st June, 2007. In addition to the EU, the product is registered in 11 countries with no deferrals, withdrawals or rejections.

Not all constituent products or strengths are separately registered in Australia. The Aminoven solution with electrolytes does not exist as a single component product hence it is not registered on the ARTG.

There are no Glucose 42% or Glucose 12.7% solutions registered on the Australian Register of Therapeutic Goods (ARTG).

SMOFlipid 20% emulsion containing 4 different types of oils (Soya oil, Medium Chain Triglycerides (MCT), Olive oil and Fish oil) is registered on the ARTG (AUST R 158359) for parenteral use. Fish Oil and Medium Chain Triglycerides are not registered on the ARTG.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Product

Eight presentations, four of SmofKabiven and four of SmofKabiven Electrolyte Free are proposed for registration, the details of which are tabulated below. The products are hypertonic.

Lipid emulsion (mL)	Amino acid solution (mL)	Glucose solution (mL)	Total volume (mL)
188	500	298	986
281	750	446	1477
375	1000	595	1970
469	1250	744	2463

The 986 mL and 1477 mL presentations will be provided in packs of 1 or 4 bags, whilst the 1970 mL and 2463 mL presentations will be provided in packs of 1 or 2 bags.

Other than the electrolytes added to the amino acid solution, the four SmofKabiven presentations are identical to their SmofKabiven Electrolyte Free counterparts. The electrolytes other than zinc sulfate heptahydrate (calcium chloride dihydrate, magnesium sulfate heptahydrate, potassium chloride, sodium acetate trihydrate and sodium glycerophosphate) are present in other TPN products registered in Australia (Kabiven G11% and Kabiven G19%). An IV infusion containing zinc sulfate 50 mg/mL is also registered in Australia (AUST R 22857).

The specifications applied to all active ingredients in the proposed presentations correspond to the appropriate European Pharmacopoeia (Ph. Eur.) Monograph except for taurine, which is tested for compliance with US Pharmacopiea (USP) requirements. All excipients but two also comply with relevant Ph. Eur. Monographs; purified egg phospholipids complies with the specifications approved for SMOFlipid as does sodium oleate except that the limit for peroxide value has been tightened from ≤ 15.0 to ≤ 10.0.

The specifications and test methods applied to the lipid component are identical to those approved for SMOFlipid, whilst the glucose component complies with the British Pharmacopiea (BP) Monograph for Glucose Intravenous Infusion. Apart from the addition of identification and assay tests for sodium, potassium, calcium, magnesium, phosphorus and zinc, the specifications applied to the amino acid solution with or without electrolytes are identical to those approved for Aminoven 10%.

Adequate stability data have been provided to support the proposed shelf life of 2 years below 25°C.

Sterility and safety endotoxins aspects of the submission have been evaluated independently and were considered acceptable.

Bioavailability

Bioavailability data were not required for this type of application.

Quality Summary and Conclusions

There were no objections in respect of Chemistry, Manufacturing and Controls to registration of these products.

III. Nonclinical Findings

Introduction

No nonclinical studies with SmofKabiven were submitted with the current Australian submission. The sponsor is relying solely on nonclinical data previously submitted to support the registration of SMOFlipid and amino acid containing parenteral agents. The nonclinical evaluator noted that as there is unlikely to be sufficient human experience with the combined use of the components, and according to the TGA adopted EU guideline,[1] this is considered a deficiency. However, regarding this issue, concerns were somewhat lessened by:

- the extensive clinical experience with similar TPN products, namely Kabiven G11%, Kabiven G19%, OliClinomel N4-550E, OliClinomel N4-800E, OliClinomel N4-900E and OliClinomel N4-1000E;
- there is a lower risk of hyperketonaemia with a MCT/glucose combination (as in SmofKabiven) than with MCT alone (as in SMOFlipid)[2,3,4];
- the presence of an MCT containing lipid component (SmofKabiven) has a protein sparing effect that is not seen with long chain only lipid containing TPNs (as in currently registered TPNs)[5,4];
- no significant differences in clinical signs or plasma insulin levels were seen in dogs receiving a long chain triglyceride containing TPN compared to those receiving a MCT containing TPN[4];
- the lipid infusion rate of SmofKabiven is lower than that of SMOFlipid (0.076 g fat/kg/h compared to 0.15 g fat/kg/h), reducing the risk of acidosis and neurotoxicity associated with high plasma levels of medium chain fatty acids;
- exacerbated toxicities are not predicted as there are no common target organ toxicities for each of the three components (lipid, amino acid and glucose).

At the maximum recommended human dose (MRHD) of SmofKabiven for a 70 kg individual, the daily zinc dose is at the upper level currently recommended for parenteral

[1] EMEA/CHMP/SWP/258498/2005 Guideline on the nonclinical development of fixed combinations of medicinal products. http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf

[2] Kolb, S. And D. Sailor. (1984) Effect of fat emulsions containing medium-chain triglycerides and glucose on ketone body production and excretion. *J. Parenter. Enteral Nutr.* **8:** 285-289.

[3] Johnson, R.C. and R. Cotter. (1986) Metabolism of medium-chain triglyceride lipid emulsion. *Nutr. Internat.* **2:** 150-158.

[4] Grancher, D., C. Jean-Blain, A. Frey, H. Schirardin and A.C. Bach. (1987) Studies on the tolerance of medium chain triglycerides in dogs. *J. Parenter. Enteral Nutr.* **11:** 280-286.

[5] Mok, K.T., A. Maiz, K. Yamazaki, J. Sobrado, V.K. Babayan, L.L. Moldawer, B.R. Bistrian and G.L. Blackburn. (1984) Structured medium-chain and long-chain triglyceride emulsions are superior to physical mixtures in sparing body protein in the burned rat. *Metabolism* **33:** 910-915.

nutrition. In patients >70 kg, a reduction in the total daily dose of SmofKabiven may be warranted to limit exposure to zinc.[6]

Nonclinical Assessment

The formulation of SmofKabiven is similar to currently registered TPN agents, apart from the inclusion of taurine in the amino acid component, zinc sulfate in the electrolyte solution, and medium chain triglycerides (MCT) and fish oil in the lipid component. However, taurine is an ingredient of the registered product Aminoven, MCT and fish oil are contained in SMOFLipid, and zinc sulfate is approved as a TPN additive. At the maximum recommended human dose (MRHD) of SmofKabiven, the final clinical doses of all the ingredients, with the possible exception of zinc (see below), will be similar to or lower than the doses achieved at the MRHDs of the currently approved parenteral nutrition agents.

Zinc has been approved as an additive to TPN solutions (Zinc Sulphate Injection 50mg/1mL (5%); Phebra); the Product Information document of this product gives the MRHD of zinc as 4 mg/day, with 6 mg/day suggested for acute catabolic states. Zinc (10 µmol/mL) is also present in Addamel N (Fresenius Kabi NZ Ltd), a parenteral nutrition product registered in New Zealand (but not Australia), for which the MRHD of 10 mL/day delivers 0.1 mmol/day zinc (6.54 mg/day). SmofKabiven (but not SmofKabiven EF) contains 6.6 mg/L zinc sulfate, equivalent to 2.67 mg/L zinc (0.04 mmol/L). Thus, at the MRHD of SmofKabiven (35 mL/kg/day), a 50 kg individual may receive 1750 mL/day SmofKabiven (4.67 mg/day zinc), and a 70 kg individual 2450 mL/day SmofKabiven (6.54 mg/day zinc). A dose of 6.54 mg/day zinc is consistent with that achieved at the MRHD of Addamel N and only slightly greater than the MRHD for zinc recommended in the Zinc Sulphate Injection (Phebra) Product Information. In patients >70 kg, a reduction in SmofKabiven dosage may be advisable to avoid excessive administration of zinc; this issue was referred to the Clinical Evaluator for clinical assessment.[6]

Nonclinical Summary and Conclusions

- No nonclinical studies using SmofKabiven were submitted with the current Australian submission. The sponsor relied on previously submitted data using SMOFlipid and amino acid containing parenteral agents.
- Based on previous nonclinical studies performed separately with SMOFlipid and amino acid containing parenteral agents, no exacerbated toxicities are predicted. However, in the absence of nonclinical data with the fixed combination product, potential safety issues will need to be addressed solely by clinical data. Notwithstanding MRHD of SmofKabiven of 35 mL/kg/day, a maximal total daily dosage of 2450 mL may be advisable to limit total exposure to zinc.[6]

IV. Clinical Findings

Introduction

Study 03-3CB7-001 was included in the sponsor's previous submission to register SMOFlipid and was also used in the registration of Aminoven.

[6] Sponsor's comment: The sponsor provided a response to the TGA comment regarding zinc during the clinical evaluation of SmofKabiven/SmofKabiven EF. The sponsor's justifications were based on the "AuSPEN guidelines for intravenous trace elements and vitamins 1999" and ESPEN guidelines 2009 for the intensive care patients. Please see the complete response in section *Response from Sponsor* below, see page 23-25.

