



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Amino acids, Lipids and Glucose, with and without Electrolytes

Proprietary Product Name: PeriOlimel N4-600E,
Olimel N5-860E, Olimel N7-960, Olimel N7-960E,
Olimel N9-840, Olimel N9-840E

Sponsor: Baxter Healthcare Pty Ltd

October 2013

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- 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.
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I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New fixed combination of previously approved active ingredients
<i>Decision:</i>	Approved
<i>Date of decision:</i>	23 July 2013
<i>Active ingredients:</i>	Amino acids (L-alanine, L-arginine, L-aspartic acid, L-glutamic acid, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine (as L-lysine acetate), L-methionine, L-phenylalanine, L-proline, L-serine, L-threonine, L-tryptophan, L-tyrosine, L-valine) Lipids (refined soya oil, refined olive oil) Glucose (with or without calcium chloride dihydrate) With and without electrolytes (sodium glycerophosphate hydrate, magnesium chloride hexahydrate, potassium chloride, sodium acetate trihydrate).
<i>Product names</i>	PeriOlimel N4-600E, Olimel N5-860E, Olimel N7-960, Olimel N7-960E, Olimel N9-840, Olimel N9-840E
<i>Sponsor's name and address:</i>	Baxter Healthcare Pty Ltd 1 Baxter Drive, Old Toongabbie NSW 2146
<i>Dose form:</i>	Emulsion
<i>Strengths:</i>	Amino acids/lipids/glucose (with and without electrolytes) in the individual compartments of the three-compartment bag: 6.3%/15%/18.75% (PeriOlimel N4-600E); 8.2%/20%/28.75% (Olimel N5-860E); 11.1%/20%/35% (Olimel N7-960, Olimel N7-960E); 14.2%/20%/27.5% (Olimel N9-840, Olimel N9-840E)
<i>Container:</i>	Three-compartment multilayer infusion bags
<i>Pack sizes:</i>	1000, 1500, 2000 and 2500 mL
<i>Approved therapeutic use:</i>	Olimel/PeriOlimel is indicated for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated.
<i>Route of administration:</i>	Intravenous infusion

Dosage (abbreviated): The maximum daily doses of each constituent of Olimel/PeriOlimel should be based on individual total nutritional requirements and patient tolerance.

ARTG numbers: 197416, 197417, 197418, 197419, 197420, 197421

Product background

Total parenteral nutrition (TPN) takes the form of a lipid emulsion to provide essential fatty acids and energy, an amino acid solution to provide a source of nitrogen and essential amino acids, glucose solution to provide a ready source of carbohydrates/energy, and trace elements, vitamins and electrolytes.

While the patient's clinical condition may require individual balance of some of these elements, there are numerous commercial products currently available, either to mix together (for example, separate lipid emulsions, amino acid solutions, fat or water soluble vitamins), or as combination packs. The latter are often presented as multi-chamber bags to simplify the mixing and delivery of TPN.

This AusPAR describes the application by Baxter Healthcare Pty Ltd (the sponsor) to register ready-to-use, triple-chamber TPN products containing amino acids, lipids and glucose with and without electrolytes under the trade names PeriOlimel N4-600E, Olimel N5-860E, Olimel N7-960, Olimel N7-960E, Olimel N9-840 and Olimel N9-840E.

The products are proposed for intravenous (IV) infusion for the following indication:

for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

The 'N5', 'N7' or 'N9' in the product name represents the concentration of nitrogen rounded-up to the nearest g/L of the reconstituted ternary mixture, while the numbers '840', '860' or '960' represent the amount of non-protein calories rounded-up to the nearest kcal/L in the reconstituted ternary mixture. An 'E' at the end of the product name indicates the formulation includes electrolytes; for example, N4-600E indicates the PeriOlimel formulation has approximately 4 g/L of nitrogen, 600 kcal/L of non-protein calories, and contains electrolytes.

The prefix "Peri" was added to the trade name "Olimel" to distinguish it from the rest of the formulations as it may be administered via either peripheral or central veins (the other 5 formulations of Olimel are for administration via the central vein only).

Regulatory status

The Olimel and PeriOlimel products received initial registration on the Australian Register of Therapeutic Goods (ARTG) in August 2013.

At the time this application was considered by the TGA, a similar application was approved in Colombia (2012), Croatia (2012), Philippines (2011), South Korea and the following countries or regions:

Table 1. Overseas registration status for Olimel/PeriOlimel

Country/region	Approval date	Indication
European Union (EU)	12 July 2008- 22 January 2010 depending on Country.	Olimel/PeriOlimel/Triomel* is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or

Country/region	Approval date	Indication
		contraindicated.
Switzerland	24 March 2009	Same as for the EU
Canada	29 Jun 2010	Olimel/PeriOlimel (Amino Acids, Dextrose, Lipids, with /without Electrolytes) is indicated for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated.
New Zealand	28 February 2013	Olimel/PeriOlimel is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is not possible, insufficient, or contraindicated.

*Triomel is the trade name used in UK and some European countries.

Product Information

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

II. Quality findings

The proposed TPN products are qualitatively similar in formulation to Baxter's OliClinomel products (registered in Australia since 2007) but contain two additional amino acids: L-aspartic acid and L-glutamic acid.

These two amino acids, which are found in the blood and are normal components of cell proteins, are included in Baxter's Primene 10% amino acids solution for injection bottle (AUSTR 79618), and also in Fresenius' registered Kabiven products. There are no known incompatibilities between either aspartic or glutamic acid and any of the other components of either the amino acid solution with or without electrolytes, or the ternary mixture.

The proposed formulations also differ from the OliClinomel products in that the amino acid lysine is present as the acetate salt instead of the hydrochloride salt.

