IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0167/109/005
Case No: 2075276

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Baxter Healthcare Limited

Caxton Way, **Thetford**, **Norfolk IP24 3SE**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

OLICLINOMEL N6-900, emulsion for infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/02/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OLICLINOMEL N 6-900, emulsion for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

This medicinal product is presented in the form of a 3-compartment bag.
There are four presentations, which have the following different volumes:

Compartment	**1000 ml**	**1500 ml**	**2000 ml**	**2500 ml**
Lipid emulsion	200 ml	300 ml	400 ml	500 ml
Amino acid solution	400 ml	600 ml	800 ml	1000 ml
Glucose solution	400 ml	600 ml	800 ml	1000 ml

Composition of a 1000ml bag:

Active substances	**20% lipid emulsion compartment** (corresponding to 20g/100ml) **(200 ml)**	**8.5%amino acid solution compartment** (corresponding to 8.5g/100ml) **(400 ml)**	**30% glucose solution compartment** (corresponding to 30g/100ml) **(400 ml)**
Refined olive oil + refined soya oil*	40.00 g		
Alanine		7.04 g	
Arginine		3.91 g	
Glycine		3.50 g	
Histidine		1.63 g	
Isoleucine		2.04 g	
Leucine		2.48 g	
Lysine (As lysine hydrochloride)		1.97 g (2.46 g)	
Methionine		1.36 g	
Phenylalanine		1.90 g	
Proline		2.31 g	
Serine		1.70 g	
Threonine		1.43 g	
Tryptophan		0.61 g	
Tyrosine		0.14 g	
Valine		1.97 g	
Anhydrous glucose (As glucose monohydrate)			120.00 g (132.00 g)

* Mixture of refined olive oil (approximately 80%) and refined soya oil (approximately 20%)

For full list of the excipients, see section 6.1

After the contents of the three compartments have been mixed, the ternary mixture for each of the bag presentations provides the following:

Per bag	**1 litre**	**1.5 litres**	**2 litres**	**2.5 litres**
Nitrogen (g)	5.6	8.4	11.2	14.0
Amino acids (g)	34	51	68	85
Glucose (g)	120	180	240	300
Lipids(g)	40	60	80	100
Total calories (kcal)	1015	1525	2030	2540
Non-protein calories (kcal)	880	1320	1760	2200
Glucose calories (kcal)	480	720	960	1200
Lipid calories (kcal)	400	600	800	1000
Non-protein calorie/nitrogen ratio (kcal/g N)	157	157	157	157
Phosphate (mmol)**	3	4.5	6	7.5
Acetate (mmol)	31	47	62	78
Chloride (mmol)	14	20	27	34
pH	6	6	6	6
Osmolarity (mOsm/l)	1100	1100	1100	1100

** Phosphates provided by the lipid emulsion

3 PHARMACEUTICAL FORM

After reconstitution:
Emulsion for infusion.

Appearance prior to reconstitution:
- The lipid emulsion is an homogeneous liquid with a milky appearance,
- The amino acid and glucose solutions are clear and colourless or slightly yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Appearance after reconstitution: homogeneous liquid with a milky appearance

Posology

The dosage will depend on metabolic requirements, energy expenditure and the patient's clinical condition.

The administration may be continued for as long as is required by the patient’s clinical conditions.

In adults

Requirements

Average nitrogen requirements are 0.16 to 0.35 g/kg/day (approximately 1 to 2 g of amino acids/kg/day).

Energy requirements vary depending on the patient's nutritional state and level of catabolism. On average these are 25 to 40 kcal/kg/day.

Maximum daily dose
The maximum daily dose is 40 ml/kg body weight (equivalent to 1.36 g of amino acids, 4.8 g of glucose and 1.6 g of lipids per kg), i.e. 2,800 ml of the emulsion for infusion for a patient weighing 70 kg.

In children above two years old of age

Requirements
Average nitrogen requirements are 0.35 to 0.45 g/kg/day (approximately 2 to 3 g of amino acids/kg/day).

