IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0167/141/002
Case No: 2075471

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

Transferred from PA0854/001/002.

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

Clinoleic 20 %, emulsion for infusion, plastic bags

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 **15/01/2010**.

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

ClinOleic® 20%, emulsion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 100 ml
Refined olive oil and refined soya bean oil* ..... 20.00 g
corresponding to a content of essential fatty acids ..... 4.00 g

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

Energy content..... 2000 kcal/l (8.36 MJ/l)
Lipid content (olive and soya bean oil) ..... 200 g/l
Osmolarity ..... 270 mOsm/l
pH ..... 6 -8
Density..... 0.986

Phospholipids provide 47 milligrams or 1.5 mmol of phosphorus per 100 ml

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Emulsion for infusion
Milk-like homogeneous liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indicated as a source of lipids for patients requiring parenteral nutrition, when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Clinoleic 20% contains 200 g/l of lipids corresponding to 200 mg/ml.

Route of administration

Intravenous infusion:

- when administered as part of a complete nutrition admixture (with glucose and amino acids) the central or peripheral venous route should be chosen depending on the osmolarity of the final admixture.

- in rare cases, when infused alone as a complementary support to oral or enteral nutrition, ClinOleic 20% can be administered via peripheral vein.

Dosage

IN ADULTS:
The dosage is 1 to a maximum of 2 g lipids/kg/day. The initial infusion rate must be slow and not exceed 0.1 g lipids or 0.5 ml (10 drops) per minute for 10 minutes then gradually increased until reaching the required rate after half an hour.

Never exceed 0.15 g lipids/kg/hour (0.75 ml/kg/hour

	Adults per kg of body weight	Adults for 70 kg
Usual lipid dosage	1 to 2 g/kg/day	70 to 140 g/day
Infused volume of ClinOleic 20%	5 to 10 ml/kg/day	350 to 700 ml/day

IN CHILDREN:
ClinOleic 20% should be administered as a continuous 24h/day infusion.
It is recommended not to exceed a daily dose of 3g-lipids/kg b.w. and an infusion rate of 0.15 g lipids/kg b.w./h.
Daily dose should be increased gradually during the first week of administration.

IN PREMATURE NEWBORNS AND LOW BIRTH WEIGHT INFANTS:
The use of ClinOleic 20% is restricted to premature infants of 28 weeks of gestational age or more.
ClinOleic 20% should be administered as a continuous 24h/day infusion.
The initial daily dose should be 0.5-1.0g lipids/kg b.w. The dose may be increased by 0.5-1.0g lipids/kg b.w. every 24 hours up to a daily dose of 2.0 g lipids/kg b.w.

Usage in nutritive admixtures (with glucose and amino acids)

Lipids present only one component in parenteral nutrition. For a complete parenteral nutrition the concomitant substitution with aminoacids, carbohydrates, electrolytes, vitamins, and trace elements is necessary. Before administration to the patient, the compatibility of the components and stability of the admixture must be checked. Admixing should be accompanied by gentle agitation during preparation under strict aseptic conditions.

“Breaking” or “oiling out” of the emulsion can be visibly identified by accumulation of yellowish droplets or particles in the admixture.

4.3 Contraindications

The use of ClinOleic is contra-indicated in the following situations:
- hypersensitivity to egg protein, soya protein or peanut protein or to any of the active substances or excipients
- severe dyslipidemia and non corrected metabolism disorders including lactic acidosis and uncompensated diabetes,
- severe sepsis
- severe liver disease,
- blood coagulation disorders, thrombophlebitis,
- myocardial infarction

4.4 Special warnings and precautions for use

Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormalities occur, the infusion must be stopped.

The infusion must be stopped immediately if any abnormal signs or symptoms of an allergic reaction (such as sweating, fever, shivering, headache, skin rashes or dyspnoea) develop. This medicinal product contains soya-bean oil and egg phospholipids, which may rarely cause hypersensitivity reactions. Cross-allergic reactions between soya proteins and peanut proteins have been observed.