Four of the six presentations proposed for Australia will include sodium acetate trihydrate, sodium glycerophosphate hydrate, potassium chloride and magnesium chloride hexahydrate in the amino acid component, and calcium chloride dihydrate in the glucose component, with these also being present in the OliClinomel products currently registered in Australia that contain electrolytes.

The amino acids, electrolytes, glucose, lipids and the amino acid blend are tested by the finished product manufacturer to the requirements of the corresponding European Pharmacopoeia (Ph Eur) monographs. Individual amino acids are not currently used in the manufacture of the finished products.

The excipients, all of which are used in Baxter's OliClinomel products, are also tested to Ph Eur requirements, except for the sodium oleate and purified egg phospholipids for which the specifications and test methods are as used in relation to Baxter's OliClinomel products.

Data was evaluated on the composition and nutritional characteristics of the proposed finished products with and without electrolytes and on the different bag sizes that are proposed. No overages are employed.

The triple-chamber container in which the finished products will be packaged is identical to that used for the OliClinomel product range; viz., a non-polyvinylchloride (non-PVC), multilayered, lipid-compatible plastic bag (primary packaging), wrapped in a clear oxygen-barrier plastic over-wrap (secondary packaging) that contains an oxygen absorber and oxygen indicator. The three chambers, each fitted with a port tube allowing the filling of the solutions/emulsion, are separated by optional peel seals. Prior to intravenous (IV) administration the seals are opened (activated) by rolling the chambers and the emulsion and solutions are mixed together (admixed) to form the final product.

The pH of the hypertonic ternary mixture is approximately 6.4. The stability data support a shelf life for the unmixed finished products of 24 months stored below 25°C and protected from light. Whilst the in-use data support Baxter's claim that the ternary mixture is stable when stored at 2°-8°C protected from light for 7 days followed by 48 h at either 25°C ± 2°C or 30°C ± 2°C exposed to normal transmitted light illumination (approximately 700 lux), the company is aware that microbiological considerations preclude storage for longer than 24 h at 2°-8°C as indicated in the draft PI document.

Limits proposed for an impurity controlled in the finished product specifications and for a degradant are acceptable.

Sterility and safety-endotoxins aspects of the submission have been evaluated independently and all matters have been resolved.

Advisory committee considerations

This application was presented to the March 2013 Meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

The PSC noted the absence of any reference to stability testing of future batches (for example, one batch a year) of the drug products and advised that commitment should be sought from the sponsor on this issue.

Overall, the PSC endorsed all the questions raised by the TGA in relation to quality and pharmaceutical aspects of the submission and agreed that the outstanding issues especially in relation to good manufacturing practice (GMP) clearance should be addressed to the satisfaction of the TGA.

Quality summary and conclusions

There are no objections in respect of chemistry, manufacturing and controls to registration of these products, provided issues regarding GMP are addressed.

III. Nonclinical findings

Introduction

Baxter Healthcare Pty Ltd has applied to register the new combination products, Olimel and PeriOlimel. Six formulations are proposed, with the formulations being qualitatively similar to OliClinomel, with the exception of 2 additional amino acids: aspartate and glutamate. These additional amino acids are not considered to pose a safety concern as their proposed maximum daily dosage levels are below those currently approved for other TPN agents. The amino acid solutions used in the submitted toxicity studies did not contain either of these amino acids.

The maximum daily dose levels of the majority of the remaining components of Olimel/PeriOlimel are at or below the approved levels obtained from other TPN agents, with the following exceptions: the amino acids alanine, methionine and phenylalanine, the electrolytes calcium chloride and potassium chloride, and sodium glycerophosphate. The acceptability of the proposed levels of these components is discussed below.

Alanine, methionine and phenylalanine

Alanine, methionine and phenylalanine were present in the 5% synthetic amino acid solution (SAAS) used in the submitted 30 day repeat-dose toxicity study in dogs. At the no observed adverse effect level (NOAEL; 120 mL/kg/day), the levels of these amino acids were above that expected clinically (on a body surface area basis) (Table 2) and therefore are considered acceptable.

Table 2. Relative dose of different amino acids in the 30 day repeat-dose toxicity study in dogs

Amino acid	Conc. in batch (g/L)	Dose at the NOAEL		Maximum clinical dose		Relative dose
		mg/kg/day	g/m ²	mg/kg/day	g/m ²	
Alanine	10.4	1248	25	330	11	2.3
Methionine	2.9	348	7.0	114	3.8	1.8
Phenylalanine	3.1	372	7.4	158	5.2	1.4

Potassium chloride

The maximum proposed dose level of potassium chloride from Olimel/PeriOlimel is only marginally higher than that from registered TPN agents (89.6 mg/kg/day compared with 80.5 mg/kg/day in SmofKabiven) and below the daily dose recommended to prevent hypokalaemia (3.3 g/day K⁺ from Olimel/PeriOlimel compared with 5.9 g/day maximum dose from Pfizer's Sterile Potassium Chloride concentrate). Therefore, the proposed level is considered acceptable.

Calcium chloride

The maximum proposed dose level of CaCl₂.2H₂O from Olimel/PeriOlimel is at least 1.7 times that from other TPN agents (20.8 mg/kg/day compared with 12 mg/kg/day in OliClinomel and Kabiven G 19%). The dose of Ca²⁺ (397 mg/day) is also higher than the recommended daily dose for the treatment of acute hypocalcaemia in adults (140-280 mg/day Ca²⁺; Phebra Calcium Chloride Injection). Therefore, there are some safety concerns (including an increased risk of arrhythmias) regarding the high dose of calcium, especially in individuals who have not developed calcium depletion at the start of treatment. Provided plasma electrolyte levels are monitored during clinical use and the dose adjusted to prevent hypercalcaemia the level of Ca²⁺ in Olimel/PeriOlimel is not considered a major safety concern. However, appropriate warnings in the PI document may be required to ensure monitoring of electrolyte levels and to convey a warning of the increased risk of arrhythmias associated with high calcium levels (as is seen with other calcium chloride injection products).