Energy requirements vary depending on the patient's age, nutritional state and level of catabolism. On average these range between 60 and 110 kcal/kg/day.

Posology
The dosage is based on fluid intake and daily nitrogen requirements.
These intakes should be adjusted to take account of the child's hydration status.

Maximum daily dose
The maximum daily dose is 75 ml/kg body weight (equivalent to 2.55 g of amino acids, 9 g of glucose and 3 g of lipids per kg body weight).

As a general rule do not exceed doses of 3 g/kg/day of amino acids and/or 17 g/kg/day of glucose and/or 3 g/kg/day of lipids, except in particular cases.

Method of administration

For instructions for preparation and handling of the emulsion for infusion see section 6.6.

BY INTRAVENOUS ADMINISTRATION THROUGH A CENTRAL VEIN

The recommended duration of the parenteral nutrition infusion is between 12 and 24 hours.

The administration flow rate should be adjusted to take account of the dose being administered, the characteristics of the final mixture being infused, the daily volume intake and the duration of the infusion *(see section 4.4).*

Normally, the flow rate should be increased gradually during the first hour.

Maximum infusion rate

As a general rule, do not exceed 2ml/kg/hour of the emulsion for infusion, i.e. 0.07 g of amino acids, 0.24 g of glucose and 0.08 g of lipids per kg body weight per hour.

Additions

This product does not contain electrolytes, trace elements or vitamins. OliClinomel can be used as such or after supplementation with electrolytes, trace elements or vitamins, when required. *(see sections 4.4 and 6.6).*

Electrolytes

The following concentrations of electrolytes must not be exceeded for each litre of the final mixture *(see also section 4.4).*

- sodium: 150 mmol/l
- potassium: 150 mmol/l
- magnesium: 5.60 mmol/l
- calcium: 5 mmol/l

Trace elements and vitamins

There are authorised formulae for adults, which are mutually exclusive.

Paediatric formulations are required for children.

4.3 Contraindications

Use of OLICLINOMEL is contra-indicated in the following situations:

- in premature neonates, infants and children less than 2 years old, as the calorie-nitrogen ratio and energy supply are inappropriate.
- known hypersensitivity to egg or soya proteins or to any other ingredient.
- severe renal insufficiency without the possibility of haemofiltration or dialysis.

- severe hepatic insufficiency.
- congenital abnormalities of amino acid metabolism.
- severe blood coagulation disorders.
- severe hyperlipidaemia.
- hyperglycemia, which requires more than 6 units insulin/h.

The general contraindications for administrating an intravenous infusion are as follows:

- acute pulmonary oedema, hyperhydration, uncompensated cardiac insufficiency and hypotonic dehydration.
- unstable conditions (for example, following severe post-traumatic conditions, uncompensated diabetes mellitus, acute phase of circulatory shock, acute myocardial infarction, severe metabolic acidosis, severe sepsis and hyperosmolar coma).

4.4 Special warnings and precautions for use

Do not administer through a peripheral vein.

Water and electrolyte equilibration disorders and metabolic disorders must be corrected before starting the infusion.

Because this product does not contain electrolytes, vitamins or trace elements, any such additions must be defined and supplementation provided depending on these requirements. The osmolarity of the final admixture after additions must be defined before administration.

Caution should be exercised in administering OliClinomel to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction.

Strict aseptic conditions must be observed when the catheter is inserted or handled all along infusion.

Specific clinical monitoring is required when an intravenous infusion is started.

Normally, the flow rate should be increased gradually during the first hour.

This medicinal product contains soya oil, which may rarely cause severe hypersensitivity reactions.

The infusion must be stopped immediately if any abnormal signs or symptoms of an allergic reaction (such as fever, shivering, skin rashes or respiratory difficulties) develop.

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 compartments) and if the amino acids solution and the glucose solution are clear.

After opening the bag, the content must be used immediately and must never be stored for a subsequent infusion.