Pharmacokinetics

No clinical pharmacokinetic (PK) have been carried out for SmofKabiven emulsions.

Pharmacodynamics

As for SMOFlipid, no clinical pharmacology PD studies have been submitted for SmofKabiven emulsions.

Pharmacodynamic interactions

The following is a summary from the previous TGA evaluation of SMOFlipid:

> Peroxidation may occur during manufacture, storage and intravenous (IV) delivery (when TPN is unprotected from light and ultraviolet (UV) therapy). It may occur *in vivo* in infants and in adults on home TPN,[7] as indicated by the presence of malonic dialdehyde (MDA) in the urine. Polyunsaturated fatty acids can act as substrates for the formation of lipid hyperoxides (which may in themselves be pro inflammatory),[8] mediated by free radicals. Olive oil, with its lower content of polyunsaturated fatty acids, undergoes less peroxidation *in vivo* and *in vitro.*[9]
>
> α-Tocopherol acts as a free radical scavenger both *in vivo* and *in vitro* countering the risk of hypeperoxide damage. The content varies with the source of the oils. α-Tocopherol is inserted between phospholipids in cell membranes and lipoprotein surfaces.

This was not discussed in the sponsor's Clinical Summary, however the proposed PI states:

> Chemical and physical in use stability of the mixed three chamber bag has been demonstrated for 36 hr at 25°C. [10]

Efficacy

The exposure of patients in Study 03-3CB7-001 was given only as total volumes with a maximum of 1970 mLs in a 24 h period being given. This corresponds to the recommended maximum dose (35 mL/kg/day) for a 56 kg patient. Patient mean/median weight was ~73 kg with a maximum of 93 kg. The dose selection was based on "General guidelines for Clinical Nutrition *(not identified)* and SmPC for Kabiven and SMOFlipid."[11]

No efficacy studies have been submitted for SmofKabiven emulsions.

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[7] Carpentier Y A, Dupont lE. (2000). Advances in intravenous lipid emulsions. *World J Surg*. 24(12): 1493-7.

[8] Trebble T, Arden NK, Stroud MA, Wootton SA, Burdge GC, Miles EA Ballinger AB, Thompson RL, Calder PC. (2003). Inhibition of tumour necrosis factor-alpha and interleukin 6 production by mononuclear cells following dietary fish-oil supplementation in healthy men and response to antioxidant co-supplementation. *Br J Nutr.* 90(2):405-12.

[9] Pironi L, Guidetti M, Zolezzi C, Fasano MC, Paganelli F, Merli C, Bersani G, Pizzoferrato A, Miglioli M. (2003). Peroxidation potential of lipid emulsions after compounding in all-in-one solutions. *Nutrition* 19(9):784-8.

[10] Sponsor's comment: The sponsor provided a response to this during the evaluation of SmofKabiven/SmofKabiven EF (please refer to *Response from Sponsor* section of this report , see page 26) and the AusPAR for SMOFlipid; the peroxidation of SMOFlipid is controlled with respect to raw material, process and packaging. The results show consistently low values. Furthermore, no propensity to light induced peroxidation has been found in light exposure studies. Clinical studies with SMOFlipid showed that lipid peroxidation indicators (LDL-TBARS and MDA-TBARS) were comparable between SMOFlipid and a soybean oil emulsion. Further detailed information can be found in the AusPAR for SMOFlipid.

[11] As per sponsor's Study report.

Safety

The only Clinical Safety study submitted with the current Australian application (Study 03-3CB7-001) has already been evaluated by TGA as part of the previous submission (see above).

Study 03-3CB7-001

Limited amounts of oral/enteral nutrition were permitted.

The following is a summary from the previous TGA evaluation:

This was an open label, randomised, active controlled, parallel group study of safety and tolerance of SmofKabiven versus Kabiven during 5 to 7 days in post operative patients requiring TPN in a single centre. Patients received Continuous Central Infusion of SmofKabiven or Kabiven: (*intended dose*) at:

Day 1 15.0mL/kg/d (0.57g SmofKabiven lipid/kg/day);

Days 2-4 22.5-30.0 mL/kg/d (0.86-1.14g SmofKabiven lipid/kg/day);

Days 5-7 15.0-30.0 mL/kg/d (0.57-1.14g SmofKabiven lipid/kg/day).

SmofKabiven has higher glucose and amino acid content than Kabiven.

The Clinical Evaluator noted that in this study, infusion pumps were not used[12] and the infusion was controlled manually. Patients were statistically considered completers if they received ≥50% of the study medication for 5 to 7 days. Of a total of 53 intent to treat (ITT) patients (60 enrolled), only two SmofKabiven and one Kabiven patient received the full treatment for 7 days.[13] Eight SmofKabiven and nine Kabiven patients withdrew from the study prematurely and 19 SmofKabiven and 18 Kabiven completed an infusion on Day 5. There were adverse events (AEs) in 25 SmofKabiven (5 serious AEs (SAEs)) patients and 23 Kabiven (2 SAEs) patients whereas four SmofKabiven patients and four Kabiven patients had severe AEs. Seventeen SmofKabiven and 11 Kabiven patients had possibly or probably treatment related AEs (none were SAEs). Eight SmofKabiven patients and five Kabiven patients withdrew due to AEs.

The mean glucose plasma level had increased by 27.13 ± 71.10 and 27.46 ± 45.26 mg/dL in the SmofKabiven and Kabiven groups, respectively, by the Final Examination (last observation carried forward (LOCF)). Individual glucose levels were highly variable in both groups since diabetic and non diabetic patients were included. Four patients in the SmofKabiven group and two patients in the Kabiven group showed at least one clinically relevant increase in serum glucose.

Except for the proportion of granulocytes and bilirubin and C-reactive protein (C-RP) concentrations, the changes in any mean laboratory parameter were similar in SmofKabiven and Kabiven treated patients.[14] The reduction in bilirubin serum

[12] The proposed PI says: 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, for example a volumetric pump.

[13] Sponsor comment: As described in the Statistical Analyses Plan, a patient completed the study regularly if he/she received at least 50% of minimum trial treatment dose over each of at least 5 periods. According to this definition of 53 intent to treat (ITT) patients (60 enrolled), the study was completed in 18/26 (69.2 %) and 18/27 (66.7 %) patients in the SmofKabiven and Kabiven group, but with the exception of 2/26 (7.7%) and 1/27 (3.7%) patients, respectively, all these patients terminated the study before completing Period 7.

[14] The sponsor commented that between baseline and the Final Examination, the proportion of granulocytes decreased slightly faster in the Kabiven group than in the SmofKabiven group.

concentration was more pronounced in the Kabiven group than in the SmofKabiven group but this reduction occurred from an already raised baseline.[15]

Table 1. Premature study termination according to CRF.

	All subjects N = 53		SmofKabiven N = 26		Kabiven N = 27	
	n	%	n	%	n	%
Premature terminated subjects	50	83.3	24	80.0	26	86.7
Primary reason	50	83.3	24	80.0	26	86.7
Technical failure	1	1.7	1	3.3		
Recovered	32	53.3	14	46.7	18	60.0
Adverse events	7	11.7	5	16.7	2	6.7
Consent withdrawn	9	15.0	3	10.0	6	20.0
Other	1	1.7	1	3.3		
Secondary reason*	10	16.7	6	20.0	4	13.3
Technical failure	2	3.3	1	3.3	1	3.3
Recovered	1	1.7	1	3.3		
Adverse events	6	10.0	3	10.0	3	10.0
Consent withdrawn	2	3.3	2	6.7		

Table 2. Number of study drug infusions.

Number of infusions	All subjects N = 53		SmofKabiven N = 26		Kabiven N = 27	
	n	%	n	%	n	%
1	2	3.8	2	7.7	-	-
2	5	9.4	3	11.5	2	7.4
3	4	7.5	1	3.8	3	11.1
4	5	9.4	1	3.8	4	14.8
5	31	58.5	15	57.7	16	59.3
6	3	5.7	2	7.7	1	3.7
7	3	5.7	2	7.7	1	3.7

[15] The sponsor commented that both groups showed a reduction of the mean CRP level during the study, however, this reduction was slightly more pronounced in the Kabiven group compared to the SmofKabiven group.

Table 3. Volume of study medication infused.