Sodium glycerophosphate

The maximum daily dose of sodium glycerophosphate from Olimel/PeriOlimel (148 mg/kg/day) is at least 1.8 times higher than the level from other TPN agents (compared with 84 mg/kg/day from OliClinomel) and any other sodium glycerophosphate-containing IV product currently in the ARTG. Sodium glycerophosphate is provided as a phosphate source. Serum phosphate levels can be reduced in patients fed

parenterally for 7–10 days and the addition of phosphate supplements, such as sodium glycerophosphate, at 10–15 mmol/day IV could normalise serum levels (Travis *et al.*, 1971¹). The dose of 10–15 mmol/day is equivalent to a sodium glycerophosphate dose of 2.16–3.24 g/day, at least 3 times less than that from Olimel/PeriOlimel (10.36 g/day). Therefore, the daily intake of phosphate from Olimel at the maximum proposed dose exceeds the daily requirement. As with calcium, there appears a need to monitor phosphate levels during clinical use to prevent hyperphosphataemia.

Leachables

Two studies examined the leachable profile of the ready-to-use and triple bag container system. This container system is made with the same film as that used in the infusion bag for ClinOleic and OliClinomel, which contain the same lipid component. Several toxicity studies with extracts from this film have been evaluated previously and there were no findings which would preclude its use.

Nonclinical summary and conclusions

- The levels of alanine, methionine and phenylalanine were considered acceptable based on a submitted toxicity study.
- The maximum dose level of potassium is below the dose recommended to prevent hypokalaemia and is considered acceptable.
- The maximum dose levels of calcium and glycerophosphate exceed the doses used to treat hypocalcaemia and prevent hypophosphataemia, respectively. Therefore, these levels may pose safety concerns, especially in individuals who have not developed calcium or phosphate depletion at the time of treatment.

Nonclinical recommendation

Provided electrolyte levels are monitored during clinical use there are no nonclinical objections to the registration of Olimel/PeriOlimel. However, appropriate warnings may be necessary in the PI document to indicate the risks associated with, in particular, the high calcium levels. This was brought to the attention of the clinical evaluator.

Recommended revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction and clinical rationale

Olimel/PeriOlimel is 3-compartment bag containing a glucose solution (with/without calcium), a [registered] lipid emulsion (ClinOleic) and a 15% amino acid solution (not registered; with/without electrolytes). There are no registered 15% amino acid solutions; the maximum concentration registered is 10%.

¹ Travis, SF *et al.* Alterations of red-cell glycolytic intermediates and oxygen transport as a consequence of hypophosphatemia in patients receiving intravenous hyperalimentation. *New Eng. J. Med* 1971;285:763–768.

The proposed indication is:

Olimel/PeriOlimel is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

The sponsor appears to claim the combined preparations are similar to registered products that are the result of combinations made immediately prior to administration of currently registered products. The sponsor also appears to have considered them as a fixed combination used for up to 9 days after mixing (from the proposed PI):

After reconstitution:

It is recommended that the product is used immediately after the non-permanent seals between the 3 compartments have been opened. However, the stability of the reconstituted emulsion has been demonstrated for 7 days (between 2°C and 8°C) followed by 48 hours at temperature not exceeding 25°C.

The rationale for development of the formulation is unclear. The sponsor argues that the formulations have been developed to meet the nutritional requirements for a wide range of clinical conditions and patients yet at the same time says these formulations are similar to OliClinomel formulations which are currently registered in Australia.

Contents of the clinical dossier

The submission contained the following clinical information:

- Module 2
 - Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, and literature references.
- Module 5 contained only
 - Study ICS1063B/P01/03/Mu.F: Efficacy and safety of OliClinisol (Olimel) N9-840 versus OliClinomel N8-800, carried out over five days in parallel groups in patients requiring parenteral nutrition.
 - Olimel/PeriOlimel Periodic Safety Update Reports (PSURs), covering the periods 21 July 2008 to 31 Jan 2012
 - 11 literature references for amino acids (from 1985 to 1992, out of 94 submitted references)

In addition, the sponsor provided reference to studies on lipids not previously submitted to the TGA; reference to studies on lipids previously submitted to the TGA to support other applications; and reference to studies on OliClinomel previously submitted. None of these were included in the clinical evaluation.

Paediatric data

The submission included no relevant paediatric data. The studies were outside the proposed age limit or did not use 15% amino acids.

Good clinical practice

Study ICS1063B/P01/03/Mu was conducted according to good clinical practice guidelines.

Pharmacokinetics

No specific studies were submitted. The sponsor provided general information on the individual compartment components.

Pharmacodynamics

No specific studies were submitted.

Efficacy**Dosage selection for the pivotal study**

According to the study report the dose administered was dependant on patient oral intakes, metabolic and energy requirements and patient's clinical condition. Parenteral nutrition was considered in some cases as a complementary PN to oral/enteral intake for a patient in which this was not contraindicated but for which intakes were not sufficient.

Studies providing efficacy data***Olimel/PeriOlimel***

One pivotal efficacy study, Study ICS1063B/P01/03/Mu.F, was submitted. This study compared the proposed combined preparation Olimel containing a 15% amino acid preparation (Clinisol; not registered in Australia) with a combined preparation not registered in Australia that contained a 10% amino acid preparation Synthamin (also not registered in Australia). From the study report OliClinomel N8-800 was chosen as the ready to use (RTU) ternary admixture reference product because it has a similar composition except for the amino acid solution and lipido-glucidic ratio.