Monitor water and electrolyte balance, serum osmolarity, acid/base balance, blood glucose and liver function tests throughout treatment.

Serum triglyceride concentrations and the ability of the body to remove lipids must be checked regularly.

Serum triglyceride concentrations must not exceed 3 mmol/l during the infusion. These concentrations should not be determined before a minimum of a 3-hour period of continuous infusion.

If a lipid metabolism abnormality is suspected, it is recommended that tests be performed daily by measuring serum triglycerides after a period of 5 to 6 hours without administering lipids. In adults, the serum must be clear in less than 6 hours after stopping the infusion containing the lipid emulsion. The next infusion should only be administered when the serum triglyceride concentrations have returned to normal values.

In addition, regular clinical and laboratory tests are required particularly in cases of:

- amino acid metabolism disorders.
- hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia *(see section 4.3).*
- renal insufficiency, particularly if hyperkalaemia is present; risk of developing or worsening metabolic acidosis and hyperazotemia if extra-renal waste removal is not being performed *(see section 4.3).*
- metabolic acidosis (administration of carbohydrates is not recommended in the presence of lactic acidosis).
- diabetes mellitus: monitoring of glucose concentrations, glucosuria, ketonuria and, where applicable, adjustment of insulin dosages.
- coagulation disorders.
- anaemia.
- hyperlipidaemia (because of the presence of lipids in the emulsion for infusion).

The blood count and coagulation factors must be monitored more carefully during long term administration (several weeks).

Special precautions in paediatrics

Dosage should be adapted according to age, nutritional status and disease and, when necessary, additional energy or protein will be given orally/enterally.

When administered to children more than 2 years old, it is essential to use a bag which has a volume corresponding to the daily dosage.

Vitamin and trace element supplementation is always required. Paediatric formulations should be used.

4.5 Interaction with other medicinal products and other forms of interaction

This emulsion for infusion must not be administered simultaneously with blood through the same infusion tubing because of the possibility of pseudoagglutination.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, blood haemoglobin) if the blood sample is taken before the lipids have been eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

4.6 Pregnancy and lactation

There are not at present sufficient relevant clinical findings to assess the tolerability of the ingredients in OliClinomel in women who are pregnant or breast-feeding.

In the absence of data, the prescriber must assess the risks / benefits before deciding to administer this emulsion either during pregnancy or to women who are breast-feeding.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Potential undesirable effects may occur as a result of inappropriate use: for example, overdose, excessively fast infusion rate *(see sections 4.4 and 4.9).*

The effects which may occur and which require the treatment to be stopped are as follows: hyperthermia, excessive sweating, tremors, nausea, headaches, dyspnoea.

Transient rises in liver function parameters (alkaline phosphatase, transaminases, bilirubin) have been reported, particularly during long term parenteral nutrition lasting several weeks.

Hepatomegaly and jaundice have developed in rare cases.

Reduced ability to remove the lipids contained in OliClinomel may result in a "fat overload syndrome" which may be caused by overdose but may also occur at the start of an infusion according to instructions, and is associated with a sudden deterioration in the patient's clinical condition.

The fat overload syndrome is characterised by: hyperlipidaemia, fever, fatty infiltration, hepatomegaly, anaemia, leucopaenia, thrombocytopaenia, coagulation disorders and coma.

All of these symptoms are reversible when the lipid emulsion infusion is stopped.

Rare cases of thrombocytopaenia have been reported in children receiving lipid infusions.

4.9 Overdose

In the event of inappropriate administration (overdose and/or infusion rate higher than recommended), signs of hypervolaemia and acidosis may occur.

Hyperglycaemia, glucosuria, and a hyperosmolar syndrome may develop if excessive glucose is administered.

An excessively fast infusion or administration of too large a volume may cause nausea, vomiting, shivering and electrolyte disturbances. In such situations the infusion should be stopped immediately.

