PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

OLIMEL 4.4%
Amino acids, dextrose, lipids
Injectable Emulsion
4.4% w/v, 14% w/v, 4% w/v

OLIMEL 5.7%
Amino acids, dextrose, lipids
Injectable Emulsion
5.7% w/v, 11% w/v, 4% w/v

OLIMEL 7.6%
Amino acids, dextrose, lipids
Injectable Emulsion
7.6% w/v, 7.3% w/v, 3.5% w/v

Intravenous Nutritive Supplements

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Canada

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RECENT MAJOR LABEL CHANGES

2 CONTRADICTIONS	07/2023
6 WARNINGS AND PRECAUTIONS, Immune	07/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OLIMEL (amino acids, dextrose, lipids) is indicated for parenteral nutrition for adults when oral or enteral nutrition is impossible, insufficient or contraindicated.

1.1 Pediatrics

Pediatrics (<18 years of age): There have been no studies performed in the pediatric population.

1.2 Geriatrics

Geriatrics (> 65 years of age): There are no known differences in safety and effectiveness of parenteral nutrition formulations in the adult population based upon age.

2 CONTRAINDICATIONS

The use of OLIMEL (amino acids, dextrose, lipids) is contraindicated in the following populations/situations:

- Known hypersensitivity to egg, soybean or peanut products, olive products or any of the active substances, excipients, or components of the container. For a complete listing, see the **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the product monograph.
- Known allergy to corn or corn products since the products contain corn-derived dextrose
- Patients with acute renal failure and without undergoing renal replacement therapy.
- Patients with severe liver failure or hepatic coma.
- Congenital abnormalities of amino acid metabolism
- Severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia
- Hypertriglyceridemia-associated acute pancreatitis
- Severe hyperglycemia

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Dosing of OLIMEL (amino acids, dextrose, lipids) is based upon protein, energy, and electrolyte requirements of the individual patient.

Some patients with renal and hepatic disease may benefit from reduced protein intakes.

Some patients with diabetes mellitus or glucose intolerance may benefit from reduced carbohydrate intake.

Patients with parenteral nutrition induced liver disease may benefit from reduction in lipid intake.

Patients with renal disease have decreased capacity to excrete phosphorus. Levels of this electrolyte should be carefully monitored in these patients.

3.2 Recommended Dose and Dosage Adjustment

Adults

Due to its high osmolarity (1120-1360 mOsmol/L), OLIMEL must only be administered through a central vein.

The dosage depends on the patient's energy expenditure, clinical status, body weight, and ability to metabolize the constituents of OLIMEL, as well as additional energy or proteins/amino acids given orally/enterally; therefore, the bag size should be chosen accordingly.

The average daily requirements in adults are:

- Protein/amino acids: 0.16 to 0.35 g nitrogen /kg body weight (1 to 2 g of amino acids/kg), depending on the patient's nutritional status and degree of catabolic stress. Special populations may require up to 0.4 g nitrogen/kg body weight (2.5 g of amino acids/kg).

- Energy: 20 to 40 kcal/kg,

- Fluid: 20 to 40* mL fluid /kg, or 1 to 1.5 mL per expended kcal.

*This is dependent on not over feeding the patient calories or protein.

The maximum daily dose should not be exceeded. Due to the static composition of the multi-chamber bag, the ability to simultaneously meet all nutrient needs of the

patient may not be possible. Clinical situations may exist where patients require amounts of nutrients varying from the composition of the static bag. In this situation the impact of any volume (dose) adjustments must take into consideration the resultant effect this will have on the dosing of all other nutrient components of OLIMEL products. For example, patients may require greater than 0.2 mmol/kg/day of phosphate. In those situations, healthcare professionals may consider adjusting the volume (dose) of OLIMEL in order to meet these increased requirements.

The reconstituted emulsion provides the following for each of the formulations and bag sizes:

OLIMEL 4.4%

	1000 mL	**1500 mL**	**2000 mL**
Lipids	40 g	60 g	80 g
Amino acids	44.3 g	66.4 g	88.6 g
Nitrogen	7.0 g	10.5 g	14.0 g
Dextrose Anhydrous	140.0 g	210.0 g	280.0 g
Energy:			
Total calories approx.	1140 kcal	1710 kcal	2270 kcal
Non-amino acid calories approx.	960 kcal	1440 kcal	1920 kcal
Glucose calories	560 kcal	840 kcal	1120 kcal
Lipid calories approx.(1)	400 kcal	600 kcal	800 kcal
Non-amino acid calories/ nitrogen ratio	137 kcal/g	137 kcal/g	137 kcal/g
Glucose / lipid calories ratio	58/42	58/42	58/42
Lipid / total calories	35%	35%	35%
Electrolytes:			
Phosphate(2)	3.0 mmol	4.5 mmol	6.0 mmol
Acetate	31 mmol	46 mmol	62 mmol
pH approx.	6.4	6.4	6.4
Osmolarity approx.	1220 mosm/L	1220 mosm/L	1220 mosm/L

[1] Includes calories from purified egg phosphatides
[2] Phosphate provided by the lipid emulsion

OLIMEL 5.7%

	1000 mL	1500 mL	2000 mL
Lipids	40 g	60 g	80 g
Amino acids	56.9 g	85.4 g	113.9 g
Nitrogen	9.0 g	13.5 g	18.0 g
Dextrose Anhydrous	110.0 g	165.0 g	220.0 g
Energy:			
Total calories approx.	1070 kcal	1600 kcal	2140 kcal
Non-amino acid calories approx.	840 kcal	1260 kcal	1680 kcal
Glucose calories	440 kcal	660 kcal	880 kcal
Lipid calories approx.(1)	400 kcal	600 kcal	800 kcal
Non-amino acid calories / nitrogen ratio	93 kcal/g	93 kcal/g	93 kcal/g
Glucose / lipid calories ratio	52/48	52/48	52/48
Lipid / total calories	37%	37%	37%
Electrolytes:			
Phosphate(2)	3.0 mmol	4.5 mmol	6.0 mmol
Acetate	40 mmol	60 mmol	80 mmol
pH approx.	6.4	6.4	6.4
Osmolarity approx.	1170 mosm/L	1170 mosm/L	1170 mosm/L

[1] Includes calories from purified egg phosphatides
[2] Phosphate provided by the lipid emulsion

OLIMEL 7.6%

	650 mL	1000 mL	1500 mL	2000 mL
Lipids	22.8 g	35.0 g	52.5 g	70.0 g
Amino acids	49.4 g	75.9 g	113.9 g	151.9 g
Nitrogen	7.8 g	12.0 g	18.0 g	24.0 g
Dextrose Anhydrous	47.7 g	73.3 g	110.0 g	146.7 g
Energy:				
Total calories approx.	620 kcal	950 kcal	1420 kcal	1900 kcal
Non-amino acid calories approx.	420 kcal	640 kcal	960 kcal	1280 kcal
Glucose calories	190 kcal	290 kcal	430 kcal	580 kcal
Lipid calories approx.(1)	230 kcal	350 kcal	530 kcal	700 kcal
Non-amino acid calories / nitrogen ratio	53 kcal/g	53 kcal/g	53 kcal/g	53 kcal/g
Glucose / lipid calories ratio	45/55	45/55	45/55	45/55
Lipid / total calories	37%	37%	37%	37%
Electrolytes:				
Phosphate(2)	1.7 mmol	2.6 mmol	3.9 mmol	5.2 mmol
Acetate	35 mmol	54 mmol	80 mmol	107 mmol
pH approx.	6.4	6.4	6.4	6.4
Osmolarity approx.	(1130 mosm/L	(1130 mosm/L	(1130 mosm/L	(1130 mosm/L

[1] Includes calories from purified egg phosphatides
[2] Phosphate provided by the lipid emulsion

As a general rule, daily doses of 2 g/kg of amino acids and/or 7 g/kg of dextrose and/or 2 g/kg of lipids and/or 40 kcal/kg and/or 40 mL fluid/kg should not be exceeded, except in particular cases when specific demands exceed the usual recommendations. The first of these doses to be reached sets the maximum daily dose.