This was a multicenter, prospective, randomised, double-blind, parallel group study in hospitalised adults carried out over five days. There were 24 patients in the Olimel arm and 26 in the OliClinomel arm (Intent-to-Treat (ITT) population).

Primary objective: to provide clinical information on safety of Olimel N9-840 in a practical therapeutic use after 5 consecutive days of parenteral nutrition.

Secondary objective: No difference in clinical outcomes or laboratory tests was expected for the differences in product composition; nevertheless, transthyretin² was collected as a nutritional marker for efficacy.

Individual components***15% amino acid component (Clinisol)***

There were no studies of the use of Clinisol submitted. Instead an unjustified³ selection of literature trial reports was submitted. It included only one study with products containing 15% amino acids and it also included some studies outside the age group proposed. One literature study used Synthamin 17 which the authors and sponsor described as containing 17% amino acids.⁴ The product on the ARTG and the sponsor's website is described as containing 10% amino acids.

² Transthyretin, also known as prealbumin, is one of the plasma proteins that may be used to assess nutritional status.

³ There was no evidence submitted of a literature search.

⁴ The 17 refers to g/L of nitrogen

- Broyles JE *et al.* Fluid Balance in Fluid-restricted Patients Receiving 10% Amino acids or 15% Amino acids as Part of Parenteral Nutrition. *Hosp Pharm*, 24: 995-998; 1989.

This study compared the use of a 15% amino acid solution to a 10% amino acid solution as part of parenteral nutrition in fluid-restricted patients. It was a randomised, parallel groups study for 7-14 days in fluid-restricted intensive care unit (ICU) patients.

Lipid component (Clinoleic)

Reference was made to the previous TGA evaluation reports and discussions related to its registration.

Glucose (Component)

This is an historically registered product.

Evaluator's conclusions on clinical efficacy of combined product

The evidence for efficacy rests on a single study in 24 patients.

- Some of the patients had a considerable additional enteral intake.
- The study lasted only 5 days.
- The comparator was a preparation not registered in Australia.
- Although the products had differing lipid/glucose ratios effects on glucose or triglycerides were not specifically considered except in discussion,⁵ possibly because of the use of additional glucose infusions.
- The evaluator believes this is insufficient information to establish efficacy to the level required.

Evaluator's conclusions on clinical efficacy of separate components

The glucose and lipid components are registered and their efficacy is accepted.

The 15% amino acid preparation (Clinisol) is not registered and the single literature trial in 10 patients for 7 days failed to achieve a clinically significant difference in its primary endpoint. Evidence of nutritional efficacy was lacking.

The evaluator believes this is insufficient information to establish efficacy.

Safety

Studies providing safety data

Olimel/PeriOlimel

Study ICS1063B/P01/03/Mu.F was the only source of safety data, other than post marketing reports, for the combined product. The safety population in Study ICS1063B/P01/03/Mu.F comprised 28 patients on Olimel and 28 patients on OliClinomel.

Safety of Individual components

15% Amino Acids Study Broyles JE et al. 1989

This Study included no safety information.

⁵ This did not influence overall lipid tolerance nor blood glucose results, but on a nutritional point of view, this follows the trends to limit glucose intakes and risks of hyperglycaemia in this critically ill population exposed to inflammatory syndrome and insulin resistance [Study Report]

Lipid (Clinoleic)

Reference was made to the TGA Delegate's overview for a previous application to register Clinoleic, which was approved for registration in 2004.

Glucose with/without calcium

The safety of a higher concentration of calcium (0.52 versus 0.3 g/L) was not discussed.

Post-marketing experience***Periodic Safety Update Reports (PSURs) for Olimel***

The product was first launched in March 2009. PSURs to 31 January 2012 were submitted. There was no summary of total exposure and the evaluator could not calculate it from the PSURs submitted.

Evaluator's overall conclusions on clinical safety***Safety of the combination***

The safety of Olimel rests on only 28 patients in a clinical trial supplemented by only 3 years of PSURs since first marketed.

This is inadequate for a combination including an unregistered product.

Safety of the individual components*Amino acids (Clinisol)*

The only data submitted in relation to 15% amino acid solution is a published study (Broyles JE *et al.* 1989) that contains no safety data. The sponsor repeatedly refers to data for Synthamin, a 10% amino acid solution that is already registered and which has different composition from Clinisol.

The data provided is insufficient to register Clinisol either as a component or separately.

Lipid (Clinoleic)

The product is already registered having been evaluated and reviewed post marketing.

Glucose with/without calcium

The product is already registered but the added calcium concentration is higher (0.52 versus 0.3 g/L). It is noted that the PSUR 01 Feb 2009 through 31 Jul 2009 advised of changes to the Company Core Data Sheet (CCDS) relating to calcium.⁶

List of questions

Nil

⁶ 4.4 Special Warnings and Precautions for Use: - addition of warning regarding excess addition of calcium and phosphorus that may result in formation of precipitates of calcium phosphate that could lead to vascular occlusion; 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction: - addition of wording mentioning that ceftriaxone must not be coadministered with calcium containing IV solutions.

Benefit-risk assessment

Assessment of benefits

In the letter of application the sponsor discussed the benefits of Olimel/PeriOlimel in the proposed usage:

- increased physiochemical shelf-life, since the components are not mixed until just prior to use,
- reduced risk of contamination during preparation, and
- a reduction in the number of steps required to prepare a parenteral nutrition product.

The first statement makes little sense as the shelf life is the same whether they are 3 separate components until the components are mixed or 3-in-1 bag components. There are already 2 preparations: OliClinomel and SmofKabiven, that are 3-in-one nutrition preparations that are registered in Australia and offer the same latter two advantages as claimed above.

Other advantages claimed relate principally to the amino acid component:⁷

- The use of an amino acid solution already registered in the USA (Clinisol) that contains two additional amino acids as compared to Synthamin (15 amino acid solution in OliClinomel): aspartic acid and glutamic acid,
- A higher nitrogen concentration.