Reduced ability to remove lipids may result in a "fat overload syndrome", the effects of which are reversible after the lipid infusion is stopped *(see also section 4.8).*

In some serious cases, haemodialysis, haemofiltration or haemo-dia-filtration may be necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition/mixtures ATC code: B05 BA 10.

This is a ternary mixture enabling the nitrogen/energy balance to be maintained from the nitrogen source (L series amino acids) and energy in the form of glucose and essential fatty acids.

This formulation without electrolytes allows individual electrolyte intake to be adapted to meet specific requirements.

The amino acid solution contains 15 L series amino acids (including 8 essential amino acids), which are indispensable for protein synthesis.

The amino acids also represent an energy source, their oxidation resulting in excretion of nitrogen in the form of urea.

The amino acid profile is as follows:

- essential amino acids/total amino acids: 40.5%
- essential amino acids (g)/total nitrogen (g): 2.5
- branched chain amino acids/total amino acids: 19%

The carbohydrate source is glucose (120 g/l).

The lipid emulsion is an association of refined olive oil and refined soya 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 improves the status of their upper derivatives while correcting EFA deficiency.

Olive oil contains significant amount of alpha tocopherol which, combined with a moderate PUFA intake, contributes to improve vitamin E status and reduce lipid peroxidation.

5.2 Pharmacokinetic properties

The ingredients of the emulsion for infusion (amino acids, glucose, lipids) are distributed, metabolised and removed in the same way as if they had been administered individually.

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

The elimination rate of lipid emulsions depends on particle size. Small lipid particles appear to delay clearance whereas they increase lipolysis by lipoprotein lipase.

The size of the lipid particles in the emulsion contained in OliClinomel is close to that of chylomicrons and this emulsion therefore has a similar elimination rate.

5.3 Preclinical safety data

No preclinical studies have been performed on the OliClinomel finished product.

Preclinical studies performed using the solutions of amino acids and glucose contained in OliClinomel of different qualitative compositions and concentrations have not, however, revealed any specific toxicity.

Preclinical toxicity studies performed using the lipid emulsion contained in OliClinomel have identified the changes, which are conventionally found with a high intake of a lipid emulsion: fatty liver, thrombocytopaenia and elevated cholesterol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid emulsion compartment:

- Purified egg lecithin
- Glycerol
- Sodium oleate
- Sodium hydroxide (for pH adjustment)
- Water for injections

Amino acid solution compartment:

- Glacial acetic acid (for pH adjustment)
- Water for injections

Glucose solution compartment:

- Hydrochloric acid (for pH adjustment)
- Water for injections

6.2 Incompatibilities

Do not add other medicinal products or substances to one of the three components of the bag or to the reconstituted emulsion without firstly confirming their compatibility with the mixture of the three components and the stability of the resulting preparation (in particular stability of the lipid emulsion).

Incompatibilities may be produced for example by excessive acidity (low pH) or inappropriate content of divalent cations (Ca^{2+} and Mg^{2+}), which may de-stabilise the lipid emulsion.

Check compatibility with solutions administered simultaneously through the same giving set, catheter or cannula.

Do not administer before, simultaneously with or after blood through the same equipment because of the risk of pseudoagglutination.

6.3 Shelf Life

2 years if the overwrap is not damaged.

It is recommended that the product is used immediately after the non-permanent seals between the 3 compartments have been opened.

The reconstituted emulsion has, however, been shown to be stable for a maximum of 7 days at between +2^{o} and +8^{o}C followed by a maximum of 48 h at temperatures not exceeding + 25^{o}C.

After addition of supplements *(electrolytes, organic phosphate, trace elements, vitamins; see section 6.6):*
For specific admixtures, chemical and physical in-use stability has been demonstrated for 7 days at 2 to 8°C followed by 48 hours below 25°C. From a microbiological point of view, any admixture should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless addition of supplements has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.

Keep container in the outer carton.