Plasma triglyceride levels and clearance should be monitored daily. The triglyceride concentration in serum under infusion should not exceed 3 mmol/l. Infusion should only be started when serum triglyceride levels have returned to baseline level.

Reduced ability to remove lipids 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 instruction, the effects of which are usually reversible after the lipid infusion is stopped (see also Section 4.8).

Elevated liver enzymes and cholestasis have been reported with lipid products.

During short-term or long-term intravenous nutrition, alkaline phosphatases and total bilirubin should be checked at regular intervals, depending on the health status of the patient.

Hydroelectrolytic or metabolism disorders should be corrected before ClinOleic 20% administration.

Fat emulsions should be administered simultaneously with carbohydrates and amino acids to avoid occurrence of metabolic acidosis.

The blood sugar, the acid-base balance, electrolytes, and the blood count must be checked at regular intervals.

As for any parenteral infusion, particular attention should be given on water balance, especially in patients with acute oliguria or anuria.

As other lipid emulsions, ClinOleic 20% should be used in extremely premature and/or very low birth-weight infant under the close supervision of a neonatologist. There is clinical experience for ClinOleic 20% infusion time, up to 7 days in neonates and up to 2 months in children.

ClinOleic 20% should be administered with caution in case of neonatal hyperbilirubinemia (total serum bilirubin > 200 µmol/ l). Total bilirubin levels should be monitored closely.

4.5 Interaction with other medicinal products and other forms of interaction

Complete information about incompatibilities is not available.

Never add medication or electrolytes directly to the lipid emulsion. If it is necessary to introduce additives, verify the compatibility and mix thoroughly before administration to the patient. The compatibility with solutions administered simultaneously via a common end section must be ensured.

4.6 Pregnancy and lactation

The safety of administration of ClinOleic 20% during pregnancy and lactation has not been established. Therefore, ClinOleic 20% should not be used during pregnancy and lactation except after special consideration.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Adverse drug reactions (ADRs) that occurred after administration of ClinOleic 20% are presented with their relative frequencies; these include ADRs documented in clinical trials and those from post-marketing reports. ClinOleic was administered to 274 adult patients in the clinical trials and therefore the frequencies of ARs are limited to very common to uncommon, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/100 to <1/1,000); rare (≥1/10,000 to <1/1,000); very rare (≥1/10,000); and unknown (cannot be estimated from the available data).

The most frequent ADRs noted for ClinOleic 20% in clinical trials were nausea/vomiting, which occurred in more that 2% of the patients.

Clinical Trial and Post-Marketing Adverse Drug Reactions Reported for ClinOleic 20%

System Organ Class (SOC)	*Frequency*	*MedDRA Preferred Term*
Blood and lymphatic system disorders	Uncommon	Leukopaenia
	Unknown[1]	Thrombocytopaenia
Gastrointestinal disorders	Common	Nausea, Vomiting
	Uncommon	Abdominal distension, Abdominal pain, Epigastric discomfort
General disorders and administration site conditions	Unknown[1]	Chills
Hepatobiliary disorders	Uncommon	Cholestasis
Immune system disorders	Unknown[1]	Hypersensitivity
Investigations	Common	Mean arterial pressure decreased
	Uncommon	Bilirubin conjugated increased, Blood bilirubin increased, Hepatic enzyme increased, Blood triglycerides increased
Metabolism and nutrition disorders	Common	Hyperglycaemia
Skin and subcutaneous disorders	Unknown[1]	Urticaria
[1] Adverse reaction observed during post-marketing experience: The frequency of post-marketing adverse reactions cannot be estimated from the available data.		

Fat overload syndrome:
Reduced ability to remove the lipids 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. It is characterized by hyperlipidaemia, fever, liver fatty infiltration, hepatomegaly, anaemia, leucopaenia, thrombocytopaenia, coagulation disorders and coma, requiring hospitalisation. All of these symptoms are usually reversible when the lipid emulsion infusion is stopped.