Volume infused [ml]	All subjects N = 53			SmofKabiven N = 26			Kabiven N = 27		
	Mean*	SD	n	Mean*	SD	n	Mean*	SD	n
Period 1	1036.0	281.6	53	989.5	325.3	26	1080.7	229.3	27
Period 2	1543.6	341.0	51	1484.9	364.6	24	1595.9	316.2	27
Period 3	1553.7	401.7	46	1549.5	276.6	21	1557.2	488.6	25
Period 4	1781.0	521.3	42	1755.0	413.5	20	1804.6	612.2	22
Period 5	1618.6	413.1	37	1508.6	440.6	19	1734.6	357.6	18
Period 6	1663.3	441.3	6	1415.0	198.9	4	2160.0	339.4	2
Period 7	1630.0	693.5	3	1230.0	42.4	2	2430.0	-	1

* arithmetric mean. SD-Standard deviation

Table 4. Treatment emergent AEs with at least possible relationship to the study drug.

		All subjects N = 53		SmofKabiven N = 26		Kabiven N = 27	
		n	%	n	%	n	%
Subjects with AEs		48	90.6	25	96.2	23	85.2
Probable	Subjects with remarks	1	1.9	1	3.8	-	-
	Nausea	1	1.9	1	3.8	-	-
Possible	Subjects with remarks	27	50.9	16	61.5	11	40.7
	Nausea	11	20.8	4	15.4	7	25.9
	Vomiting NOS	9	17.0	7	26.9	2	7.4
	Flatulence	5	9.4	4	15.4	1	3.7
	Abdominal Pain NOS	1	1.9	-	-	1	3.7
	Hyperglycaemia NOS	1	1.9	1	3.8	-	-
	Hypertension NOS	1	1.9	1	3.8	-	-
	Oedema NOS	1	1.9	1	3.8	-	-

Multiple responses possible. AEs are coded according to MedDRA 6.0. NOS=not otherwise specified.

Table 5. Main parameters of clinical chemistry (ITT population).

		SmofKabiven N = 26				Kabiven N = 27			
		Period 1	Period 4 (LOCF)	Period 6 (LOCF)	Period X (LOCF)	Period 1	Period 4 (LOCF)	Period 6 (LOCF)	Period X (LOCF)
Total bilirubin (mg/dL)	Mean	0.99	0.81	0.78	0.82	1.30	0.92	0.84	0.84
	SD	1.07	0.89	0.87	0.88	2.03	1.59	1.22	1.22
AST (U/L)	Mean	181.04	102.00	99.58	101.63	98.35	40.04	39.50	39.42
	SD	315.47	294.26	293.39	293.01	169.98	20.51	19.47	19.30
ALP (U/L)	Mean	57.57	85.00	102.96	106.13	68.69	97.04	116.65	118.73
	SD	17.16	48.66	57.90	57.70	36.19	45.82	57.45	58.17
Triglycerides (mg/dL)	Mean	87.71	149.79	163.21	162.25	77.25	135.29	143.29	144.00
	SD	55.32	58.53	64.98	65.89	29.84	50.22	51.13	50.60
Glucose (mg/dL)	Mean	126.33	154.88	152.58	153.46	109.69	139.46	139.88	137.15
	SD	45.22	73.18	75.05	74.68	28.91	40.95	43.61	44.37

AST= aspartate aminotransferase, ALP=alkaline phosphatase

Table 6. Number of patients changing to low or high clinical laboratory values after start of treatment (Period 1 until Period 4 (LOCF).

	SmofKabiven N = 26						Kabiven N = 27					
	Change to low			Change to high			Change to low			Change to high		
	n	%	n at risk	n	%	n at risk	n	%	n at risk	n	%	n at risk
Total bilirubin (mg/dL)	0	0.0	24	0	0.0	15	0	0.0	26	0	0.0	17
AST (U/L)	0	0.0	24	0	0.0	10	0	0.0	26	3	30.0	10
ALP (U/L)	0	0.0	23	3	13.0	23	0	0.0	26	4	16.7	24
Triglycerides (mg/dL)	0	0.0	13	1	4.2	24	0	0.0	13	2	8.3	24
Glucose (mg/dL)	0	0.0	24	6	50.0	12	0	0.0	24	10	62.5	16

AST= aspartate aminotransferase, ALP=alkaline phosphatase

Patients with observations at Period 1 only.

At risk for a change to high: patient with a value below or within the normal range at Period 1 (baseline)
At risk for a change to low; patient with a value within or above the normal range at Period 1(baseline)

Table 7. Number of patients changing to low or high clinical laboratory values after start of treatment (Period 1 until Final Examination (LOCF).

	SmofKabiven N = 26						Kabiven N = 27					
	Change to low			Change to high			Change to low			Change to high		
	n	%	n at risk	n	%	n at risk	n	%	n at risk	n	%	n at risk
Total bilirubin (mg/dL)	0	0.0	24	1	6.7	15	0	0.0	26	0	0.0	17
AST (U/L)	0	0.0	24	4	40.0	10	0	0.0	26	4	40.0	10
ALP (U/L)	0	0.0	23	4	17.4	23	0	0.0	26	7	29.2	24
Triglycerides (mg/dL)	0	0.0	13	1	4.2	24	0	0.0	13	1	4.2	24
Glucose (mg/dL)	0	0.0	24	6	50.0	12	0	0.0	24	10	62.5	16

Patients with observations at Period 1 only. ALP=alkaline phosphatase, AST= aspartate aminotransferase

At risk for a change to high: patient with a value below or within the normal range at Period 1 (baseline)
At risk for a change to low; patient with a value within or above the normal range at Period 1(baseline)

Patient Exposure

The Clinical Evaluator noted, in the sponsor's study report, that the exposure of patients was given only as total volumes with a maximum of 1970 mLs in a 24 hr period . This corresponds to the recommended maximum dose (35 mL/kg/day) for a 56 kg patient. Patient mean/median weight was ~73 kg with a maximum of 93 kg.

Evaluator's Comment: Given that the proposed dose in the trial and the recommended/maximum doses in the proposed PI are in mL/kg/day, the failure in the report to provide details of exposure (mean, range) in this format makes safety assessment of exposure impossible. The sponsor's Summary of Clinical Safety provided mean daily volume/mean patient weight administered; this result was a maximum average of 24 mL/kg/day well below the recommended maximum of 35 mL/kg/day[16].

Postmarketing experience at the time of submission

Postmarketing safety data from patients receiving the dose specified in the European Summary of Product Characteristics (SmPC) have not revealed any safety concerns related to dosing.

Between the time of the first registration on 21 June 2007 to the time of the current submission four Product Safety Update Reports (PSURs) have been prepared.

Only one reported ADR (polyarthralgia) was received.

There was one case reported in the literature of a sea-blue histiocyte syndrome and death from multi-organ failure.[17]

[16] Sponsor's Comment: The sponsor has provided a response to this comment, please refer to *Response from Sponsor* below, see page 23.

[17] Egana N, ParOn L, Cuerda C, Bretón I, Camblor M, Velasco C, Garcia-Pens P: Sea-Blue Histiocyte Syndrome Associated with Home Parenteral Nutrition Nutr Hosp. 2009 May-Jun; 24(3): 36 1-363.

Safety related to Drug-Drug interactions and Other interactions

See the *Pharmacodynamic Interactions* section above for a previous TGA evaluation of SMOFlipid.

Evaluator's Comment: This was not discussed in the sponsor's Clinical Summary, however in a PSUR there was a study reported[18] which looked at peroxides in parenteral nutrition with soya oil lipid and found a significant relationship of urinary MDA levels to added multivitamins as well light exposure.

In the sponsor's Clinical Overview it states:

> No interactions are expected with the final admixture - SmofKabiven emulsion.[10]

Other safety issues

A literature search found no relevant clinical data for this product. Therefore, the only clinical data generated to support the use of SmofKabiven are the sponsor's two clinical trials submitted with the current application.

Evaluator's Overall Conclusions on Clinical Safety[19]

The submission is supported only by an open trial study where the technique of infusion used is not recommended in the sponsor's Clinical Overview. The trial had 26 patients in the SmofKabiven group and only two of these completed the full treatment for the trial.[20] An assessment of the patient exposure (mode, mean, range) on the recommended basis of mL/kg/day was not submitted. The sponsor's Summary of Clinical Safety provided the mean daily volume/mean patient weight administered; a maximum average of 24 mL/kg/day was used, well below the recommended maximum of 35 mL/kg/day. The amount of oral/nutrition could not be determined by the evaluator thus the safety of the indication (when oral or enteral nutrition is impossible or contraindicated) was not demonstrated.

At the time of submission, the PSURs submitted covered a period of less than one year of marketing.

The literature review found no articles relevant to the safety of the product and no published articles to support safety were submitted, yet the sponsor's Clinical Overview states:

> All components of SmofKabiven: SMOFlipid 20%, Glucose 42%, Aminoven 10%, and Electrolytes are already approved for use as constituents of PN, indeed there is clinical and experimental literature available on each of these components when used separately, attesting to their safety and efficacy as constituent solutions for use during PN.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

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[18] Bassiouny MR *et al* (2009). A Randomized Controlled Trial on Parenteral Nutrition, Oxidative Stress, and Chronic Lung Diseases in Preterm Infants. *Journal of Pediatric Gastroenterology & Nutrition*. 48:363-369.