Both relate to the inclusion of a 15% amino acid preparation which is not registered in Australia. The only evidence submitted for this preparation was a literature study report that failed to show clinically relevant improvement in the primary endpoint.

- Updated glucose calorie/lipid calorie ratio.

In the comparison with an unregistered formulation of OliClinomel the sponsor did not show any advantage, possibly because of the small numbers (24 versus 23) involved.

The evaluator believes the data provided are inadequate for registration.

Evaluator comment: The marketing data suggests that the reason for prescribing Olimel is the higher (than 10% Synthamin) amino acid concentration rather than the additional 2 amino acids from the unregistered Clinisol.

Assessment of risks

The risks of Olimel in the proposed usage are reliant on a trial with 28 patients for 5 days supplemented by only 3 years of PSURs since first marketed.

Further, of the individual components, there was no safety data for a 15% amino acid preparation.

The evaluator finds the data available for assessment of risk inadequate.

Assessment of benefit-risk balance

The benefit-risk balance of Olimel, given the proposed usage, is unfavourable.

⁷ Clinical Overview - Product Development Rationale

Recommendation regarding authorisation

It is **not** recommended that approval be given for the registration of PeriOlimel N4600E, Olimel N5-860E, Olimel N7-960, Olimel N7-960E, Olimel N9-840 or Olimel N9-840E.

Should the Delegate decide to approve registration of these products the clinical aspects of the draft PI are not entirely satisfactory and should be revised, having regard to the comments below.⁸

Indications

The sponsor proposes to insert: *Olimel/PeriOlimel is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.*

The proposed PI itself states: There have been no studies performed in the paediatric population. Further the CCDS only gives Indication for adults.

It is recommended that should the preparations be approved it be for adults only.

V. Pharmacovigilance findings

The TGA exempted RMP requirements for this application.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

Baxter Healthcare Australia Pty Ltd has submitted an application to register a new combination of mostly registered active ingredients in Australia. The proposed lipid component is registered as part of ClinOleic; the glucose and/or calcium preparations are also in registered products, however, the identical amino acids component is registered overseas (as Clinisol) but not in Australia.

There are six proposed formulations of Olimel/PeriOlimel (4 with electrolytes and 2 without electrolytes in volumes ranging from 1000 to 2500 mL:

Table 3. Proposed Olimel/PeriOlimel products

	Concentration			Bag presentation (mL)			
	Amino acid solution	Glucose solution	Lipid emulsion				
PeriOlimel							
N4-600E	6.3%	18.75%	15%	1000	1500	2000	2500
Olimel							
N5-860E	8.2%	28.75%	20%	-	1500	2000	2500
N7-960E	11.1%	35%	20%	1000	1500	2000	-
N7-960	11.1%	35%	20%	1000	1500	2000	-
N9-840E	14.2%	27.5%	20%	1000	1500	2000	-
N9-840	14.2%	27.5%	20%	1000	1500	2000	-

⁸ Details of recommended revisions to the PI other than to the *Indications* section are beyond the scope of the AusPAR.

PeriOlimel contains the lowest concentrations of glucose, amino acids and lipids in the Olimel product line and is intended for patients with lower nitrogen needs or for patients in whom fluid volume and calories are less important. The electrolyte content of PeriOlimel is also lower than the other formulations of Olimel; therefore, PeriOlimel is more suitable for peripheral administration due to a lower osmolarity compared to the rest of the product line.

Regarding the product description, the sponsor stated that:

Olimel/PeriOlimel is a ready-to-use parenteral nutrition product containing amino acids, lipids and glucose, with or without electrolytes. It is presented as a triple-chamber bag comprising of:

1. A larger outer chamber which contains a glucose solution with or without calcium;
2. A middle chamber which contains a solution of 17 amino acids with or without electrolytes (sodium, potassium, magnesium, and phosphate provided as sodium glycerophosphate); and
3. A smaller outer chamber which contains a lipid emulsion (ClinOleic).

The chambers are separated during storage by non-permanent, peelable seals. Prior to administration, the triple-chamber bag is manually rolled to release the non-permanent seals between the chambers thereby allowing the contents of the chambers to be mixed. The benefits of presenting the parenteral nutrition components in triple chamber bags include:

- increased physiochemical shelf-life, since the components are not mixed until just prior to use,
- reduced risk of contamination during preparation, and
- a reduction in the number of steps required to prepare a parenteral nutrition product.

Similar TPN products in triple-chamber bags currently registered in Australia include OliClinomel and Kabiven.

Proposed indication:

Olimel/PeriOlimel is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

Details of the proposed dosage and administration regimens and method of preparation, as proposed in the PI, are beyond the scope of the AusPAR.

Quality

- A shelf life of 24 months when stored below 25°C, with the additional warnings “Do not freeze. Store in original container”, has been assigned to the (intact) finished products.
- A (revised) generic PI document was provided. This is acceptable from the perspective of the chemistry and quality evaluation section.
- The revised bag and overwrap labels are acceptable.
- The provisional ARTG details remain incomplete in respect of GMP requirements for some manufacturers or sites.

- Acceptable mock-ups of the release and expiry specifications have been submitted for the finished products, together with an assurance that the corresponding “formal” specifications will be identical in content.

Quality recommendation

Subject to submission of current GMP clearance letters for specific manufacturers⁹, there are no objections to registration from a quality perspective.

Nonclinical

Nonclinical recommendation

Provided electrolyte levels are monitored during clinical use, there are no nonclinical objections to the registration of Olimel/PeriOlimel. However, appropriate warnings may be necessary in the PI document to indicate the risks associated with the high calcium levels, in particular. This is referred to the Clinical Evaluator.