The OLIMEL formulations may be limited by fluid (40 ml/kg/day), energy (40 kcal/kg/day total calories) or amino acids intakes (2g/kg/day). In Continuous Renal Replacement (CRRT) and patients with morbid obesity, the maximal daily dose is defined by amino acids intake. The maximal daily dose delivers the following:

	OLIMEL 4.4%	OLIMEL 5.7%	OLIMEL 7.6%	OLIMEL 7.6%*
Fluid volume (mL/kg/day)	35	35	26	33
Energy (kcal/kg/day)	40	37	24.7	31.2
Amino Acids (g/kg/day)	1.5	2	2.0	2.5**
Dextrose (g/kg/day)	4.9	3.9	1.9	2.4
Lipid (g/kg/day)	1.4	1.4	0.9	1.2

* In Continuous Renal Replacement (CRRT) and patients with morbid obesity

** In patients with morbid obesity, dosing is based on ideal body weight (IBW)

The maximal infusion rates for the average patient receiving OLIMEL formulations over a 24 hour administration period are as follows:

Formulation	Maximal infusion rate	Amino acids (g/kg/hour)	Dextrose (g/kg/hour)	Lipids (g/kg/hour)
OLIMEL 4.4%	1.7 mL/kg/hour	0.08	0.24	0.07
OLIMEL 5.7%	1.8 mL/kg/hour	0.1	0.19	0.07
OLIMEL 7.6%	1.3 mL/kg/hour	0.10	0.10	0.05

The flow rate should be increased gradually during the first hour. The administration flow rate must be adjusted to take into account the dose being administered, the daily volume intake and the duration of the infusion (see **OVERDOSAGE**).

3.3 Administration

For instructions for preparation and handling of the emulsion for infusion see **SPECIAL HANDLING INSTRUCTIONS**.

The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours. Treatment with parenteral nutrition may be continued for as long as is required by the patient's clinical conditions.

Monitoring of laboratory and clinical parameters is recommended (see **WARNINGS AND PRECAUTIONS and Monitoring and Laboratory Tests**).

The compatibility with solutions administered simultaneously via a common end section must be ensured.

Additions:

Although there is a natural content of trace elements and vitamins in the product, the levels of such substances may not be sufficient to meet body's requirements and need to be supplemented in sufficient quantities to meet individual patient requirements and to prevent deficiencies from developing. However, no addition of any other substances or medicinal products to the bag should be made without first confirming their compatibility and/or suitability to prevent formation of precipitates, destabilization of the lipid emulsion and/or overloading of electrolytes which may result in serious adverse reactions (see **DRUG INTERACTIONS** and **SPECIAL HANDLING INSTRUCTIONS**).

For OLIMEL, calcium and phosphate ratios must be considered. Excess addition of calcium ion and/or inorganic and/or organic phosphate may result in the formation of calcium phosphate precipitates.

Iron ions should NOT be added to the bag since they may destabilize the lipid emulsion.

3.4 Missed Dose

In the event of a missed dose, the infusion should be restarted at the recommended dose and flow rate. Doses should NOT be doubled.

4 OVERDOSAGE

In the event of inappropriate administration (overdose and/or infusion rate higher than recommended), nausea, vomiting, chills, headache, hot flush, hyperhidrosis and electrolyte disturbances and signs of hypervolemia or acidosis may occur and result in severe or fatal consequences. In such situations the infusion must be stopped immediately. If medically appropriate, further intervention may be indicated.

Hyperglycemia, glucosuria, and heperosmolar syndrome may develop if dextrose infusion rate exceeds clearance.

In some serious cases, hemodialysis, hemofiltration or hemo-diafiltration may be necessary.

The reduced or limited ability to metabolize lipids may result in fat overload syndrome, the results of which are usually reversible after infusion of the lipid emulsion is stopped. (See **WARNINGS AND PRECAUTIONS** section).

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Emulsion for Infusion / OLIMEL 4.4% Amino acids, dextrose, lipids Injectable Emulsion 4.4% w/v, 14% w/v, 4% w/v OLIMEL 5.7% Amino acids, dextrose, lipids Injectable Emulsion 5.7% w/v, 11% w/v, 4% w/v OLIMEL 7.6% Amino acids, dextrose, lipids Injectable Emulsion 7.6% w/v, 7.3% w/v, 3.5% w/v	<u>Lipid emulsion chamber:</u> Glycerol Nitrogen Purified egg phosphatide Sodium hydroxide for pH adjustment Sodium oleate Water for injections <u>Amino acid without electrolytes solution chamber:</u> Glacial acetic acid for pH adjustment Nitrogen Water for injections <u>Dextrose (glucose) without calcium solution chamber:</u> Hydrochloric acid for pH adjustment Nitrogen Water for injections

OLIMEL (amino acids, dextrose, lipids) is presented in the form of a 3-chamber bag. Each bag contains a sterile dextrose (glucose) solution without calcium, a sterile amino acid solution without other electrolytes and a sterile lipid emulsion as described below:

OLIMEL 4.4%	**Content per bag**		
	1000 mL	**1500 mL**	**2000 mL**
35% Dextrose solution (35 g/100 mL)	400 mL	600 mL	800 mL
11.1% Amino acid solution (11.1 g/100 mL)	400 mL	600 mL	800 mL
20% Lipid emulsion (20 g/100 mL)	200 mL	300 mL	400 mL

OLIMEL 5.7%	**Content per bag**		
	1000 mL	**1500 mL**	**2000 mL**
27.5% Dextrose solution (27.5 g/100 mL)	400 mL	600 mL	800 mL
14.2% Amino acid solution (14.2 g/100 mL)	400 mL	600 mL	800 mL
20% Lipid emulsion (20 g/100 mL)	200 mL	300 mL	400 mL

OLIMEL 7.6%	**Content per bag**			
	650 mL	**1000 mL**	**1500 mL**	**2000 mL**
27.5% Dextrose solution (27.5 g/100 mL)	173 mL	267 mL	400 mL	533 mL
14.2% Amino acid solution (14.2 g/100 mL)	347 mL	533 mL	800 mL	1067 mL
17.5% Lipid emulsion (17.5 g/100 mL)	130 mL	200 mL	300 mL	400 mL

After mixing the contents of the three chambers, the composition per liter of the reconstituted emulsion is given in the following table for each formulation:

Active substances	Composition per Liter of Reconstituted Emulsion		
	OLIMEL 4.4%	**OLIMEL 5.7%**	**OLIMEL 7.6 %**
Refined olive oil + refined soybean oil [1]	40.00 g	40.00 g	35.00 g
L-Alanine	6.41 g	8.24 g	10.99 g
L-Arginine	4.34 g	5.58 g	7.44 g
L-Aspartic acid	1.28 g	1.65 g	2.20 g
L-Glutamic acid	2.21 g	2.84 g	3.79 g
Glycine	3.07 g	3.95 g	5.26 g
L-Histidine	2.64 g	3.40 g	4.53 g
L-Isoleucine	2.21 g	2.84 g	3.79 g
L-Leucine	3.07 g	3.95 g	5.26 g
L-Lysine acetate (equivalent to Lysine)	4.88 g (3.48 g)	6.32 g (4.48 g)	8.43 g (5.97 g)
L-Methionine	2.21 g	2.84 g	3.79 g
L-Phenylalanine	3.07 g	3.95 g	5.26 g
L-Proline	2.64 g	3.40 g	4.53 g
L-Serine	1.75 g	2.25 g	3.00 g
L-Threonine	2.21 g	2.84 g	3.79 g
L-Tryptophan	0.74 g	0.95 g	1.26 g
L-Tyrosine	0.11 g	0.15 g	0.20 g
L-Valine	2.83 g	3.64 g	4.86 g
Dextrose (Glucose monohydrate) (equivalent to Glucose anhydrous)	154.0 g (140 g)	121.0 g (110.0 g)	80.67 g (73.33 g)

[1] Mixture of refined olive oil (approximately 80%) and refined soybean oil (approximately 20%) corresponding to a ratio essential fatty acids / total fatty acids of 20%.