[19] Sponsor's comment: The sponsor has provided a response to the Evaluator's Overall Conclusions on Clinical Safety, please refer to *Response from Sponsor*, see page 20.

[20] The sponsor commented that the number of patients that completed the full treatment was 18/26 in the SmofKabiven group.

Safety

1. Given that the proposed dose in Study 03- 3CB7-001 and the recommended/maximum doses in the proposed PI are in mL/kg/day, please provide details of exposure (daily mean, mode, range) in this format.
2. Please indicate if the glucose is derived from corn (maize).
3. *Adverse Effects* Tabular listing. Please indicate whence or how this listing was arrived at.

The questions raised by the Clinical Evaluator have been addressed in the *Response from Sponsor* below.

Clinical Summary and Conclusions

Benefit-Risk Assessment [21]

Benefits

The proposed benefits of SmofKabiven in the usage are for the simplification of therapy:

- *Preparation*. While the basic components are easier to mix (as against 3 separate bags under laminar flow) –additional components (such as vitamins and electrolytes) still need to be added under laminar flow conditions. Further, it also creates the problem of storage and selection from multiple preparations rather than storage and mixing amounts of only 3 preparations.
- There may be less risk of infection but this benefit is lessened if there are added components.
- *Administration*. It is hard to see how this may improve administration simplicity when PN solutions are usually supplied pre mixed from pharmacies in one bag. There may be a possible advantage for home PN but this was not discussed and since the patient exposure was calculated at an average of 5 days, home PN is clearly not considered a frequent likelihood.

Of the relevant references submitted (Washawsky 1992) related to hospital compounded all in one mixtures while the ESPEN guidelines[22] did not clearly distinguish between commercially or hospital compounded all in one mixtures.

Risks

The risks of SmofKabiven (based on the PIs of the individual constituents) in the proposed usage are multiple, however not all appear in the proposed draft PI and not all have been discussed in the current Australian submission.

If there are risks associated with a premixed solution not seen in the alternative separately registered preparations (such as peroxidation) this was not discussed in the current submission. While it is common practice to administer all the ingredients for 24 hours of PN mixed in a single bag (all-in-one), these preparations are usually compounded in hospital pharmacies and TGA approval is not required.

Of the proposed constituents:

[21] Sponsor's comment: The sponsor has provided a response to the Clinical Evaluator's Benefit-Risk Assessment in section *Response from Sponsor*, see page 21-22.

[22] Singer *et al* (2009). ESPEN Guidelines on Parenteral Nutrition: Intensive care. *Clinical Nutrition* **28**: 387–400. http://www.espen.org/documents/0909/Intensive%20Care.pdf

- Aminoven EL has not been registered.
- Glycerophosphate is not a constituent of Aminoven, SMOFlipid or Glucose. It is proposed in higher concentrations than in Kabiven G. Its presence was not discussed in the clinical part of the submission. It appears to be justified for use on the basis of a study in cats and an *in vitro* study.

Benefit-Risk Balance

The clinical evaluator believed that concerns of safety have been inadequately addressed, with virtually no data submitted (one trial of 26 patients in which only two patients had the full treatment[20], 9 months of postmarketing PSUR and no safety literature),

Any benefit is limited and was not adequately discussed.

Based on these considerations of minimal benefit versus uncertain safety, the benefit risk balance of SmofKabiven for the proposed usage is unfavourable.

It was recommended that the registration of SmofKabiven not be approved.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections in respect of Chemistry, Manufacturing and Controls to registration of these products.

Nonclinical

- No nonclinical studies with SmofKabiven were submitted with the current Australian application. Concerns and deficiencies identified by the nonclinical evaluator are outlined under III Nonclinical Findings above.
- At the MRHD of SmofKabiven for a 70kg individual, the daily zinc dose is at the upper level currently recommended for parenteral nutrition. In patients >70 kg, a reduction in the total daily dose of SmofKabiven may be warranted to limit exposure to zinc. Notwithstanding the MRHD of SmofKabiven of 35 mL/kg/day, a maximal total daily dosage of 2450 mL may be advisable to limit exposure to zinc.[6]

Clinical

The clinical evaluator (CE) has not identified either pharmacokinetic (PK) or pharmacodynamic (PD) data pertaining specifically to either SmofKabiven or SmofKabiven-EF.

The CE also stated that no efficacy studies have been submitted for SmofKabiven/SmofKabiven-EF emulsions.

The CE has identified a previously submitted Study 03-3CB7-001 with safety data on SmofKabiven.

On *Safety* outcomes, the CE summarised that:

- Mean glucose levels had increased by 27.13 ± 71.10 and 27.46 ± 45.26 mg/dL in the SmofKabiven and Kabiven groups, respectively, by the Final Examination (LOCF). Glucose levels showed a high individual variability in both groups since diabetic and non diabetic patients were included. Four patients in the SmofKabiven group and two patients in the Kabiven group showed at least one clinically relevant increase in serum glucose.
- Except for the proportion of granulocytes and plasma bilirubin and C-reactive protein (C-RP) concentrations, the changes in mean laboratory parameters were similar in SmofKabiven and Kabiven treated patients. The reduction in the bilirubin serum concentration was more pronounced in the Kabiven group than in the SmofKabiven group but this reduction occurred from an already raised baseline.

CE's concerns and comments:

- In this study, infusion pumps were not used and the infusion was controlled manually.
- The exposure of patients was given in the study report only as total volumes with a maximum of 1970 mLs in a 24 hr period being given. This corresponds to the recommended maximum dose (35 mL/kg/day) for a 56 kg patient. Patient mean/median weight was ~ 73 kg with a maximum of 93 kg. Given that the proposed dose in the trial and the recommended/maximum doses in the proposed PI are in mg/kg/day, the failure in the report to provide details of exposure (mean, range) in this format makes safety assessment of exposure impossible. The summary of clinical safety provided mean daily volume/mean patient weight administered; this result was a maximum of 24 mL/kg/day and well below the recommended maximum of 35 mL/kg/day. The CE requested that details of exposure (daily mean, mode, range) to be provided in the mg/kg/day format.
- The CE requested that an indication be given if the glucose is derived from corn (maize).
- Regarding postmarketing experience at the time of submission, the CE stated that only one adverse effect report of polyarthralgia.

Overall, the CE has not recommended that the registration of either SmofKabiven or SmofKabiven-EF be approved for the following reasons:

1. Insufficient safety data: two out of the 26 patients enrolled in the only open clinical trial submitted received the full treatment[20].
   i Concerns about the only open clinical trial submitted: Infusion pumps were not used (infusion was manually controlled)
   ii Patients' dose exposure was expressed in volume (mL) with a maximum of 1970 mLs per 24 hr. Given the maximum recommended dose of 35 mL/kg/day, the 1970 mLs maximum daily dose stated in the open trial only equates to the maximum recommended dose for a 56 kg patient. Given that the patient mean/median weight in the trial was 73 kg with a maximum of 93 kg, dose safety data is lacking for those patients weighing >56 kg. Moreover, the maximum dose of 24 mL/kg/day stated in the summary of clinical safety provided is well below the recommended maximum of 35 mL/kg/day23,

[23] Sponsor's Comment: The sponsor has provided a response to this comment, please refer to *Response from Sponsor* below, see page 23.

iii The amount of oral nutrition could not be determined and thus the safety of the indication of "PN when oral or entered nutrition is impossible or contraindicated" was not established.

1. Limited PSUR data (≤ 1 year) were provided despite the fact that versions of SmofKabiven were registered as early as 2007[24].
2. No literature review articles on safety were provided despite the sponsor's claim that all components of SmofKabiven are already approved for use as constituents of PN and that there are indeed both clinical and experimental literature available on each of these solutions when used separately, attesting to their safety and efficacy as constituent solutions for use during PN[25].

The CE believes that the sponsor's perceived benefit of having combination packs of standard nutrient solutions (all-in-one admixtures) to simplify the mixing and delivery of TPN is outweighed by the following points.

1. The issue of having to add additives under laminar flow conditions with the risk of contamination/infection,
2. The stated contraindications/precautions in the PI**,**
3. The associated peroxide formation with SMOFlipid (a registered component of SmofKabiven) under light and UV therapy (lipid hyperoxides can be pro inflammatory) and
4. The presence of unregistered component (Aminoven Electrolytes) in SmofKabiven. (The sponsor noted that Aminoven with Electrolytes does not exist as a single component product hence it is not registered).

Risk Management Plan

There was no Risk Management Plan submitted with this application.