Clinical

Overview of clinical data

On pharmacokinetics, the clinical evaluator stated that there were no formal studies conducted by the sponsor. On pharmacodynamics, the clinical evaluator stated that the sponsor claimed that Clinisol represents an advance over Synthamin, the amino acid source in the marketed product OliClinomel, through the addition of glutamic acid and aspartic acid.

Glutamic acid is an important amino acid whose supply may be limited during states of critical illness. Glutamic acid is an intermediate for amino acid interconversions. It is a precursor for proline (required for wound healing), ornithine, glutamine, arginine (required for synthesis of creatine, nitric oxide, and many other functions), polyamines (cell growth factors) and neurotransmitters (such as gamma amino butyric acid). Aspartate is important for synthesis of urea, pyrimidines and neurotransmitters. It is also an important gluconeogenic precursor.

The clinical evaluator identified one pivotal efficacy study (ICS1063B/POI/03/Mu.F). This is a multicenter, prospective, randomised, double-blind, parallel group study in hospitalised adults of the efficacy and safety of Olimel N9-840 versus OliClinomel N8-800 in parenteral nutrition, carried out over five days (D0 to D+4) involving centres in France and Germany and one centre in Spain (from 24/01/2005 to 20/12/2005).

Fifty six (56) hospitalised patients (age range 18–85 years) with any pathology requiring balanced parenteral nutrition representing at least 50% of the daily non-protein energy requirements during five days were enrolled (n=28 for both Olimel and OliClinomel). For the Inten-to-Treat (ITT) population, n=24 (mean age 56 ± 15.1, range 21–76 years) for Olimel, and n=26 (mean age 52 ± 21.1, range 18–84 years) for OliClinomel. For the per-protocol (PP) population, n=24 for Olimel and n=23 for OliClinomel. Patients’ severity of illness status was similar in the two treatment groups at baseline.

According to the clinical evaluator, the proposed combination product Olimel N9-840 contains the Australian registered lipid component ClinOleic and the overseas registered

⁹ All issues relating to quality were resolved prior to a decision being made on this application.

amino acid preparation Clinisol. The comparator combination product OliClinomel N8-800 is registered overseas but its lipid component is similar to ClinOleic and its amino acid preparation is similar to the Australian registered Synthamin. Clinisol is a 15% amino acid preparation while Synthamin is a 10% amino acid preparation.

Regarding treatment, the clinical study report indicates that the dose administered was dependant on patient oral intakes, metabolic and energy requirements and patient's clinical condition. Parenteral nutrition was considered in some cases as a complementary PN to oral/enteral intake for a patient in which this was not contraindicated but for which intakes were not sufficient.

From D0 to D+4, the patient received a balanced parenteral nutrition representing at least 50% of the daily needs. The energy calculation during those 5 days (D0 to D+4) was based on the medical expertise of the investigator. Patients also received additional glucose than that in the combined preparations. This resulted in more lipids and less glucose intake, respectively, with also less complementary glucose administered besides the bag.

The primary objective was to provide clinical information on the safety of Olimel N9-840 in a practical therapeutic use after 5 consecutive days of parenteral nutrition.

The secondary objective was to determine any differences in clinical outcomes or laboratory tests that may be expected from the differences in product composition. The latter was measured by assessing transthyretin (g/L) evolution as a nutritional efficacy parameter, at D0 before first infusion and at D-end after last infusion at D+5.

Statistical analysis was based on both PP and ITT populations and employed a general linear model (GLM). The model included 'treatment effect'. Baseline value was used as a covariate. A two-sided approach with $\alpha=5\%$ was used. No data transformation (log) was retained to improve or increase power analysis and no imputation of missing data was done.

On the secondary objective of nutritional efficacy as per transthyretin (g/L) levels before and after treatment (infusion), the evaluated data recorded no difference between the two treatment groups (Table 4):

Table 4. Transthyretin (g/L) evolution during treatment period

Mean \pm sd (Min - Max)	n	Oliclinisol			N	Oliclinomel			Treat. Pr>F ^a
		Baseline	D+5/End	Delta		Baseline	D+5/End	Delta	
PP Population	24	0.144 \pm 0.075 (0.03 - 0.33)	0.206 \pm 0.142 (0.06 - 0.72)	0.062 \pm 0.135 (-0.06 - 0.61)	23	0.139 \pm 0.078 (0.02 - 0.39)	0.172 \pm 0.080 (0.06 - 0.39)	0.032 \pm 0.069 (-0.08 - 0.20)	0.3191
ITT Population	24	0.144 \pm 0.075 (0.03 - 0.33)	0.206 \pm 0.142 (0.06 - 0.72)	0.062 \pm 0.135 (-0.06 - 0.61)	26	0.146 \pm 0.083 (0.02 - 0.39)	0.181 \pm 0.082 (0.06 - 0.39)	0.035 \pm 0.067 (-0.08 - 0.20)	0.3664

^a Model: Two-sided, based on a GLM (General Linear Model) model including treatment main effect and baseline value as covariate for comparing Olimel and OliClinomel.

Regarding safety and therefore the primary objective of the trial study, the clinical evaluator stated that a total of 53 adverse events (AEs) occurred under treatment: 29 in the Olimel group versus 24 in the OliClinomel group. Only 7 were estimated to be related to Olimel and only 8 were estimated to be related to OliClinomel. There was one death on Olimel (due to septic shock and not felt related to treatment), one case of oesophagobronchical fistula on Olimel (thought unrelated), one case of acute pulmonary oedema on OliClinomel (thought unrelated) and one case of hypersensitivity on OliClinomel (thought related).