Packaging

The three-chamber bag is a multi-layer non-Polyvinyl Chloride bag. The inner (contact) layer of the bag material is made of a blend of polyolefinic copolymers and is compatible with amino acid solutions, dextrose solutions and lipid emulsions. Other layers are made of poly-ethylene vinyl acetate, and of a copolyester.

The dextrose chamber is fitted with an injection site to be used for addition of supplements.

The amino acids compartment is fitted with an administration site for insertion of the spike of the infusion set.

To protect from air contact, the bag is packaged in an oxygen barrier overpouch, which contains an oxygen absorber.

Pack sizes:

650 mL bag: 1 carton with 10 bags

1000 mL bag: 1 carton with 6 bags

1500 mL bag: 1 carton with 4 bags

2000 mL bag: 1 carton with 4 bags

6 WARNINGS AND PRECAUTIONS

General

No substances or medicinal products other than the provided components of the products should be added to the bag without first confirming their compatibility and/or suitability to prevent formation of precipitates, destabilization of the lipid emulsion which may result in serious adverse reactions (see **DRUG INTERACTIONS** and **SPECIAL HANDLING INSTRUCTIONS**).

Due to presence of phosphate ion in OLIMEL (amino acids, dextrose, lipids), administration of these products may result in precipitation of calcium phosphate in patients with hyperphosphatemia, hypercalcaemia and /or co-administrated with a calcium ion-containing IV solution. Caution must be exercised when calcium-containing agents are added in the product since this may result in formation of precipitates which can lead to serious or even fatal reactions (See Respiratory subsection below and **SPECIAL HANDLING INSTRUCTIONS**).

The infusion must be stopped immediately if any signs or symptoms of an allergic reaction (such as fever, shivering, sweating, headache, skin rashes, or dyspnea) develop. Specific clinical monitoring is required when an intravenous nutrition infusion is started.

Infection and sepsis may occur as a result of improper use of intravenous catheters to administer parenteral formulations, poor maintenance of catheters or contaminated solutions. Immunosuppression and other conditions such as hyperglycemia, malnutrition and/or their underlying disease state may predispose patients to infectious

complications. Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device, and hyperglycemia can help recognise early infections. The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement and maintenance as well as aseptic technique in nutritional formula preparation.

"Fat overload syndrome" has been reported with similar products. This may be caused by inappropriate administration (e.g. overdose and/or infusion rate higher than recommended, see **ADVERSE REACTIONS** and **OVERDOSAGE**); however, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions. The reduced or limited ability to metabolize the lipids contained in OLIMEL may result in a fat overload syndrome. This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterized by hyperlipidemia, fever, jaundice, liver fatty infiltration (hepatomegaly), deteriorating liver function (hepatosplenomegaly), and hypoxia with or without respiratory insufficiency, anemia, leucopenia, thrombocytopenia, coagulation disorders and central nervous system manifestations (e.g. coma). These symptoms are usually reversible when the infusion of lipid emulsion is stopped.

Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patients becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications. This syndrome has been reported with similar products.

OLIMEL must only be administered through a central vein.

Do not connect bags in series in order to avoid air embolism due to possible residual gas contained in the primary bag.

Carcinogenesis and Mutagenesis
See **NON-CLINICAL TOXICOLOGY** in Part II of the Product Monograph.

Cardiovascular
Use with caution in patients with pulmonary edema or heart failure. Fluid status should be closely monitored. The level of triglyceride should be monitored to avoid hypertriglyceridemia when administrating OLIMEL in patients with acute myocardial infarction.

Endocrine and Metabolism

Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of

inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient's needs.

Serum triglycerides concentrations and the ability of the body to metabolize lipids must be monitored regularly. If a lipid metabolism abnormality is suspected, daily monitoring of serum triglycerides is recommended. Hypertriglyceridemia left untreated can lead to the development of pancreatitis, altered pulmonary function, and immune dysfunction.

Hypercholesterolemia may be caused by excessive amounts of phospholipids in the parenteral formula.

In the event of hyperglycemia, the infusion rate of OLIMEL must be adjusted and/or insulin administered.

Fructose

This product may contain fructose as an impurity in the dextrose material. Exercise caution when this product is used in patients with hereditary fructose intolerance. In these patients, fructose may result in hypoglycemia, metabolic acidosis, liver toxicty which manifests as vomiting, nausea, sweating, jaundice, hemorrhage, seizures or coma or even death. The severity of the reactions is dependent on the amount and duration of fructose intake.

Hyperglycemia

Rapid administration of dextrose solutions may produce substantial hyperglycemia which may result in or contribute to electrolyte losses, dehydration and hypovolemia due to osmotic diuresis and hyperosmolar syndrome. At certain clinical conditions it also may increase the risk of hypoosmotic hyponatremia by shifting of intracellular water to extracellular space. Use with caution in critically ill patients in whom hyperglycemia commonly occurs due to diabetes, impaired glucose intolerance, impaired fasting glucose, or is stress-induced. Hyperglycemia may increase the risk of cardiac complications, infection, systemic sepsis, acute renal failure and even death in certain clinical conditions, especially in acute stress conditions. In order to avoid hyperglycemia the infusion rate should not exceed the patient’s ability to utilize glucose. To reduce the risk of hyperglycemia-associated complications, the infusion rate must be adjusted and/or insulin administered if blood glucose levels exceed levels considered acceptable for the individual patient.

Extravasation

Extravasation has been reported with the administration of OLIMEL.

Gastrointestinal

Patients may develop nausea or diarrhea.

Hepatic/Biliary/Pancreatic

Parenteral nutrition in general especially those containing amino acids, such as OLIMEL, should be used with caution in patients with preexisting liver disease or liver insufficiency. Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonemia.

Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition. The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

Elevated bilirubin and hepatic enzymes may occur in patients receiving parenteral nutrition and may result from excess administration of carbohydrate or lipid, lack of enteral nutrient stimulation, infection, or underlying disease.

Immune

Hypersensitivity to the constituents of the parenteral nutrition formulation such as egg, soybean or peanut products, amino acids, olive products, or any of the active substances, excipients, or components of the containers may occur. See **CONTRAINDICATIONS**.

Since dextrose in OLIMEL products is derived from corn, these products should not be used in patients with known allergy to corn or corn products. See **CONTRAINDICATIONS**.

Monitoring and Laboratory Tests

Monitor water and electrolyte balance, serum osmolarity, serum triglycerides, acid/base balance, blood glucose, liver and kidney function, blood count, including platelets, and coagulation parameters throughout treatment. Daily monitoring is recommended during initiation of parenteral nutrition and until the patient and laboratory measurements are stable.

Renal

Use with caution in patients with renal insufficiency. Fluid and electrolyte status should be closely monitored in these patients.

Severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders should be corrected before starting the infusion.

Respiratory

Pulmonary vascular precipitates causing pulmonary vascular emboli and pulmonary distress have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution. Precipitation distal to the in-line filter and suspected precipitate formation in the blood stream have also been reported.

In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates.

If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated.

Parenteral nutrition containing lipid emulsions should be given cautiously to patients with acute respiratory distress syndrome.

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate data on use of OLIMEL in pregnant women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing OLIMEL.

