Baxter

ClinOleic 20%

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 homogenous 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.

Posology:

The posology depends on energy expenditure, the patient's clinical status, body weight, and ability to metabolize ClinOleic 20%, as well as additional energy given orally/enterally. Therefore, the dosage should be individualized and the bag size chosen accordingly.

In Adults:

The posology 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. (body weight) 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.

Method 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.

It is recommended that after opening the bag, the contents should be used immediately, and should not be stored for a subsequent infusion.
The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours, depending on the clinical situation.
Treatment with parenteral nutrition may be continued for as long as it is justified by the clinical situation of the patient. However, when long term administration is required, the benefit/risk ratio should be evaluated regularly in particular in order to schedule the return to oral and/or enteral nutrition.
See instructions on administration, preparation and handling of the emulsion for infusion (Section 6.6)

Usage in nutritive admixtures (with glucose and amino acids):
"Breaking" or "oiling out" of the emulsion can be visibly identified by accumulation of yellowish droplets or particles in the admixture.

4.3 Contra-Indications

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

4.4 Special warnings and special precautions for use

Warnings
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. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean and peanut proteins have been observed.

<u>Infection and Sepsis Complications</u>
Vascular access infection and sepsis are complications that may occur in patients receiving parenteral nutrition particularly in case of poor maintenance of catheters and contaminated solutions.

Immunosuppression and other factors such as hyperglycemia, malnutrition and/or their underlying disease state may predispose patients to infectious complications.
During severe sepsis the infusion of lipid emulsions may interfere with immune resistance and specific caution should be taken to consider benefit/risk for the patient until sepsis treatment has stabilized the patient.
Careful monitoring of signs, symptoms and laboratory test results for fever/chills, leukocytosis and hyperglycemia and frequent checks for technical complications of the access device can help recognize 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 the preparation of the nutritional formula.

<u>Hepatic Insufficiency</u>
Use with caution in patients with hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia.

<u>Hematologic and Thrombophlebitis</u>
Use with caution in patients with coagulation disorders and anaemia. Blood count and

coagulation parameters should be closely monitored.
Thrombophlebitis may develop, particularly if peripheral veins are used. The catheter insertion site must be monitored daily for local signs of thrombophlebitis.

Fat Overload Syndrome

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).

Refeeding Syndrome

ClinOleic 20% is administered as part of a parenteral nutrition regimen. Refeeding severely undernourished patients with parenteral nutrition may result in the refeeding syndrome. The syndrome is characterized by the intracellular shift of potassium, phosphorus, and magnesium as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes, while avoiding overfeeding, can prevent these complications.
Patients at risk of refeeding syndrome include those with anorexia nervosa, chronic malnutrition (due to age or carcinoma), chronic alcoholism, prolonged fasting, or postoperative patients.
Do not make additions directly to the ClinOleic 20% bag.
If ClinOleic 20% is mixed with glucose and/or amino acid solutions, the compatibility should be checked before administration (see Sections 6.2 and 6.6). Formation of precipitates could result in vascular occlusion.

Precautions

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. To avoid air embolism due to possible residual gas contained in the primary bag, do not connect flexible bags in series. Air embolism can result if residual gas in the bag is not fully evacuated prior to administration if the flexible bag is pressurized to increase flow rates.
As for any parenteral infusion, particular attention should be given on water balance, especially in patients with acute oliguria or anuria and in patients with pulmonary edema or heart failure.
Severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders must be corrected before starting the infusion.
Fat emulsions should be administered simultaneously with carbohydrates and amino acids to avoid occurrence of metabolic acidosis.
The blood sugar, serum triglycerides, the acid-base balance, electrolytes, serum osmolarity, kidney function, coagulation parameters and the blood count must be checked at regular intervals. 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. During short-term or long-term intravenous nutrition, alkaline phospha
tases and total bilirubin should be checked at regular intervals, depending on the health status of the patient. Parenteral nutrition should be used with caution in patients with pre-existing liver disease or liver insufficiency. Liver function parameters should be closely monitored in these patients (see below).
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.

Use in Paediatric Population

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.