4.9 Overdose

In case of overdosing (an abnormal triglyceride rise under infusion of fat) causing special reactions (general symptoms such as fever or evocating an hemodynamic instability, emesis, algia, liver function abnormalities, hepato or splenomegalia, hemostasis disorders, hyperlipidemia, hypersensitivity) fat infusion should be stopped or if necessary, continued at a reduced dosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: B05BA02

The combination of olive and soybean oils allows a content of fatty acids in an approximate ratio of:

- Saturated fatty acids: 15% (SFA)
- Mono-unsaturated fatty acids: 65% (MUFA)
- Essential Poly-unsaturated fatty acids: 20% (EPUFA)

The moderate level of essential fatty acids (EFA) probably facilitates their utilisation, enables a correct status of EFA upper derivatives and corrects EFA deficiency.
In comparison with soybean oil:

- in preterm infants above 28 weeks of gestational age, treated for 7 days, the higher content in α tocopherol related to the presence of olive oil, results in an improved vitamin E status.
- in children (8 per treatment group) under long-term parenteral nutrition, for 2 months, a better vitamin E / EPUFA ratio results in reduced lipid peroxydation.

These properties have been verified for doses ranging from 1 to 3 g/kg/day.

The high-energy content of the emulsion enables the administration of a large quantity of calories in a small volume.

5.2 Pharmacokinetic properties

Clearance rate of lipid emulsions is dependent on particle size:

Small lipid droplet size tends to delay the clearance, while it improves lipolysis by liprotein lipase.

Clinoleic 20%, which has droplet size close to that of chylomicrons has a similar elimination rate.

5.3 Preclinical safety data

Toxicological studies showed that the product is well tolerated.
Toxicity studies showed the usual modifications due to high intake of lipid emulsions: fat and pigments deposits in the liver, thrombocytopenia, and hypercholesterolemia.

A decrease of lipid peroxidation and improved vitamin E status has been experimentally showed for high intake of Clinoleic 20% compared to soybean emulsions.

One in vitro study performed on human cells, and one in vivo study performed in rats in comparison with soybean oil-based emulsions, have shown that ClinOleic 20%, emulsion for infusion, maintains lymphocyte proliferation, cell activation markers expression, and IL-2 release. The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Egg phosphatides
Glycerol
Sodium oleate
Sodium hydroxide
Water for Injections

6.2 Incompatibilities

Complete information about incompatibilities is not available.

Never add medication or electrolytes directly to the lipid emulsion. If it is necessary to introduce additives, verify the compatibility and mix thoroughly before administration to the patient.

6.3 Shelf Life

18 months in plastic bag in its overwrap.

6.4 Special precautions for storage

Do not store above 25°C
Do not freeze
Keep the container in the outer carton.

6.5 Nature and contents of container

ClinOleic 20% can be packaged:
- in bag container. This bag is a multi-layer plastic bag (EP-SEBS/EVA/EVA2/PCCE) packaged in an oxygen barrier outer packaging. An oxygen absorber/ oxygen indicator is included inside of the overwrap; discard the sachet after removing the overwrap.

Presentations:

In bag:

100 ml in bag: Box of 24 or 10 units.
250 ml in bag: Box of 20 or 10 units.
350 ml in bag: Box of 12 or 10 units.
500 ml in bag: Box of 12 or 10 units.
1000 ml in bag: Box of 6 units.

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

Once opened, use immediately and discard partly used containers.
For single use only

BAG
Before opening the overwrap, check the colour of the Oxygen indicator. Compare it to the reference colour printed next to the OK symbol and depicted in the printed area of the indicator label. Do not use the product if the colour of the oxygen indicator does not correspond to the reference colour printed next to the OK symbol.
a. To open

- Tear the protective overwrap
- Confirm the integrity of the bag
- Use only if the bag is not damaged

b. Positioning the infusion

-Suspend the bag
-Remove the plastic protector from the administration outlet
-Firmly insert the infusion spike into the administration outlet

c. Additions

If it is necessary to introduce additives, verify the compatibility and mix thoroughly before administration to the patient.

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

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Limited
Caxton Way
Thetford
Norfolk IP24 3SE
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 167/141/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 October 2002

Date of last renewal: 28 November 2005

10 DATE OF REVISION OF THE TEXT

January 2010