6.1.2 Breast-feeding

There are no adequate data on use of OLIMEL in lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing OLIMEL.

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

6.1.3 Pediatrics

There have been no studies performed in the pediatric population.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

See **WARNINGS AND PRECAUTIONS**.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety and clinical efficacy of OLIMEL (amino acids, dextrose, lipids) was assessed in a double-blind randomized controlled study over five days. Fifty-six (56) patients requiring parenteral nutrition were enrolled, of whom twenty-eight (28) were treated with OliClinomel (a triple-chamber parenteral nutrition product similar to OLIMEL, that contains the same olive oil/soybean oil lipid, a similar amino acid profile, and dextrose) and twenty-eight (28) were treated with OLIMEL. The goal of the study was to provide information on the safety and nutritional efficacy of OLIMEL in a clinical setting.

A total of fifty-three (53) adverse events occurred during treatment; twenty-nine (29) adverse events were observed in fourteen (14) patients in the OLIMEL group versus twenty-four (24) adverse events observed in eleven (11) patients in the OliClinomel (control) group. Of the twenty-nine (29) adverse events observed in the OLIMEL group, seven (7) adverse events were designated as related to treatment. Of the twenty-four (24) adverse events observed in the OliClinomel (control) group, seven (7) patients presented with adverse events that were reported as related to treatment.

Summary of Treatment-Related Adverse Drug Reactions in the OLIMEL Study

System Organ Class	Adverse Event	Reported Incidence by Treatment Group			
		OLIMEL (n=28) up to 40 mL/kg/day		OLICLINOMEL (n=28) up to 40 mL/kg/day	
		N*	%	N*	%
Cardiac disorders	Tachycardia	1	3.57	0	0.00
Gastrointestinal disorders	Abdominal pain	1	3.57	0	0.00
	Diarrhea	1	3.57	1	3.57
	Nausea	1	3.57	0	0.00
Immune system disorders	Hypersensitivity	0	0.00	1	3.57
Investigations	Blood alkaline phosphatase increased	0	0.00	1	3.57
	Gamma-glutamyltransferase increased	0	0.00	1	3.57

Metabolism and nutrition disorders	Decreased appetite	1	3.57	0	0.00
	Hypertriglyceridemia	1	3.57	0	0.00
Renal and urinary disorders	Azotemia	0	0.00	1	3.57
Respiratory, thoracic and mediastinal disorders	Respiratory failure	0	0.00	1	3.57
Vascular disorders	Hemodynamic instability	0	0.00	1	3.57
	Hypertension	1	3.57	0	0.00

*Number of patients reporting the related event

7.3 Post-Market Adverse Reactions

In addition, the following adverse reactions have been reported in the postmarketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term (PT) in order of severity.

GASTROINTESTINAL DISORDERS: Vomiting

SKIN AND SUBCUTANEOUS SKIN DISORDERS: Rash

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Injection site extravasation, Pyrexia, Chills

Class Reactions

The following adverse reactions have been reported with similar products:

Pruritus, Fat overload syndrome, Cholestasis, Elevated liver enzymes and Azotemia

Pulmonary vascular precipitates (pulmonary vascular emboli and pulmonary distress) (see **WARNINGS AND PRECAUTIONS**)

8 DRUG INTERACTIONS

8.1 Overview

No interaction studies have been performed with OLIMEL (amino acids, dextrose, lipids).

OLIMEL must not be administered simultaneously with blood through the same infusion tubing because of the risk of pseudoagglutination.

8.2 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table - Established or Potential Drug-Drug Interactions

<Proper/Common name>	Source of Evidence	Effect	Clinical comment
COUMADIN (or coumarin derivatives including warfarin)	T	Decreased anticoagulant effect	Soybean oil has a natural content of vitamin K that may counteract the anticoagulant activity of coumarin derivatives, including warfarin. Levels of vitamin K vary in the formulation. Caution is warranted and therapeutic monitoring of coagulation status is recommended.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Due to the risk of precipitation, OLIMEL should not be admixed with ampicillin or fosphenytoin.

Due to the presence of phosphate in OLIMEL, adding calcium-containing and/or phosphate-containing products to the products may result in formation of calcium phosphate precipitates which may destabilize the emulsion status of the product (see **SPECIAL HANDLING INSTRUCTIONS**). Calcium phosphate precipitates and destabilized emulsion status of the products may result in serious health consequences.

8.3 Drug-Food Interactions

No OLIMEL - food interaction studies have been performed.

8.4 Drug-Laboratory Test Interactions

The lipids contained in this emulsion may interfere with the results of certain laboratory tests if the blood sample is taken before lipids are eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids). Potential assay interference associated with lipemia should be considered when interpreting the results of lipemic samples.

8.5 Drug-Lifestyle Interactions

Interactions with lifestyle have not been evaluated.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Amino acids administered intravenously are directly bioavailable to the body. The amino acids are transported into tissues by active transporters where they supply substrate for protein or peptide synthesis, act as regulators of various enzymes and genes, or are converted to other bioactive compounds (such as nitric oxide, glutathione, and gamma amino butyric acid). Thus, amino acids have both structural and regulatory roles within the body. Amino acids are metabolized in the liver and small quantities may be excreted unchanged through the kidneys. Nitrogen waste products from amino acid metabolism are converted to urea and excreted via the kidneys.

Dextrose, as glucose, is taken up and metabolized by all cells in the body and represents the primary energy source for the body. Glucose can be stored in the body in the form of glycogen (primarily in liver and skeletal muscle). Glucose may also be converted to fatty acids and stored as triglycerides in fat tissue. Circulating glucose levels are regulated by the interplay between insulin and glucagon, with lesser contributions from catecholamines, growth hormone, and glucocorticoids.

Fatty acids (lipid) are important energy sources for the body. The human body cannot synthesize omega-6 (linoleic acid and derivatives) or omega-3 (α-linolenic acid and derivatives) polyunsaturated fatty acids and requires these from the diet. Fatty acids are also important as substrates for membranes, precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

9.2 Pharmacodynamics

The content of nitrogen (amino acids) in OLIMEL (amino acids, dextrose, lipids) and energy (dextrose and triglycerides) enables maintenance of an adequate nitrogen/energy balance. Nitrogen and energy are required for normal functioning of all cells in the body, and are important for protein synthesis, growth, wound healing, immune function, muscle function, and many other cellular activities.

The amino acid solution contains 17 amino acids (including 8 essential amino acids), which are indispensable for protein synthesis. All the amino acids used in OLIMEL / PeriOLIMEL are in the optical L-form, except glycine, whose molecule has no chiral center and is not optically active. The optical L-form is known to be more compatible to human biochemistry. Amino acids also represent an energy source, their oxidation resulting in excretion of nitrogen in the form of urea.

The amino acids profile is as follows:

- Essential amino acids/total amino acids: 44.8%

- Branched-chain amino acids/total amino acids: 18.3%.

The lipid emulsion included in OLIMEL, is a mixture of refined olive oil and refined soybean oil (ratio 80/20), with the following approximate distribution of fatty acids:

- 15% saturated fatty acids (SFA)

- 65% monounsaturated fatty acids (MUFA)

- 20% polyunsaturated essential fatty acids (PUFA)

The phospholipid/triglyceride ratio is 0.06. The moderate essential fatty acid (EFA) content may improve utilization of infused essential fatty acids for synthesis of higher derivative fatty acids.

Olive oil contains significant amounts of alpha-tocopherol that contributes to vitamin E status.

The carbohydrate source is dextrose. Dextrose (glucose) is the primary source of energy in the body.

9.3 Pharmacokinetics

Absorption: Not applicable as this drug is given intravenously.

Distribution: The constituents of the formulation are distributed to all cells in the body.