The Delegate believes that establishing the safety and the overall parenteral nutritional value of the proposed combination product is of better clinical relevance than that of the individual components or ingredients. In any event, the clinical evaluator only identified

one literature report (Broyles JE *et al*, 1989¹⁰) on the use of a 15% amino acids solution (similar to Clinisol) compared to a 10% amino acids solution. The clinical evaluator stated that the components of the 15% amino acids solution could not be determined from the report and were sought elsewhere. The clinical evaluator mentioned that the two other components (ClinOleic and glucose) are Australian registered.

On the issue of post-marketing experience, the PSUR from 01 Feb 2009 to 31 July 2009 led to the creation of a new Reference Safety Information (RSI). The PSURs from 01 August 2009 to 31 January 2011 appeared to have not properly documented the causal relationship to the listed AEs, including deaths. Although there were no changes to the CCDS following the 01 February 2011 to 31 January 2012 PSUR, tabulations of individual cases by system organ class (SOC) and by seriousness were provided.

Further details on the safety of Olimel and PeriOlimel for the proposed indication are provided in the clinical evaluation report (see AusPAR Attachment 2).

Clinical recommendation

The clinical evaluator recommended the following:

It is **not** recommended that approval be given for the registration of PeriOlimel N4600E, Olimel N5-860E, Olimel N7-960, Olimel N7-960E, Olimel N9-840 or Olimel N9-840E.

Should the Delegate decide to approve registration of these products the clinical aspects of the draft PI are not entirely satisfactory and should be revised.¹¹

Indications:

The sponsor proposes to insert:

Olimel/PeriOlimel is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

The proposed PI itself states: There have been no studies performed in the paediatric population. Further the CCDS only gives *Indications* for adults.

It is recommended that should the preparations be approved it only be for adults.

Risk management plan

TGA has granted this application a waiver from the need to submit a RMP.

Risk-benefit analysis

Delegate considerations

The clinical evaluator is not supportive of the application based essentially on the use of Clinisol (a 15% amino acid preparation) unregistered in Australia but registered overseas (USA) in the proposed Olimel/PerOlimel formulations. The Olimel preparation as a whole is registered in Europe and Canada. The clinical evaluator is concerned about the risk benefits of Olimel as it contains the unregistered (in Australia) 15% amino acid Clinisol. However, the head-to-head clinical trial comparison between Olimel and OliClinomel did not appear to uncover significant AEs specifically related to Olimel *per se*. Also, the last

¹⁰ Broyles JE *et al*. Fluid Balance in Fluid-restricted Patients Receiving 10% Amino acids or 15% Amino acids as Part of Parenteral Nutrition. *Hosp Pharm*, 1989;24: 995-998.

¹¹ Other recommendations concerning the PI are beyond the scope of the AusPAR.

PSUR data on Olimel did not list any serious AE sufficient enough to initiate changes in the CCDS. Moreover, the transthyretin levels before and after treatment with Olimel and OliClinomel revealed no difference between the two treatment groups, probably indicating equal nutritional efficacy status. In any event, the Australian Drug Evaluation Committee (ADEC, the predecessor to the ACPM) in its previous deliberations over other parenteral products (such as OliClinomel) acknowledged “the quandary that the regulators (such as TGA) found themselves (regarding safety and efficacy of parenteral products) in and suggested first, that TGA, with other regulatory agencies, work towards a more appropriate solution for such products”. In that regard, the TGA has adopted the EU *Guideline on Clinical Development of Fixed Combination Medicinal Products* (CPMP/EWP/240/95). The application to register OliClinomel in Australia ran into some difficulties because of the above adopted EU Guideline. However, the ADEC commented that “The efficacy and safety requirements then imposed for registration of a fixed combination product are very difficult to meet and actually are not appropriate for parenteral nutrition”. The sponsor claimed that the registration of Olimel/PeriOlimel in Europe was not based on the TGA adopted EU guideline but on the French Health Product Safety Agency (AFSSAPS) Guideline on Parenteral Nutrition.

Apart from in Europe, Olimel/PeriOlimel is also approved in Canada (29 June 2010). As rightly pointed out by the clinical evaluator, the submission did not include relevant paediatric data, that is, the studies were outside the proposed age limit. In this regard, it is noteworthy that the registration of the product in Canada was limited to adults on the basis that there have been no studies performed in the paediatric population.

The chemistry and quality evaluator stated that subject to submission of current GMP clearance letters for several of the manufacturers, there are no objections to registration from a quality perspective.

The toxicological evaluator stated that provided electrolyte levels are monitored during clinical use, there are no nonclinical objections to the registration of Olimel/PeriOlimel. However, appropriate warnings may be necessary in the PI document to indicate the risks associated with the high calcium levels, in particular.

Proposed action

Considering that: (i) hospitals handle large number of doses of these parenteral nutrition products in some areas, (ii) some of those being treated may be sufficiently cachectic to require 15% amino acids solution and (iii) Olimel/PeriOlimel is approved throughout Europe *via* a mutual recognition procedure and in Canada, the Delegate proposed to approve the application with a reduction in the proposed population, that is:

Olimel/PeriOlimel is indicated for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated.

Approval would be subject to ACPM deliberations and to the finalisation of issues relating to GMP and the PI to the satisfaction of the TGA.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM.

Response from sponsor

Baxter accepts the Delegate's recommendation to approve Olimel/PeriOlimel

for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated

However, the proposed indication for this application was:

Olimel/PeriOlimel is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

The Delegate has proposed to restrict the proposed population to adults, excluding the use of Olimel/PeriOlimel in children >2 years of age. Baxter believes that Olimel/PeriOlimel should also be approved for use in children >2 years of age:

1. The nutritional requirements for children >2 years are similar to those for adults. There is a clinical need for this age group for a ready-to-use parenteral nutrition (PN) product containing amino acids, lipids and glucose with/without electrolytes. Olimel/PeriOlimel contains these key PN components and is suitably formulated for use in children > 2 years (and adults).