Risk-Benefit Analysis

Delegate Considerations

- Strictly, SmofKabiven like most other TPN solutions on the market is not an absolute fixed combination product but rather a convenient simple admixture.
- The issue of limited available data may not be critical in the current submission given that SmofKabiven with or without electrolytes consists of simple admixture of nutrient products in percentage concentrations either equalling, falling within or not too dissimilar from the percentage concentration ranges associated with those nutrient products already either registered individually (SMOFlipid 20%, Aminoven 10%, Baxter Glucose 50% & 70%) or as component of other nutrient products (OliClinomel N7-1000 with 40% glucose, Kabiven with Glucose 19% and Electrolytes).
- Use of appropriate infusion pump as per each hospital setting needs to be stipulated in the PI.
- As dose safety data is lacking for those patients weighing ≥ 56 kg based on the maximum recommended dose of 35 mL/kg/day, it is recommended that the maximum recommended dose be limited to 24 mL/kg/day as per the summary of

[24] Sponsor's Comment: The sponsor has provided a response to this comment, please refer to *Response from Sponsor* below, page 23.
[25] Sponsor's Comment: The sponsor has provided a response to this comment, please refer to *Response from Sponsor, Clinical Evaluator's Conclusions on Safety* below, page 20.

clinical safety provided (≈2,160 mL for a 90 kg individual). Moreover, the nonclinical evaluator has recommended a maximum human dose of 2,450 mL per day in order to limit the total exposure to zinc. The proposed PI already has information on the "gram" content of lipid, amino acid and glucose per mL of SmofKabiven infusion.

- The limitation in PSUR data and literature review articles on safety are probably related to the fact the various TPN solutions are used in hospitals and most hospitals are likely to deal with PSUR adverse events in house without much publication.
- It is to be expected that various hospitals will have established protocols for minimising the infection/contamination risk that may be associated with adding additives to TPN solutions.
- All prescription therapeutic products contain contraindications/precautions in their PIs which do not preclude them from being registered/marketed.
- The concern regarding peroxide formation in SMOFlipid under light and UV therapy should be considered and is worthy of mentioning in the PIs for both SMOFlipid and SmofKabiven. As SMOFlipid is registered and used by various hospitals, the formation of peroxide under light and UV should not necessarily deter the registration of SmofKabiven of which SMOFlipid is a component, provided the matter is highlighted in the PI as stated above.
- Given that 'Kabiven' is a TPN emulsion of different lipid and amino acid composition to "SmofKabiven" and that the latter is essentially a mixture of 'SMOFlipid and Aminoven', the name "SmofKabiven" is considered inappropriate and unacceptable. A probable substitute is "SMOFaminoven". The latter will prevent confusion/mix up with 'Kabiven'.
- The nonclinical evaluator is not recommending rejection of the product while making some modifications to the draft PI. The quality evaluator has no objection to the product's registration either.

Proposed Action

Given the current contemporary handling of other TPN solutions in the hospital setting, the Delegate proposed to recommend approval of "SMOFaminoven (aka-SMOFKabiven) and SMOFaminoven Electrolyte Free (aka- SMOFKabiven-Electrolyte Free) emulsions for infusion contained in 986 mL, 1477 mL, 1970 mL and 2463 mL Excel bags" for the proposed indication of

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

The recommendation is subject to the finalisation of issues relating to the draft PI and the Advisory Committee on prescription Medicines (ACPM) deliberations to the satisfaction of the TGA.

The application was submitted to the ACPM for advice.

Response from Sponsor

Clinical Evaluator's Conclusions on Safety

In response to the evaluator's comments on safety, the sponsor submitted a response to indicate that the Clinical Trial was performed in a centre with regular surgical cases. It was not intended to treat these patients in a manner outside - normal clinical practice as it could be considered unethical to do so. Practice, it was proffered, differs a great deal

between doctors, wards, departments, hospitals, regions, countries and continents. Many centres do not have access to volumetric pumps for all patients in a ward in need of intravenous infusions. A shortage of pumps should not disqualify a patient to receive proper nutritional treatment. Gravity drips have been used for TPN for as long as TPN has been available, almost 50 years, and is still –used extensively.

Combination of oral/enteral nutrition is recognised as standard medical practice to provide patients- with appropriate amounts of nutrients and energy when the gut function is compromised and patient nutritional requirements need to bel supported. The concept of Enhanced Recovery after Surgery (ERAS) or Fast Track Surgery supports the usage of the gut as soon as possible. As it isimpossible to determine exactly the gut function clinically this has to be evaluated continuously in all patients at risk. The Clinical Trial demonstrated a high premature study termination due to gut function recovery (Table 7-001 in the CER). This illustrates one of many different causes for the global trend of shorter length of stay in hospitals. Even in nutrition studies, the time to return to normal gut function has started to be used as a primary endpoint for efficacy in nutrition studies.

The evaluator states in the Evaluator's Overall Conclusions on clinical safety, that "*The literature review found no safety relevant articles, no articles to support safety were submitted, yet the Clinical Overview states: All components of SmofKabiven: SMOFlipid 20%, Glucose 42%, Aminoven lO%, and Electrolytes are already approved for use as constituents of PN, indeed there is clinical and experimental literature available on each these solutions when used separately, attesting to their safety and efficacy as constituent solutions for use during PN.*" The sponsor responded that the statement in the Clinical Overview is indeed correct as there is clinical and experimental literature available on each of the components of SmofKabiven/SmofKabiven Electrolyte Free when used separately on its own. The systematic literature search conducted by the sponsor was to determine whether:

- any non-company trials conducted with the combination have been conducted
- any evidence of safety concerns for the combination has been identified in the medical literature

The search was targeted on the combination rather than on the individual component solutions. As a result of the systematic literature search conducted, there was no evidence of safety concerns for the solutions when used in combination were found hence no relevant safety articles could be submitted with the application.

Clinical Evaluator's Benefit Risk Assessment; Benefits

In response to the first point made by the evaluator, one must not disregard the workload in the hospital pharmacy as well as the problem of storage. And surely the ability of SmofKabiven to offer hospital pharmacies the convenience of one 3-chamber plastic bag is more user friendly as compared to handling separate bags or bottles of lipids, amino acids and glucose, etc.

Regarding the second point, there is indeed a less risk of infection with the 3-chamber bag system. With separate containers there is a need for 3 lines giving potential access for microorganisms at both ends, i.e. 6 connections compare with 2 connections with the multichamber bag, regardless if additives are included.

Regarding administration under the third point, 10 years of experience in Europe and Asia using the multichamber bags clearly shows the satisfaction and fulfils the expectations from hospital staff who are handling the infusions bedside. The use of long term Home Parenteral Nutrition (HPN) is certainly considered in the further development program for SmofKabiven.

As for the forth point, regarding the references made by Warshawsky 1992 and ESPEN Guidelines on Parenteral Nutrition: Intensive Care (Singer et al 2009), it needs to be emphasised that treatment protocols are very different in different medical centres. It is also dependent on the resources of a hospital. Very few hospitals in the world have a 24 hour – 7 days/week year round full service provided from the hospital pharmacy.

Clinical Evaluator's Benefit Risk Assessment; Risks

In addition to the evaluator's comment that "*While it is common practice to administer all the ingredients for 24 hours of PN mixed in a single bag (all-in-one), these preparations are usually compounded in hospital pharmacies i.e. TGA approval is not required*.", the sponsor had noted that by providing an "all-in-one" bag, the need for compounding in a hospital pharmacy are eliminated. The "all-in-one" design thus represents a convenient option for administering PN.

The risks with individually compounded preparations based on a single physician's prescription of the day must be considered much greater than a standardised combination of nutrients manufactured according to Good Manufacturing Practice (GMP) in a controlled environment in a plant that is regularly inspected by health authorities. The free compounding and admixing performed outcome of these GMP licensed plants have shown in studies presenting with lots of errors. Often a variety of plastic bags can be used without any testing for stability or compatibility with the actual composition of nutrients and the packaging material.

Regarding glycerophosphate, indeed SmofKabiven contains approx. 13mmol/L phosphate compared to Kabiven with 10mmol/L. Kabiven was the first generation of multichamber PN bags introduced on the market since the year 2000. The second generation (StructoKabiven) had a modified glucose/lipids ratio and contained also the same amino acid solution as in SmofKabiven. The lipid component contains phospholipids and it was decided to slightly increase the glycerophosphate part as provider of phosphate. During the development of SmofKabiven it was then also decided to conform to the StructoKabiven design, i.e. keeping the same amino acid solution with the same amount of glycerophosphate. As the use of organic phosphate has been the standard way to provide phosphate it was not considered a need for a special discussion or modification regarding the electrolyte content in SmofKabiven. The increase from 10 to 13mmol/L is not a safety issue. Some investigators have questioned the provision of phosphate from the emulsifier of the lipid emulsions for decades up till about 5-10 years ago. After that, it has been accepted by concerned physicians that phosphate from phospholipids is bio-available. The experience from clinical trials on TPN containing glycerophosphate demonstrates that phosphate levels are well maintained with the amount present in both Kabiven and SmofKabiven. Also post-marketing safety data up to this date of regimens containing glycerophosphate covers an exposure of millions of patients.