The ingredients of OLIMEL (amino acids, dextrose, lipids) are distributed, metabolized and eliminated in the same manner as if they had been administered individually.

The pharmacokinetic properties of the amino acids administered intravenously are essentially the same as those of amino acids supplied by oral feeding. Amino acids from food proteins, however, first pass through the portal vein before reaching the systemic circulation.

The elimination rate of lipid emulsions depends on particle size, fatty acid composition, apolipoprotein content of the lipid globules, lipoprotein lipase activity, and hepatic lipase activity. The maximal removal capacity (K1) for the lipid emulsion found for OLIMEL in normal volunteers is 176 ± 16 mg/kg/hr. In the emulsion contained in OLIMEL, the size of the lipid particles is close to that of chylomicrons and this emulsion therefore has a similar elimination rate.

Metabolism and excretion: Amino acids, dextrose, and triglycerides are metabolized by all cells in the body. Nitrogen waste is converted to urea in the liver and excreted by the kidneys. Glucose and triglycerides are metabolized to carbon dioxide and excreted by the lungs.

Special Populations and Conditions
Pharmacokinetic data have not been obtained in special patient populations or conditions.

10 STORAGE, STABILITY AND DISPOSAL

Do not freeze. Store the unmixed product in the overpouch at 15°C to 30°C.

Shelf life after reconstitution:
It is recommended that the product be used immediately after the non-permanent seals between the 3 chambers have been opened.

Shelf life after addition of supplements (electrolytes, trace elements, vitamins; see **SPECIAL HANDLING INSTRUCTIONS**):

Addition of supplements must take place under controlled and validated aseptic conditions. From a microbiological point of view, any admixture should be used immediately. If not used immediately, storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

11 SPECIAL HANDLING INSTRUCTIONS

To open

Remove the protective overpouch.

Discard the oxygen absorber.

Confirm the integrity of the bag and of the non-permanent seals. Use only if the bag is not damaged, if the non-permanent seals are intact (i.e. no mixture of the contents of the three chambers), if the amino acids solution and the dextrose solution are clear, colourless or slightly yellow, practically free of visible particles, and if the lipid emulsion is a homogeneous liquid with a milky appearance.

Mixing the solutions and the emulsion

Ensure that the product is at room temperature when breaking the non-permanent seals.

Manually roll the bag onto itself, starting at the top of the bag (hanger end). The non-permanent seals will disappear from the side near the inlets. Continue to roll until the seals are open along approximately half of their length.

Mix by inverting the bag at least 3 times.

The appearance after reconstitution is a homogeneous milk-like emulsion.

Additions

Additions must be performed under aseptic conditions and by qualified personnel.

The capacity of the bag is sufficient to enable additions of nutritional and medicinal substances such as vitamins, electrolytes and trace elements. However, other than the provided components of the product, no substance should be added to the bag without first confirming its compatibility and suitability as stated below in order to prevent formation of precipitates, and/or destabilization of the lipid emulsion which may result in serious adverse reactions.

Any addition (including vitamins) may be made into the reconstituted mixture (after the non-permanent seals have been opened and after the contents of the three chambers have been mixed). Iron ions should NOT be added to the bag since they may destabilize the lipid emulsion of the product.

Vitamins may also be added into the dextrose chamber before the mixture is reconstituted (before opening the non-permanent seals and before mixing the solutions and the emulsion).

OLIMEL formulations may be supplemented with electrolytes. Electrolyte supplementation should be dictated by the patient's clinical needs and should not exceed nutritional guidelines. When calcium-containing and/or phosphate-containing products are added to the products, caution must be exercised to prevent formation of calcium phosphate precipitates in the reconstituted mixture AND/OR in the body after administration. The maximal total levels for sodium, magnesium, potassium and calcium listed in the tables below were demonstrated by stability data, but **should not be considered as dosage recommendations** since the safety of the resulting mixture has not been adequately studied in clinical settings. If the level of calcium and/or phosphate in the reconstituted mixture exceeds the level shown in the following tables, the stability of the mixture may be compromised due to formation of calcium phosphate precipitates.

Additions to OLIMEL 4.4% and OLIMEL 5.7%:

Per 1000 mL			
	Included level	**Maximal further addition**[4]	**Maximal total level**[4]
Sodium	0 mmol	150 mmol	150 mmol
Potassium	0 mmol	150 mmol	150 mmol
Magnesium	0 mmol	5.6 mmol	5.6 mmol
Calcium	0 mmol	5.0 (3.5[2]) mmol	5.0 (3.5[2]) mmol
Inorganic	0 mmol	8.0 mmol	8.0 mmol

Phosphate			
Organic Phosphate	3 mmol [1]	- [3]	- [3]

[1] Including phosphate provided by the lipid emulsion

[2] Value in condition where inorganic phosphate is added at the maximal addition level.

[3] Organic Phosphate as a single entity may not be currently available in Canada.

[4] The values are based on stability data and should not be considered as dose recommendations.

Additions to OLIMEL 7.6 %:

Per 1000 mL			
	Included level	**Maximal further addition[4]**	**Maximal total level[4]**
Sodium	0 mmol	150 mmol	150 mmol
Potassium	0 mmol	150 mmol	150 mmol
Magnesium	0 mmol	5.6 mmol	5.6 mmol
Calcium	0 mmol	5.0 (3.5[2]) mmol	5.0 (3.5[2]) mmol
Inorganic Phosphate	0 mmol	10.0 mmol	10.0 mmol
Organic Phosphate	3 mmol [1]	22 mmol [3]	25 mmol [3]

[1] Including phosphate provided by the lipid emulsion

[2] Value in condition where inorganic phosphate is added at the maximal addition level.

[3] Organic Phosphate as a single entity may not be currently available in Canada.

[4] The values are based on stability data and should not be considered as dose recommendations

Trace elements and vitamins:

Stability has been demonstrated up to the recommended daily dose.

Trace elements and vitamins: Stability has been demonstrated with commercially available preparations of vitamins and trace elements (containing up to 1 mg of iron). Compatibility for other additives is available upon request.

To perform an addition:

- Aseptic conditions must be observed.
- Prepare the injection site of the bag.
- Puncture the injection site and inject the additives using an injection needle or a reconstitution device.
- Mix content of the bag and the additives.

Preparation of the infusion

Only administration sets and administration lines made from DEHP-free should be used.

Aseptic conditions must be observed.

Suspend the bag.

Remove the plastic protector from the administration outlet.

Firmly insert the spike of the infusion set into the administration outlet.

Administration

For single use only. Aseptic conditions must be observed. When additions are made with inorganic phosphate, 1.2 micron filters should be used.

Only administer the product after the non-permanent seals between the three chambers have been broken and the contents of the three chambers have been mixed.

Ensure that the final emulsion for infusion does not show any evidence of phase separation.

After opening the bag, the contents should be used immediately and should not be stored for a subsequent infusion. Do not reconnect any partially used bag.

Do not connect in series in order to avoid the possibility of air embolism due to gas contained in the first bag.

Any unused product or waste material and all necessary devices must be discarded.