The regulatory authorities in the EU and New Zealand have determined that Olimel/PeriOlimel are suitable for use in children and approved its use in children > 2 years (as well as for adults).

2. Similar to Olimel/PeriOlimel, OliClinomel is also a triple-chamber parenteral nutrition product which was registered in Australia on 4 September 2007. OliClinomel has the same qualitative composition as Olimel/PeriOlimel, minus the 2 additional amino acids: aspartic acid and glutamic acid (present in Olimel/PeriOlimel):

OliClinomel is approved in >50 countries worldwide. The approved indication for OliClinomel in Australia, New Zealand and the EU includes children >2 years. In fact, the approved indications for OliClinomel and Olimel /PeriOlimel are the same in the EU and New Zealand; see Table 5.

Table 5. Approved indications for OliClinomel and Olimel/PeriOlimel in the EU and New Zealand

Country/region	Approved Indications	
	OliClinomel	Olimel/PeriOlimel /TRIOMEL*
European Union	parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.	parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.
New Zealand	parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.	parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is not possible, insufficient, or contraindicated.

*TRIOMEL is the trade name used in UK and some European countries.

- The addition of the two amino acids (aspartic acid and glutamic acid) in Olimel/PeriOlimel is a step towards providing all 21 amino acids currently present in enteral nutrition formulations. Quantitatively, compared to OliClinomel, Olimel/PeriOlimel has a higher concentration of nitrogen (a marker of amino acid and protein content), which minimises the total glucose delivered and addresses the trend in clinical nutrition practice to reduce fluid administration to patients who are fluid restricted.

All 17 amino acids in Olimel/PeriOlimel (including the 2 amino acids, aspartic acid and glutamic acid) can be found in Baxter's 10% amino acid solution product, Primene

(AUSTR 79618); see Table 6. Primene is approved in Australia for use “in infants and neonates at term or premature for short-term use, of normal or low birth-weight when oral or enteral nutrition is impossible, insufficient or contraindicated. It is used as an amino acid component in a composite admixture of total parenteral nutrition.”

Table 6. Comparison of Amino Acid composition of Primene, OliClinomel and Olimel/PeriOlimel.

Products:	Amino acid solution for IV infusion	Emulsion for IV infusion (Amino acids/Glucose/Lipids +/- Electrolytes)	
	Primene [®]	Olimel/PeriOlimel range	OliClinomel range
Age group:	Approved: Infants and neonates	Proposed: Adults and children >2 years	Approved: Adults and children >2 years
AUST R:	79618	Under evaluation	Registered (32 ARTG entries ⁽¹⁾)
Number of Amino Acids:	20	17	15
Amino Acid Concentration (% by weight):	10%	2.5-5.7%	2.2-4.0%
Total Nitrogen:	15.15 g/L	4.0-9.0 g/L	3.6-6.6 g/L
Amino acid concentration in g/L:			
Alanine	8.00	3.66-8.24	4.56-8.28
Arginine	8.40	2.48-5.58	2.53-4.60
Aspartic acid	6.00	0.73-1.65	-
Glutamic acid	10.00	1.26-2.84	-
Glycine	4.00	1.76-3.95	2.27-4.12
Histidine	3.80	1.51-3.40	1.06-1.92
Isoleucine	6.70	1.26-2.84	1.32-2.40
Leucine	10.00	1.76-3.95	1.61-2.92
Lysine	11.00	1.99-4.48	1.28-2.32
Methionine	2.40	1.26-2.84	0.88-1.60
Phenylalanine	4.20	1.76-3.95	1.23-2.24
Proline	3.00	1.51-3.40	1.50-2.72
Serine	4.00	1.00-2.25	1.10-2.00
Threonine	3.70	1.26-2.84	0.92-1.68
Tryptophan	2.00	0.42-0.95	0.40-0.72
Tyrosine	0.45	0.06-0.15	0.09-0.16
Valine	7.60	1.62-3.64	1.28-2.32
Ornithine HCl	3.18	-	-
Cysteine	1.89	-	-
Taurine	0.60	-	-

- Detailed dosage recommendations for children >2 years are provided in the *Dosage and Administration* section of the proposed PI to ensure appropriate use of the Olimel/PeriOlimel products. The recommendations are consistent with those approved for Olimel/PeriOlimel for children >2 years in both the EU and New Zealand, and are based on recommended values from The European Society for Clinical Nutrition and Metabolism-Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPEN-ESPGHAN) guidelines.

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:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Olimel/PeriOlimel injection for intravenous

infusion to have an overall positive benefit-risk profile for the Delegate's amended indication¹²;

Olimel/PeriOlimel is indicated for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated.

Conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the *Precautions* section of the PI and relevant sections of the CMI to ensure monitoring of electrolytes

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 would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Olimel N9-840, Olimel N5-860E, Olimel N7-960E, PeriOlimel N4-600E, Olimel N9-840E, and Olimel N7-960 emulsions for intravenous infusion, containing amino acids, lipids and glucose, with and without electrolytes, indicated for:

Olimel/PeriOlimel is indicated for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated. Indication

Specific conditions applying to these therapeutic goods

Notwithstanding that the TGA has granted this application a waiver from the need to submit a Risk Management Plan (RMP), it remains a requirement that Routine Pharmacovigilance of this therapeutic good must be undertaken. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs) and other activities as in accordance with current regulatory requirements.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

¹² With regard to the use of the products in children, the ACPM commented: *The evidence for efficacy and safety in children is absent. Compared to recommended levels the calculated paediatric dose provides much higher doses of three amino acids and the electrolytes. Paediatric data are necessary in consideration of the apparent excess provided of both amino acids and electrolytes.*

Therapeutic Goods Administration

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