Clinical Evaluator's Benefit Risk Assessment; Benefit- Risk Balance

In response to the evaluator's comments made under this section, it is important to note that a systematic literature search following a search strategy as approved by TGA was conducted and the search resulted with no relevant literature or safety concerns with the combined use of the individual constituent products. Therefore no safety literature could be submitted with the application.

Safety data on the individual active products was not considered necessary as all the constituents of the active products have been extensively used in humans in identical or very similar combinations for a long period and the safety of such combinations is well documented.

The use of the combination pack is not claimed to provide efficacy greater than the use of the three active products delivered separately. The benefits are in simplicity and ease of administration. The 3 chamber bag design provides an "all-in-one" total nutrient admixture for PN with a long shelf life of 24 months without the need for refrigeration.

Clinical Evaluator's Comment regarding Limited PSUR Data

The most recent Periodic Safety Update Report (PSUR 5) covering the period from January 2010 to December 2010 describes the following incidence of adverse event reporting.

Overview of Reporting Incidence (data from PSUR 5)

System Organ Class (SOC)	PSUR 3	PSUR 4	PSUR 5 Jan 2010-Dec 2010
General disorders and administration site conditions	0	0	0.0004
Immune system disorders	0	0	0.0004
Musculoskeletal and connective tissue disorders	0	0.004	0

Reporting Incidence = Number reports during period / patient exposure during period

It was concluded in this report (PSUR 5), three non-serious adverse reactions were reported in association with the use of the product. Within literature review, the Marketing Authorization Holder could not identify a single case possibly related to the treatment with the product. Also search for significant safety issues from clinical trials or reviewed studies revealed no new information on the safety of the product. Based on the available safety data for SmofKabiven, the safety profile has not altered. This report has not identified any new safety hazards. Therefore, no relevant change of the risk/benefit ratio of the product was identified. There is no reason for a change of the Summary of Product Characteristics (SmPC) for the product. A copy of the PSUR 5 was provided to TGA.

Delegate's Proposed Actions:The Delegate proposed to recommend approval for SmofKabiven for the proposed indication of

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

Company Response: The sponsor agreed with the Delegate's proposed actions with no further comments.

Delegate's Comments: As dose safety data is lacking for those patients weighing ≥56 kg based on the maximum recommended dose of 35 mL/kg/day, it is recommended that the maximum recommended dose be limited to 24 mL/kg/day as per the sponsor's Summary of Clinical Safety provided (~2,160 mL for a 90kg individual). Moreover, the nonclinical evaluator has recommended a maximum human dose of 2,450 mL per day in order to limit the total exposure to zinc. The proposed PI already has information on the "gram" content of lipid, amino acid and glucose per mL of SmofKabiven infusion.

Company Response: The sponsor believes the maximum recommended daily dose as proposed in the PI stating:

> "*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.***"

is appropriate for SmofKabiven and would be in line with the current approved recommended maximum daily dose for SmofKabiven emulsions in Europe.

A response to this recommendation was provided in the our response to Clinical

Evaluation Report (CER). Supplementary to this response, additional analysis were performed by Fresenius Kabi in order to provide details of exposure (mean, range) from the submitted Study 03-3CB7-001 in the format which makes safety assessment

of exposure possible, that is, in mL/kg body weight (bw). The study products were infused via a central venous line.

It is important to note that the format of the maximum dose should correctly be referred as "mL/kg bw/day" and not as "milligram/kg/day" as indicated in the CER and in the Delegate's Overview. Hence the details of exposure will be provided in the format of mL/kg/day.

The sponsor also provided a table of "Listing of study treatment" from the additional analysis which provided the individual infused volumes in mL per kg bw for each Study Period (1 to 7).

The limiting factor of a maximum infusion rate is based on the capacity to eliminate the

infused nutrients from the blood stream. It is usually the content of glucose in an admixture that determines the dose, with this amount based on research indicating an upper limit of 4 mg/kg bw/min and corresponds to 0.24 g/kg/hr. Based on this, the maximum infusion rate per hour would be set to 2 mL/kg/hr. If SmofKabiven should be infused over 24 hours this will result in "48 mL/kg/day", which is too high for a total administration of lipids and amino acids. The recommended maximum dose for SmofKabiven is therefore set to **35mL/kg/day**, which will provide 1.33 g fat/kg/day, 0.28 g Nitrogen/kg/day (corresponding to approximately 1.8 g amino acids/kg/day) and corresponding to 31 kilo calories (kcal)/kg/day of non protein energy. These figures conform to standards used in clinical nutrition.

The maximum mean of 24 mL SmofKabiven/kg bw/day was the maximum average volume administered during Study Period 4. In fact, six patients at Study Periods 4 or 5 were given 30 mL SmofKabiven/kg bw/day.

Given that the exposure of patients to study medication provided in the study report was as total volumes, please find below in Table 9 the figures for mean volume to be infused per mean weight expressed in the format of mL/kg for each period.

Table 8. Mean volume infused per mean weight expressed in the format of mL/kg for each Study Period.

Volume to be infused (mL/kg/day)		All subjects, n=53	Treatment Group	
			SmofKabiven n=26	Kabiven n=27
Period 1	Mean	(1036/73.4) **14.1** **n=53**	(989.5/72.4) **13.7** **n=26**	(1080.7/74.4) **14.5** **n=27**
Period 2	Mean	(1543.6/74.1) **20.8** **n=51**	(1484.9/73.8) **20.1** **n=24**	(1595.9/74.4) **21.5** **n=27**
Period 3	Mean	(1553.7/73.4) **21.2** **n=46**	(1549.5/73.3) **21.1** **n=21**	(1557.2/73.4) **21.2** **n=25**
Period 4	Mean	(1781/73.5) **24.2** **n=42**	(1755/73.2) **24.0** **n=20**	(1804.6/73.9) **24.4** **n=22**
Period 5	Mean	(1618.6/73.7) **22.0** **n=37**	(1508.8/73.1) **20.6** **n=19**	(1734.6/74.4) **23.3** **n=18**
Period 6	Mean	(1663.3/81.3) **20.5** **n=6**	(1415/82.5) **17.2** **n=4**	(2160/79.0) **27.3** **n=2**
Period 7	Mean	(1630/84.3) **19.3** **n=3**	(1230/86.0) **14.3** **n=2**	(2430/81) **30.0** **n=1**

In brackets the mean (volume/mean body weight) per period are given.

The sponsor would also like to address here the recommendation made by the nonclinical evaluator:

> "*…a maximal total daily dosage of 2450mL may be advisable to limit total exposure to zinc*."

According to "The Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) guidelines for intravenous trace elements and vitamins 1999"[26], the administration of zinc via parenteral nutrition in an average patient should be in the range of 50-100 micromol/day corresponding to 3.3-6.5 mg/day. In SmofKabiven, the zinc concentration is 0.04 mmol/L. Infusion of the maximum dose of 35 mL/kg bw/day would result in an amount of 2450 mL/70 kg bw/day or 0.1 mmol zinc/70 kg bw/day corresponding to 6.4 mg zinc/70 kg bw/day, which is within the recommended range. In cases for heavier patients, at 93 kg the recommended daily dosage of SmofKabiven will only range from 13-31 mL/kg bw/day, this will correspond to 3.2 mg to 7.5 mg of zinc/93 kg bw/day. The amount of 7.5 mg of zinc/day is slightly above the upper limit of recommended range of 6.5 mg of zinc/day but should not have any impact given to the average patient. For the intensive care patients the amount of 7.5 mg zinc/day is regarded as within the range (up to 10 mg zinc/day) according to the recent ESPEN guidelines 2009[22].

Supported with the above justifications, the sponsor believed the maximum daily dose as proposed in the draft PI stating:

> "*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*"

was appropriate for SmofKabiven emulsions.

Delegate's Comments: Given that "Kabiven" is a TPN solution of different lipid and amino acid composition to "SMOFKabiven" and that the latter is essentially a mixture of "SMOFlipid and Aminoven", the name "SMOFKabiven" was considered

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http://auspen.collaborationhost.net/Home%20Page/Best%20Pratice%20Guidelines/Archived%20Best%20Practice%20Guidelines/AuSPEN%20Micronutrients%20Guidelines.pdfBy

inappropriate and unacceptable. A probable substitute is "SMOFaminoven". The latter will prevent confusion/mix-up with "Kabiven".

Company Response: The sponsor believed the proposed name of 'SmofKabiven" was the most appropriate and suitable name for the product.

The use of the trade name SMOFaminoven in place of SmofKabiven in Australia will create confusion for health professionals in the field of Clinical Nutrition in Australia and around the world. The same trade name of SmofKabiven (*with or without Central following the name*) is the approved trade name used and marketed worldwide. It is also the name recognised and used by experts/opinion leaders at international congresses, in clinical guidelines and published papers. Changing the name of the product for only one country (Australia) will add to the confusion for the prescribers of the product around the world.