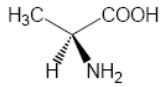
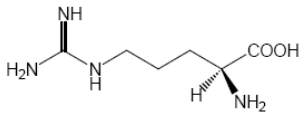
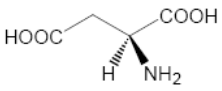
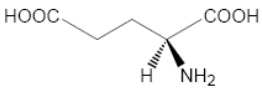
PART II: SCIENTIFIC INFORMATION

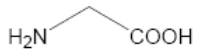
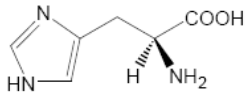
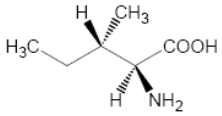
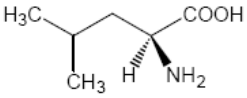
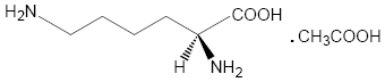
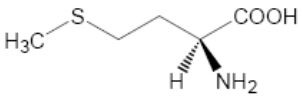
12 PHARMACEUTICAL INFORMATION

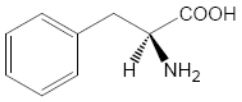
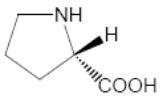
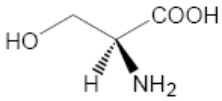
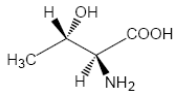
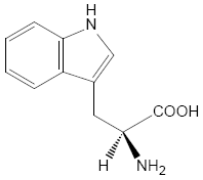
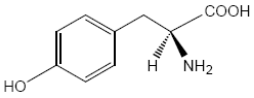
Drug Substance

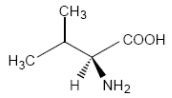
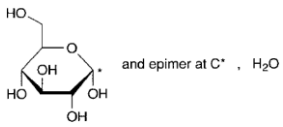
OLIMEL (amino acids, dextrose, lipids) contains the following drug substances in the three chambers.

- Dextrose solution (larger outer chamber)
- Amino acid solution without electrolytes (centre chamber)
- Lipid emulsion (a mix of refined olive oil and refined soybean oil) (smaller outer chamber)

Proper Name Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical Properties
L-Alanine (S)-2-aminopropionic acid	$C_3H_7NO_2$ 89.09		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in alcohol.
L-Arginine (2S)-2-amino-5-guanidinopentanoic acid	$C_6H_{14}N_4O_2$ 174.20		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in alcohol.
L-Aspartic Acid (S)-aminosuccinic acid	$C_4H_7NO_4$ 133.10		White or almost white crystalline powder or colourless crystals, slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Glutamic Acid (S)-2-aminoglutaric acid	$C_5H_9NO_4$ 147.13		White crystalline powder or colourless crystals, freely soluble in boiling water, slightly soluble in cold water, practically insoluble in acetic acid, in acetone and in alcohol.

Proper Name Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical Properties
Glycine Aminoacetic acid	$C_2H_5NO_2$ 75.07		White or almost white crystalline powder, freely soluble in water, very slightly soluble in alcohol.
L-Histidine (S)-2-amino-1H-imidazole-4-propionic acid	$C_6H_9N_3O_2$ 155.15		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol (96%).
L-Isoleucine (2S, 3S)-2-amino-3-methylpentanoic acid	$C_6H_{13}NO_2$ 131.17		White or almost white crystalline powder or flakes, sparingly soluble in water, slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Leucine (2S)-2-amino-4-methylpentanoic acid	$C_6H_{13}NO_2$ 131.17		White or almost white crystalline powder or shiny flakes, sparingly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Lysine Acetate (2S)-2,6-diaminohexanoic acid monoacetate	$C_6H_{14}N_2O_2 \cdot C_2H_4O_2$ 206.24		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in ethanol (96%).
L-Methionine (2S)-2-amino-4-(methylsulfanyl) butanoic acid	$C_5H_{11}NO_2S$ 149.21		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol.

Proper Name Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical Properties
L-Phenylalanine (2S)-2-amino-3-phenylpropanoic acid	$C_9H_{11}NO_2$ 165.19		White or almost white crystalline powder or shiny, white flakes, sparingly soluble in water, very slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Proline (S)-2-pyrrolidinecarboxylic acid	$C_5H_9NO_2$ 115.13		White or almost white crystalline powder or colourless crystals, very soluble in water, freely soluble in alcohol.
L-Serine (S)-2-amino-3-hydroxypropionic acid	$C_3H_7NO_3$ 105.09		White or almost white crystalline powder or colourless crystals, freely soluble in water, practically insoluble in alcohol.
L-Threonine (2S, 3R)-2-amino-3-hydroxybutanoic acid	$C_4H_9NO_3$ 119.12		White crystalline powder or colourless crystals, soluble in water, practically insoluble in ethanol.
L-Tryptophan (2S)-2-amino-3-(indol-3-yl)propanoic acid	$C_{11}H_{12}N_2O_2$ 204.23		White or almost white crystalline or amorphous powder, sparingly soluble in water, slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Tyrosine (S)-2-amino-3-(4-hydroxyphenyl) propionic acid	$C_9H_{11}NO_3$ 181.19		White crystalline powder or colourless crystals, very slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

Proper Name Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical Properties
L-Valine (2S)-2-amino-3-methylbutanoic acid	$C_5H_{11}NO_2$ 117.15		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol.
Dextrose D-glucose monohydrate	$C_6H_{12}O_6 \cdot H_2O$ 198.2		White crystalline powder with a sweet taste, freely soluble in water, sparingly soluble in alcohol.
Olive oil, refined	Complex mixture of triglycerides; predominant fatty acids in olive oil are oleic, palmitic and linoleic. Approximately 870 g/mol depending on the fatty acid composition.	CH_2-OCO-R_1 | CH-OCO-R_2 | CH_2-OCO-R_3 where R_1, R_2 and R_3 represent the fatty acids linked to the glycerol moiety of the triglyceride.	Clear, colourless or greenish-yellow, transparent liquid, practically insoluble in ethanol (96%), miscible with light petroleum (50°C to 70°C). When cooled, it begins to become cloudy at 10°C and becomes a butter-like mass at about 0°C. It has a relative density of about 0.913.
Soybean oil, refined	Complex mixture of triglycerides; predominant fatty acids in soybean oil are linoleic, oleic, palmitic and linolenic. Approximately 870 g/mol depending on the fatty acid composition.	CH_2-OCO-R_1 | CH-OCO-R_2 | CH_2-OCO-R_3 where R_1, R_2 and R_3 represent the fatty acids linked to the glycerol moiety of the triglyceride.	Clear, pale yellow, liquid, miscible with light petroleum (50°C to 70°C), practically insoluble in alcohol. It has a relative density of about 0.922 and a refractive index of about 1.475.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Study ICS1063B/P01/03/Mu.F was a prospective randomized double-blind multicenter study performed to evaluate safety and nutritional efficacy of OLIMEL 5.7% (amino acids, dextrose, lipids) compared to OLICLINOMEL N8-800 (a triple chambered bag established in Europe that contains the same olive oil/soybean oil lipid, a similar amino acid profile, and dextrose). The

study was conducted in a variety of patients (primarily post-surgery and trauma) who required balanced parenteral nutrition representing at least 50% of the daily nonprotein energy requirements for 5 days. The primary nutritional efficacy endpoint was transthyretin (pre-albumin) levels. Safety was evaluated using adverse events, vital signs, and biochemical markers for renal (urea, creatinine), hepatic (ASAT, ALAT, alkaline phosphatase, GGT, bilirubin), hematologic (RBC count, hemoglobin, hematocrit, platelets, WBCs, lymphocytes, neutrophils, monocytes, eosinophils, basophils) organ functions as well as glucose and lipid parameters (triglycerides, cholesterol).

Summary of patient demographics for clinical trials in specific indication					
Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
ICS1063B/P01/03/Mu.F	Prospective randomized double-blind multicenter controlled trial	OLIMEL 5.7%: 29 kcal/kg/day; protein 1.5 g/kg/day; 5 days OLICLINOMEL: 29 kcal/kg/day; protein 1.5 g/kg/day ; 5 days via central vein	ITT population OLIMEL 5.7%: n=24 OLICLINOMEL: n=26	OLIMEL 5.7%: 56±15 years OLICLINOMEL: 52±21 years	OLIMEL 5.7%: 17 male, 7 female OLICLINOMEL: 16 male, 10 female

13.2 Study Results

Results of study ICS1063B/P01/03/Mu.F in specific indication

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Transthyretin levels	No differences were found between the two nutritional groups for transthyretin levels. Day 1 to Day 5: 144±75 mg/L to 206±142 mg/L	Day 1 to day 5: 146±83 mg/L to 181±82 mg/L

Adverse events were similar between groups (see Clinical Trial Adverse Reactions). There were no differences between groups for glucose, lipids, renal function, hepatic function, or hematologic function.