For storage of the reconstituted emulsion, *see section 6.3*

6.5 Nature and contents of container

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

The bag is packaged in an oxygen barrier overwrap, which contains an oxygen absorber in a sachet.

The glucose compartment is fitted with an injection site to be used for addition of supplements.

The amino acid compartment is fitted with an administration site for insertion of the spike of the infusion set.
After the seals have been broken, the capacity of the bag is sufficient to enable vitamins, electrolytes and trace elements to be added.

PACK SIZES:

1000 ml in a three-compartment bag (400 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 400 ml of 30% glucose solution (corresponding to 30g/100ml)+ 200 ml of 20% lipid emulsion (corresponding to 20g/100ml))
Carton with 6 bags

1000 ml in a three-compartment bag (400 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 400 ml of 30% glucose solution (corresponding to 30g/100ml) + 200 ml of 20% lipid emulsion (corresponding to 20g/100ml))
1 bag

1500 ml in a three-compartment bag (600 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 600 ml of 30% glucose solution (corresponding to 30g/100ml) + 300 ml of 20% lipid emulsion (corresponding to 20g/100ml))
Carton with 4 bags

1500 ml in a three-compartment bag (600 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 600 ml of 30% glucose solution (corresponding to 30g/100ml) + 300 ml of 20% lipid emulsion (corresponding to 20g/100ml))

2000 ml in a three-compartment bag (800 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 800 ml of 30% glucose solution (corresponding to 30g/100ml) + 400 ml of 20% lipid emulsion (corresponding to 20g/100ml))
Carton with 4 bags

2000 ml in a three-compartment bag (800 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 800 ml of 30% glucose solution (corresponding to 30g/100ml) + 400 ml of 20% lipid emulsion (corresponding to 20g/100ml))
1 bag

2500 ml in a three-compartment bag (1000 ml of 8.5% amino acid solution(corresponding to 8.5g/100ml) + 1000 ml of 30% glucose solution (corresponding to 30g/100ml) + 500 ml of 20% lipid emulsion (corresponding to 20g/100ml))
Carton with 2 bags

2500 ml in a three-compartment bag (1000 ml of 8.5% amino acid solution (corresponding to 8.5g/100ml) + 1000 ml of 30% glucose solution (corresponding to 30g/100ml) + 500 ml of 20% lipid emulsion (corresponding to 20g/100ml))
1 bag

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

a. *To open*

- tear the protective overwrap.
- when present, discard the oxygen absorber sachet after removing the overwrap.
- 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 compartments) and if the amino acids solution and the glucose solution are clear.

b. *Mixing the solutions and the emulsion*

Ensure that the product is at ambient 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 half of their length. Mix by inverting the bag at least 3 times.

c. *Preparation of the infusion*

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.

d. *Additions*

Any additions (including vitamins) may be made into the reconstituted mixture (after the non-permanent seals have been opened and the contents of the three compartments have been mixed).

Vitamins may also be added into the glucose compartment before the mixture has been reconstituted (before opening the non-permanent seals and before mixing the solutions and the emulsion).

OliClinomel may be supplemented with:
- electrolytes: stability has been demonstrated up to a total quantity of 150 mmol of sodium, 150 mmol of potassium, 5.6 mmol of magnesium and 5 mmol of calcium per litre of the ternary mixture.
- organic phosphate: stability has been demonstrated for additions of up to 22 mmol per bag.
- trace elements and vitamins: stability has been demonstrated up to the recommended daily dose.

Micro-nutrient additions must be performed under aseptic conditions.

These additions are made into the injection site using a needle:
. prepare the injection site,
. puncture the injection site and inject,
. mix the contents of the bag and the additives.

e. *Administration*

If OliClinomel has been stored at cold temperature, ensure that the product has been brought to room temperature before use.

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

After opening the bag, the content must be used immediately and must never be stored for a subsequent infusion.

For single use only.

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

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 0167/109/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2006

Date of last renewal: 28 February 2006

10 DATE OF REVISION OF THE TEXT

June 2007