SmofKabiven is a product containing three components SMOFlipid (Lipids), Aminoven (Amino acids) with or without Electrolytes and Glucose. The suggested name SMOFaminoven would not correctly represent all the components of the product as it suggest a "two-in-one" product containing only Lipids and Amino acids without Glucose and this will be confusing and misleading.

The proposed product is most similar to the current "Kabiven" product where both are presented in a 3 chamber infusion bag. Kabiven is a well known all-in-one TPN product that health professionals recognize instantly as a 3 chamber bag that offers all PN components of Lipids, Amino acids, Glucose and Electrolytes. On the other hand, Aminoven is not a 3 chamber bag product, it is a single chamber bag containing only Amino acids. Health professionals do not recognize Aminoven as a product that provides the same all in one treatment hence using the name SMOFaminoven will create confusion.

The proposed name of SmofKabiven was to represent an all-in-one TPN product in a 3 chamber bag that offers the components of Lipid, Amino acids, Glucose and Electrolytes (which is known as Kabiven) with SMOFlipid as the lipid component. A capital "**K**" used in the name Smof**K**abiven instead of a small "k" was intended to let end users know that this is a product from the **K**abiven group. The word "**Kabi**" used in the name Smof**Kabi**ven was to identify the product as a Fresenius Kabi product. As outlined and supported with the above, it is important and relevant for the same trade name of "SmofKabiven", that is approved around the world, be approved for use in Australia as well.

Delegate's Comments: **Use of appropriate infusion pump as per each hospital setting needs to be stipulated in the PI.**

Company Response: The sponsor agrees with the Delegate's proposal and suggests to add the following sentence (underlined) to the *Precautions* section of the PI.

Precautions: "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 volumetric pump".

Delegate's Comments: The concern regarding peroxide formation in SMOFlipid under light and UV therapy should be considered and is worthy of mentioning in the PIs for both SMOFlipid and SmofKabiven. As SMOFlipid is registered and used by various hospitals, the formation of peroxide under light and UV should not necessarily deter the registration of SmofKabiven of which SMOFlipid is a component, provided the matter is highlighted in the PI as stated above.

Company Response: Photostability testing on SMOFlipid in one chamber bag (same Excel

packaging as SmofKabiven) has been conducted and result were provided to the TGA. The results for peroxides are low and in accordance with the stability results for SmofKabiven at 25°C. The results of the photostability testing demonstrated that light exposure of SMOFlipid filled in a one chamber bag does not cause any unacceptable changes to the quality of the product. Therefore, it can be concluded that the emulsion does not exhibit photosensitivity and no labelling recommendation referring to protection against light is considered necessary. Since both packaging concepts are transparent with identical secondary barrier bag, results for SMOFlipid in the tested one chamber bag are also applicable for SMOFlipid in Excel one chamber bag. Nevertheless, Fresenius Kabi commits to verify the photostability testing on one commercial batch of SmofKabiven before marketing in Australia.

A review of published studies reveals that most studies on lipid peroxidation and parenteral nutrition are performed in neonates. SmofKabiven is contraindicated in children under the age of 2 years which is an age group that has been primarily investigated with respect to lipid peroxidation.

Many parameters have been used in order to try to evaluate whether lipid peroxidation has an impact on outcome in clinical nutrition (ethane, pentane, thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), peroxides, trapping antioxidant potential (TRAP), isoprostanes). Today, isoprostanes are considered to be the most accurate but the results do not comply with older studies using other parameters. Evidence for effects on outcome is missing and results from different studies are partly contradictory. A more extensive evaluation of the current knowledge in the field including the results of the study by Bassiouny *et al* (2009)[13] is available on request. Clinical studies with SMOFlipid showed that lipid peroxidation indicators (LDL-TBARS and MDA-TBARS) were comparable between SMOFlipid and a soybean oil emulsion. Further detailed information can be found in the AusPAR for SMOFlipid[27].

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

Efficacy and Safety

The safety profiles of the individual components of this mixture are known and the ACPM agreed with the Delegate that this constituted sufficient evidence in support of the application.

- The committee advised that monitoring of zinc levels should be considered if TPN was to be continued for longer than 7 days.
- The proposed dosage was determined through an assessment of the limited evidence on the suitability for short term supplementation; however, dose adjustment is likely to be considered necessary if supplementation is to be given long term.

Indication

The ACPM considered this product to have a positive benefit-risk profile for the indication of:

Parenteral nutrition for adult patients when oral or enteral nutrition insufficient.

[27] http://www.tga.gov.au/pdf/auspar/auspar-smoflipid.pdf

PI/CMI

The ACPM advised that in addition to the changes proposed by the delegate, the Product Information (PI) and Consumer Medicines Information (CMI) amendments should include:

A statement should be added in the Dosage and Administration section and cross referenced to the Precautions section for both SmofKabiven and SmofKabiven Electrolyte Free Emulsion regarding peroxide formation in these products under light and UV.

A statement in the Dosage and Administration section stipulating the need for administration by means of an appropriate infusion pump.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided for Smofkabiven and Smofkabiven Electrolyte Free Emulsion solutions would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of SmofKabiven and SmofKabiven Electrolyte Free emulsion[28]; SMOFlipid 20%, Aminoven 10% (with or without electrolytes) and glucose 42% contained in 986 mL, 1477 mL, 1970mL and 2463 mL excel bags, for intravenous administration (recommended maximal daily dose 35 mL/kg bw/day), indicated for:

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

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

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- SMOFKABIVEN amino acids 5.1% / lipids 3.8% / glucose 12.7% / electrolytes 0.7% emulsion for intravenous infusion bag 986 mL
- SMOFKABIVEN ELECTROLYTE FREE amino acids 5.1% / lipids 3.8% / glucose 12.7% emulsion for intravenous infusion bag 986 mL
- SMOFKABIVEN amino acids 5.1% / lipids 3.8% / glucose 12.7% / electrolytes 0.7% emulsion for intravenous infusion bag 1477 mL
- SMOFKABIVEN ELECTROLYTE FREE amino acids 5.1% / lipids 3.8% / glucose 12.7% emulsion for intravenous infusion bag 1477 mL
- SMOFKABIVEN amino acids 5.1% / lipids 3.8% / glucose 12.7% / electrolytes 0.7% emulsion for intravenous infusion bag 1970 mL
- SMOFKABIVEN ELECTROLYTE FREE amino acids 5.1% / lipids 3.8% / glucose 12.7% emulsion for intravenous infusion bag 1970 mL
- SMOFKABIVEN amino acids 5.1% / lipids 3.8% / glucose 12.7% / electrolytes 0.7% emulsion for intravenous infusion bag 2463 mL
- SMOFKABIVEN ELECTROLYTE FREE amino acids 5.1% / lipids 3.8% / glucose 12.7% emulsion for intravenous infusion bag 2463 mL

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

PRODUCT INFORMATION

NAME OF MEDICINE

SmofKabiven®
(Amino acids 5.1%, lipids 3.8%, glucose 12.7% & electrolytes 0.7%)
Emulsion for infusion

DESCRIPTION

SmofKabiven consists of a three chamber bag system. Each bag contains the following partial volumes depending on the four pack sizes. Glucose and amino acid solutions are clear and colourless to slightly yellow and free from particles. The lipid emulsion is white and homogenous.

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

This corresponds to the following total compositions:

Active ingredients (g)	986 mL	1477mL	1970 mL	2463 mL	Per 1000 mL
Alanine	7.0	10.5	14.0	17.5	7.1
Arginine	6.0	9.0	12.0	15.0	6.1
Glycine	5.5	8.2	11.0	13.8	5.6
Histidine	1.5	2.2	3.0	3.7	1.5
Isoleucine	2.5	3.8	5.0	6.2	2.5
Leucine	3.7	5.6	7.4	9.4	3.8
Lysine (as acetate)	3.3	5.0	6.6	8.4	3.4
Methionine	2.2	3.2	4.3	5.4	2.2
Phenylalanine	2.6	3.8	5.1	6.4	2.6
Proline	5.6	8.4	11.2	14.0	5.7
Serine	3.2	4.9	6.5	8.1	3.3
Taurine	0.50	0.75	1.0	1.2	0.5
Threonine	2.2	3.3	4.4	5.4	2.2
Tryptophan	1.0	1.5	2.0	2.5	1.0
Tyrosine	0.20	0.30	0.40	0.49	0.20
Valine	3.1	4.6	6.2	7.6	3.1
Calcium chloride (as dihydrate)	0.28	0.42	0.56	0.69	0.28
Sodium glycerophosphate (as hydrate)	2.1	3.1	4.2	5.2	2.1
Magnesium sulfate (as heptahydrate)	0.60	0.90	1.2	1.5	0.61
Potassium chloride	2.2	3.4	4.5	5.7	2.3
Sodium acetate (as trihydrate)	1.7	2.6	3.4	4.2	1.7
Zinc sulfate (as heptahydrate)	0.0065	0.0097	0.013	0.016	0.0066
Glucose (as monohydrate)	125	187	250	313	127
Soya oil	11.3	16.9	22.5	28.1	11.4
Medium chain triglycerides	11.3	16.9	22.5	28.1	11.4
Olive oil	9.4	14.1	18.8	23.4	9.5
Fish oil	5.6	8.4	11.3	14.0	5.7

Corresponding to:

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

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

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

List of excipients:
Glycerol
Egg lecithin
dl-alpha-Tocopherol
Sodium hydroxide
Sodium oleate
Acetic acid - glacial
Hydrochloric acid
Water for injections

PHARMACOLOGY

Lipid emulsion

The lipid emulsion of SmofKabiven is composed of SMOFlipid and has a particle size and biological properties similar to those of endogenous chylomicrons. The constituents of SMOFlipid; Soya oil, Medium chain triglycerides, Olive oil and Fish oil have, except for their energy contents, their own 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 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.