14 NON-CLINICAL TOXICOLOGY

Studies on the carcinogenic potential, reproductive and developmental toxicity, and genotoxic potential have not been performed on the finished product for OLIMEL (amino acids, dextrose, lipids).

Amino Acid Compartment

The amino acid solution with electrolytes contains sodium glycerophosphate as a source of nutritional phosphorus. Single-dose and 28-day repeated dose toxicity studies have been performed in rats and dogs with sodium glycerophosphate.

Single-dose Toxicity

Rats received a single intravenous bolus infusion of sodium glycerophosphate at doses of 625, 1,250 or 2,500 mg/kg. At the 2500 mg/kg dose, 10% mortality and clinical signs of toxicity were observed. Therefore, 1250 mg/kg was identified as the maximum tolerated dose following intravenous infusion in rats.

Dogs were given a single intravenous bolus infusion at doses of 625, 1250 or 1875 mg/kg. At the 1875 mg/kg dose, vomiting, jaw discomfort, half-closed eyes, loss of balance and sneezing were observed during, or just after dosing. Vomiting was noted during infusion in the 1250 mg/kg group. The no observed effect level was considered to be 625 mg/kg/day.

Repeat-Dose Toxicity

Rats were given 312.5, 625, or 1250 mg/kg of sodium glycerophosphate intravenously daily for 28 consecutive days. No test article-related changes were observed.

Dogs received sodium glycerophosphate by daily intravenous infusion at the dose-levels of 312.5, 625 or 1250 mg/kg/day for 28 consecutive days. At 1250 mg/kg/day, vomiting, rubbing of the head on the floor, shaking head, scratching of ear(s), half-closed eyes, loss of balance, sitting position and lateral recumbency were observed primarily during the first two days of the treatment period. A slight prolongation of the QT and QTc interval durations was noted in females given 1250 mg/kg/day throughout the treatment period. An increased QT interval at the 1250 mg/kg dose could be attributed to a transient, localized hypocalcemia associated with the rapid administration rate (compared to the therapeutic rate of sodium glycerophosphate delivery in humans). Sodium glycerophosphate was clinically well tolerated and did not cause any laboratory or histopathological changes at the indicated doses.

Lipid Compartment

Single-dose Toxicity

Single-dose toxicity was investigated in the mouse and rat to compare the LD_{50} of the lipid emulsion in OLIMEL with that of 20% soybean based emulsions.

LD_{50} values were comparable at around 100-112 mL/kg (corresponding to approximately 20 g lipid/kg) in both species with rapid infusion.

Repeat-Dose Toxicity

The lipid emulsion in OLIMEL was administered to rats and dogs by intravenous infusion in studies lasting up to 91 days. The key studies conducted and the notable findings are presented in the table below.

Repeated Dose Toxicity Studies

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mL/kg/day)	Key Findings
30 Day toxicity study in the rat	Rat Sprague Dawley CD (Charles River)	IV infusion	30 days	90 at a rate of 1.2 mL/kg/min	Hematuria Decreased food consumption Regenerative anemia Mild thrombocytopenia Increased hepatic enzymes Increased serum cholesterol and phospholipids Hepatocellular vacuolation and necrosis Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation Interstitial and tubular nephritis
30 Day toxicity study in the rat	Rat Sprague Dawley CD (Charles River)	IV infusion	30 days	75 at a rate of 1.5 mL/kg/min	Hematuria Decreased food consumption Regenerative anemia Mild thrombocytopenia Increased hepatic enzymes Increased serum phospholipids Hepatic vacuolation and inflammation Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation Interstitial and tubular nephritis

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mL/kg/day)	Key Findings
90 Day toxicity study in the rat	Rat Sprague Dawley CD (Charles River)	IV infusion	90 days	15, 30 and 60 at a rate of 2 mL/kg/min	Hematuria Decreased food consumption Mild anemia at 60 mL/kg Dose-dependent hepatic vacuolation and inflammation Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation
30 Day toxicity study in the dog	Dog Beagle	IV infusion	30 days	45 at a rate of 0.2 mL/kg/min	Decreased food consumption Increased hepatic enzymes Increased serum cholesterol and phospholipids Hepatocellular vacuolation Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation
30 Day toxicity study in the dog	Dog Beagle	IV infusion	30 days	60 at a rate of 0.2 mL/kg/min	Decreased food consumption Regenerative anemia Mild thrombocytopenia Increased hepatic enzymes Increased serum phospholipids Hepatic vacuolation and inflammation, Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation Renal tubular vacuolation
30 Day toxicity study in the dog	Dog Beagle	IV infusion	30 days	60 at a rate of 0.2 mL/kg/min	Decreased food consumption Regenerative anemia Mild thrombocytopenia Increased hepatic enzymes Increased serum phospholipids Hepatic vacuolation and inflammation, Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation Renal tubular vacuolation

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mL/kg/day)	Key Findings
91 Day toxicity study in the dog	Dog Beagle	IV infusion	91 days	15, 22.5, 30 0.2 mL/kg/min	Decreased food consumption Mild anemia at 30 mL/kg Increased hepatic enzymes at ≥22.5 mL/kg Increased serum cholesterol and phospholipids Hepatocellular vacuolation at 30 mL/kg Hepatic and splenic macrophage pigmentation Splenic macrophage vacuolation

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

OLIMEL 4.4%
Amino acids, dextrose, lipids
Injectable Emulsion
4.4% w/v, 14% w/v, 4% w/v

OLIMEL 5.7%
Amino acids, dextrose, lipids
Injectable Emulsion
5.7% w/v, 11% w/v, 4% w/v

OLIMEL 7.6%
Amino acids, dextrose, lipids
Injectable Emulsion
7.6% w/v, 7.3% w/v, 3.5% w/v

Read this carefully before you start taking OLIMEL and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about OLIMEL.

What is OLIMEL used for?
OLIMEL is used to provide nutrition to adults. It is given to you through a tube into a vein when normal feeding by mouth is not possible or suitable.

OLIMEL will only be given to you under medical supervision.

How does OLIMEL work?
OLIMEL is given to you when you are unable to eat to get an adequate intake of energy, nitrogen and other nutrients. This helps treat or prevent malnutrition.

What are the ingredients in OLIMEL?
Medicinal ingredients:
OLIMEL product is an emulsion for infusion, supplied in a bag with three chambers.
one chamber contains a solution of 17 amino acids (L-Alanine, L-Arginine, L-Aspartic Acid, L-Glutamic Acid, Glycine, L-Histidine, L-Isoleucine, L-Leucine, L-Lysine Acetate, L-Methionine, L-Phenylalanine, L-Proline, Serine, L-Threonine, L-Tryptophan, L-Tyrosine, L-Valine) without electrolytes;
one chamber contains a dextrose solution
one chamber contains a lipid emulsion, which is a mix of refined olive oil and refined soybean oil.