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

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

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

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

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

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.

INDICATIONS

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

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
- 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)

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Vitamin B complex deficiency may occur with glucose administration.

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

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

Effects on fertility

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

Genotoxicity

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

Carcinogenicity

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

Use in pregnancy (Category B3)

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

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

Use in lactation

It is not known whether SmofKabiven can enter maternal milk. As zinc is excreted in milk, there is a theoretical risk of zinc-induced copper deficiency in the infant at high

doses of SmofKabiven. SmofKabiven should be used during lactation only if clearly needed.

Paediatric use

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

Interactions with other medicines

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

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

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

Effects on laboratory tests

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

Fat overload syndrome

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

Excess of amino acid infusion

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

Excess of glucose infusion

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

ADVERSE EFFECTS

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4.

	Common >1/100, <1/10	***Uncommon >1/1000, <1/100***	***Rare >1/10000, <1/1000***

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

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

DOSAGE AND ADMINISTRATION

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

The patient's ability to eliminate fat and metabolise nitrogen and glucose, and the nutritional requirements should govern the dosage and infusion rate, (please also refer to section "PRECAUTIONS").

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).

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/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).

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.

Method and duration of administration
Intravenous, infusion into a central vein.

The four different package sizes of SmofKabiven are intended for patients with high, moderately increased or basal nutritional requirements.

Paediatric patients
SmofKabiven is not recommended for use in children, (please also refer to section “PRECAUTIONS”).

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. (see 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.

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

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

Shelf life after mixing
Chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 36 hours at 25°C.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

Additives

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

Compatibility

Only medicinal or nutrition solutions for which compatibility has been documented may be added to SmofKabiven.

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.

OVERDOSAGE

Please also refer to sections “Fat overload syndrome”, “Excess of amino acid infusion” and “Excess of glucose infusion”.

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

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

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

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

STORAGE CONDITIONS

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

PRESENTATION

The container consists of a multi-chamber inner bag and an overpouch. The inner bag is separated into three chambers by peelable seals. An oxygen absorber is placed between the inner bag and the overpouch. The inner bag is made of a multilayer

polymer film - Excel. The Excel innerbag film consists of three layers. The inner layer consists of poly (propylene/ethylene) copolymer and styrene/ethylene/butylene/styrene thermoplastic elastomer (SEBS). The middle layer consists of SEBS and the outer layer consists of copolyester-ether. The infusion port is equipped with a polyolefine cap. The additive port is equipped with a synthetic polyisoprene (latex-free) stopper.

Pack sizes
1 x 986 ml, 4 x 986 ml
1 x1477 ml, 4 x 1477 ml
1 x 1970 ml, 2 x 1970 ml
1 x 2463 ml, 2 x 2463 ml

NAME AND ADDRESS OF SPONSOR
Fresenius Kabi Australia Pty Limited
964 Pacific Highway
Pymble NSW 2073
Australia
Telephone: (02) 9391 5555

Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Airport Oaks, Auckland 2022
New Zealand
Freecall: 0800 144 892

POISON SCHEDULE
Australia: Not Scheduled
New Zealand: General Sale Medicine

DATE OF TGA APPROVAL
20 Dec 2011

PRODUCT INFORMATION

NAME OF MEDICINE

SmofKabiven® Electrolyte Free
(Amino acids 5.1%, lipids 3.8% & glucose 12.7%)
Emulsion for infusion

DESCRIPTION

SmofKabiven Electrolyte Free consists of a three chamber bag system. Each bag contains the following partial volumes depending on the four pack sizes. Glucose and amino acid solutions are clear and colourless to slightly yellow and free from particles. The lipid emulsion is white and homogenous.

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

This corresponds to the following total compositions:

Active ingredients (g)	986 mL	1477mL	1970 mL	2463 mL	Per 1000 mL
Alanine	7.0	10.5	14.0	17.5	7.1
Arginine	6.0	9.0	12.0	15.0	6.1
Glycine	5.5	8.2	11.0	13.8	5.6
Histidine	1.5	2.2	3.0	3.7	1.5
Isoleucine	2.5	3.8	5.0	6.2	2.5
Leucine	3.7	5.6	7.4	9.4	3.8
Lysine (as acetate)	3.3	5.0	6.6	8.4	3.4
Methionine	2.2	3.2	4.3	5.4	2.2
Phenylalanine	2.6	3.8	5.1	6.4	2.6
Proline	5.6	8.4	11.2	14.0	5.7
Serine	3.2	4.9	6.5	8.1	3.3
Taurine	0.50	0.75	1.0	1.2	0.5
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 (as monohydrate)	125	187	250	313	127
Soya oil	11.3	16.9	22.5	28.1	11.4
Medium chain triglycerides	11.3	16.9	22.5	28.1	11.4
Olive oil	9.4	14.1	18.8	23.4	9.5
Fish oil	5.6	8.4	11.3	14.0	5.7

Corresponding to:

	986 mL	1477 mL	1970 mL	2463 mL	Per 1000 mL
• Amino acids (g)	50	75	100	125	51
• Nitrogen (g)	8	12	16	20	8
• Lipids (g)	38	56	75	94	38
• Carbohydrates – Glucose (anhydrous) (g)	125	187	250	313	127
• 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	

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

[1] *Contribution from amino acid solution*
[2] *Contribution from lipid emulsion*

List of excipients:
Glycerol
Egg lecithin
dl-alpha-Tocopherol
Sodium hydroxide
Sodium oleate
Acetic acid - glacial
Hydrochloric acid
Water for injections

PHARMACOLOGY

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, their own 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.

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

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

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

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

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

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.

INDICATIONS

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

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)

PRECAUTIONS

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 and corn (maize) and corn products which may rarely cause allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut.

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

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

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

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

Vitamin B complex deficiency may occur with glucose administration.

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

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

Effects on fertility

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

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.

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 fetal 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 fetus.

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.

Paediatric use

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

Interactions with other medicines

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.

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.

Fat overload syndrome

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

Excess of amino acid infusion

As with other amino acid solutions, the amino acid content in SmofKabiven 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.

ADVERSE EFFECTS

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4.

	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.

DOSAGE AND ADMINISTRATION

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

The patient's ability to eliminate fat and metabolise nitrogen and glucose, and the nutritional requirements should govern the dosage and infusion rate, (please also refer to section "PRECAUTIONS").

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).

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).

Method and duration 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.

Paediatric patients

SmofKabiven Electrolyte Free is not recommended for use in children, (please also refer to section "PRECAUTIONS").

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. (see 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.

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

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

Shelf life after mixing

Chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 36 hours at 25°C.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C.

Additives

To provide total parenteral nutrition, trace elements, vitamins and possibly electrolytes should be added to SmofKabiven Electrolyte Free 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.

Compatibility

Only medicinal or nutrition solutions for which compatibility has been documented may be added to SmofKabiven Electrolyte Free.

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.

OVERDOSAGE

Please also refer to sections “Fat overload syndrome”, “Excess of amino acid infusion” and “Excess of glucose infusion”.

If symptoms of overdose of fat or amino acids occur, the infusion should be slowed down or discontinued. There is no specific antidote for overdose. Emergency procedures should be general supportive measures, with particular attention to

respiratory and cardiovascular systems. Close biochemical monitoring would be essential and specific abnormalities treated appropriately.

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

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

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

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

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

Pack sizes
1 x 986 ml, 4 x 986 ml
1 x1477 ml, 4 x 1477 ml
1 x 1970 ml, 2 x 1970 ml
1 x 2463 ml, 2 x 2463 ml

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POISON SCHEDULE
Australia: Not Scheduled
New Zealand: General Sale Medicine

DATE OF TGA APPROVAL
20 Dec 2011