Non-medicinal ingredients:
Glacial acetic acid (for pH adjustment)
Glycerol
Hydrochloric acid (for pH adjustment)
Nitrogen
Purified egg phosphatide
Sodium hydroxide (for pH adjustment)
Sodium oleate
Water for injection

OLIMEL comes in the following dosage forms:
OLIMEL 4.4% (4.4% w/v amino acids, 14% w/v dextrose, 4% w/v lipids) Injectable Emulsion

OLIMEL 5.7% (5.7% w/v amino acids, 11% w/v dextrose, 4% w/v lipids) Injectable Emulsion

OLIMEL 7.6 % (7.6% w/v amino acids, 7.3% w/v dextrose, 3.5% w/v lipids) Injectable Emulsion

Do not use OLIMEL if:

- You are allergic to any ingredients (such as egg, soybean or peanut proteins, olive products.) or any ingredients in OLIMEL or components of the container. (See **What the medicinal ingredients are** and **What the important nonmedicinal ingredients are**.)
- You have liver failure or coma resulting from liver failure.
- You have kidney failure and are not on dialysis
- You have an allergy to corn or corn products since this product contains dextrose from corn.
- Your body has problems processing certain amino acids that are included in OLIMEL.
- Your body has severe problems metabolizing (breaking down) fat.
- You have especially high levels of fats in your blood.
- You have acute pancreatitis (severe inflammation of pancreas) in association with hyperlipidemia (high blood fat levels).
- You have hyperglycemia (too much sugar in your blood), which is not controlled.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OLIMEL. Talk about any health conditions or problems you may have, including if you:

- are allergic to any ingredients (such as egg, soybean or peanut proteins, olive products, corn.)
- suffer from metabolic acidosis (when the blood is excessively acid)
- have kidney problems
- have liver problems
- have heart problems or have had heart problems
- have lung or breathing problems
- have diabetes
- have a disorder where your body cannot break down fats properly
- have acute respiratory distress syndrome. This is a serious condition where fluid builds up in the lungs.
- are taking any other medicines on a regular basis
- are pregnant or intend to become pregnant

- are breastfeeding or intend to breastfeed
- have hereditary fructose intolerance. This is a condition where your body cannot break down fructose properly. This product may contain small amounts of fructose

Other warnings you should know about:
In all cases, your doctor will give you OLIMEL based on factors such as age, weight, condition, and any tests results that they have done. Always be sure to check with your doctor if anything about your condition changes.

Your doctor will need to monitor how you are doing while you are on this medicine. This means that you will need to have laboratory tests done on a routine basis.

Precipitates (e.g. solid particles) can appear in OLIMEL when a calcium-containing product is added to it. It has been reported that these injected precipitates can block an artery in the lungs, cause breathing difficulties and even death. Your doctor will decide with caution, whether a calcium-containing product will be mixed with OLIMEL.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OLIMEL:
- OLIMEL must NOT be given at the same time with blood through the same infusion tubing
- Blood thinner medicines such as warfarin.
- Medicines or infusions containing calcium or phosphate.

How to take OLIMEL:
OLIMEL can be given in a hospital or managed care facility, or at home under the supervision of a doctor or other health care professional.

After appropriate training and with the agreement of your medical team, you may be able to administer OLIMEL yourself. Your doctor's instructions must be followed exactly when taking OLIMEL.

Before using the product, the bag must be prepared as shown in the pictures.

Use only if the solutions are clear, colourless or slightly yellow, practically free of visible particles and if the emulsion is homogeneous and milk-like.

Use only if the bag is not damaged and if the non-permanent seals between the chambers are intact (no mixing of the 3 chambers contents).

Make sure the product is at room temperature.

Aseptic conditions must be followed (cleaning of hands).

OLIMEL must be delivered through a central vein.

Your healthcare professional will provide instructions on the preparation of the site and route of administration (central vein).

OLIMEL should only be used once. Discard unused portion, do not use a partially used bag.

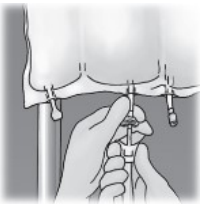
1. 
Tear from the top to open the overpouch.

2. 
Peel the front of the overpouch to reveal the OLIMEL bag. Discard the overpouch and oxygen absorber.

3. 
Place the bag flat on an horizontal and clean surface with handle in front of you.

4. 
Lift the hanger area to remove solution from the upper bag.
Roll firmly the upper bag until peal seals are fully open (approximately half way).

5. 
Mix by turning the bag upside-down at least 3 times.

6. 
Hang the bag.
Twist off the protector from the Administration outlet.Firmly plug the spike connector.

Usual adult dose:
Your doctor will select the appropriate OLIMEL for you, based on your body weight. They will also consider how much energy you need and how well your body can handle the amino acids, and lipids in the different solutions

Your doctor will also specify a flow rate corresponding to your needs and medical condition.

Always use OLIMEL exactly as your doctor has told you to. You should check with your doctor if you are not sure.

The product infusion may continue for as long as the doctor advises, depending upon your medical condition. The infusion of one triple-chamber bag usually lasts between 12 and 24 hours. The maximum daily dose should not be exceeded.

Overdose:
If your dose is too high or is infused too quickly, the following may happen:

- the amino acid content may make your blood too acidic;
- the dextrose content may increase the glucose in your blood and urine;
- the lipid content may increase the fats in your blood.

Giving too high a volume may cause nausea, vomiting, headache, hot flush, excessive sweating and shivering.

In some severe cases, your doctor may have to give you temporary renal dialysis to help your kidneys get rid of any extra nutrients.

To help prevent these events, your doctor will routinely check your condition, and test your blood and urine.

If you feel you have been given too much or have taken too much OLIMEL, contact your healthcare professional, hospital emergency department or the regional poison control centre, even if there are no symptoms.

Missed Dose:
If you miss or forget to take one or more doses of OLIMEL, contact your doctor as soon as possible. Your doctor will instruct you about how to re-start your treatment and what flow rate to use.

DO NOT take a double dose to make up for forgotten individual doses.

What are possible side effects from using OLIMEL?
These are not all the possible side effects you may feel when taking OLIMEL. If you experience any side effects not listed here, contact your healthcare professional.

If you notice any changes in the way you feel during or after the treatment, tell your doctor or another member of your medical team immediately.

OLIMEL can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

Side effects may include:
- nausea
- diarrhea
- abdominal pain
- decreased appetite
- vomiting
- rash
- fever
- chills
- itchiness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Allergic reaction: difficulty swallowing or breathing, fever, headache, shivering, skin rash or hives, shortness of breath, swelling of the face, lips, tongue or throat.			√

Tachycardia (abnormally fast heartbeat)		√	
Azotemia (high nitrogen levels in the body): fatigue, fever, chills, nausea, swelling of feet or ankles, dark or red-coloured urine, change in how often you urinate			√
Respiratory Failure: blue color on skin, lips, and fingernails; feel sleepy; irregular heartbeats; loss of consciousness; sudden worsening of shortness of breath			√
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, racing pulse or heart palpitations		√	
RARE			
Liver Problems: yellow colour to skin, whites of the eyes (jaundice), Abdominal pain, itching, fatigue, fever, confusion, sleepiness		√	
Decreased Platelets: bruising, bleeding, fatigue and weakness		√	
Fat Overload Syndrome (too much fat in the blood): fever, jaundice (yellowing of the skin and eyes), blood clotting, fatigue, irregular heartbeats, pale complexion, trouble breathing, coma			√
Precipitates in the Blood Vessels Leading to or from the Lungs: difficulty breathing, shortness of breath, chest pain, coughing			√
Injection Site Reaction: pain, redness and/or swelling at the injection site		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not freeze. Store the unmixed product in the overpouch at 15°C to 30°C.

Do not use OLIMEL after the expiry date which is printed on the container and the outer packaging (MM/YYYY). The expiry date refers to the last day of that month.

Once the seals between the three chambers have been broken and the product has been mixed, the product should be used **immediately**.

This medicine must be at room temperature to be administered.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of reach and sight of children.

If you want more information about OLIMEL:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the Baxter website (Baxter.ca), or by calling 1-888-719-9955.

This leaflet was prepared by Baxter Corporation, Mississauga, Ontario L5N 0C2, Canada

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