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 Interactions with Other Medicinal Products and Other Forms of Interaction

Complete information about incompatibilities is not available.
No interaction studies have been performed with ClinOleic 20%.
Olive and soybean oils have a natural content of Vitamin K1 that may counteract the anticoagulant activity of coumarin derivatives, including warfarin.
The lipids contained in this emulsion may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, haemoglobin) if the blood sample is taken before the lipids are eliminated from the serum (these are generally eliminated after a period of 5 to 6 hours without receiving lipids). Refer to the laboratory testing system product information regarding potential assay interference associated with lipemic samples.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 (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000); and unknown (cannot be estimated from the available data).

The most frequent ADRs noted for ClinOleic 20% in clinical trials were nausea/vomiting, and muscle spasm which occurred in more than 2% of the patiens.

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

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency[1]**	**Frequency Percentage or Ratio[1]**
Blood and lymphatic system disorders	Leukopaenia	Uncommon	1 (0.4%)
Metabolism and nutrition disorders	Hyperglycaemia	Common	9 (3.4%)
	Hypoproteinaemia	Common	7 (2.7%)
	Hyperlipidemia	Common	6 (2.3%)
Vascular Disorders	Mean arterial pressure decreased	Common	3 (1.1%)
	Circulatory collapse	Uncommon	1 (0.4%)
	Hypotension	Uncommon	1 (0.4%)
	Hot flush	Uncommon	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	Dyspnea	Uncommon	1 (0.4%)
Gastrointestinal disorders	Vomiting/Nausea	Common	17 (6.5%)
	Abdominal pain	Uncommon	2 (0.8%)
	Abdominal distension	Common	3 (1.1%)
	Epigastric discomfort	Uncommon	1 (0.4%)
Hepatobiliary disorders	Cholestasis	Common	3 (1.1%)
	Cytolytic hepatitis	Uncommon	1 (0.4%)
Musculoskeletal and connective tissue and bone disorders	Muscle spasms	Common	6 (2.3%)
	Back pain	Uncommon	1 (0.4%)
General disorders	Pyrexia	Uncommon	2 (0.8%)
	Asthenia	Common	3 (1.1%)
	Malaise	Uncommon	1 (0.4%)
Investigations	Blood bilirubin increased**	Common	3 (1.1%)
	Liver function test abnormal‡	Common	24 (9.2%)
	Pancreatic enzyme increased	Uncommon	2 (0.8%)
	Blood triglycerides increased†	Common	4 (1.5%)

† Includes reports of Hypertriglyceridemia
‡ Includes reports of Hepatic Function Abnormal, Hepatic Enzyme Increased, Blood Alkaline Phosphatase Increased, Gamma Glutamyl Transferase Increased, Blood Alkaline Phosphatase Abnormal, Gamma Glutamyl Transferase Abnormal ** Includes Bilirubin Conjugated Increased

Post-marketing Adverse Reactions
The following additional 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: Diarrhea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Pruritus
INVESTIGATIONS: International normalized ratio decreased

Class Reactions
Thrombocytopenia

Fat overload syndrome (very rare): Fat overload syndrome has been reported with similar products. Reduced ability to remove the lipids contained in ClinOleic 20% may result in a "fat overload syndrome", which may be caused by overdose, however, the signs and symptoms of this syndrome may also occur at the start of an infusion when the product is administered according to instructions. This syndrome is associated with a sudden deterioration in the patient's clinical condition as is characterised by hyperlipidemia, fever, liver fatty infiltration hepatomegaly, deteriorating liver function, anemia, leukopenia, thrombocytopenia, coagulation disorders and coma, requiring hospitalization. These symptoms are usually reversible when the lipid emulsion infusion is stopped.

4.9 Overdose
A reduced ability to remove the lipids may result in a “fat overload syndrome” which may be caused by overdose, the effects of which are usually reversible after the lipid infusion is stopped (see also Section 4.8).

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.
This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

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 Reg. No. DKI0910700249A1
250 mL in bag Reg. No. DKI0910700249A1

6.6 Special Precautions for Disposal and Other Handling
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
- Discard the oxygen absorber/indicator
- Confirm the integrity of the bag
- Use only if the bag is not damaged and if the emulsion is a homogeneous liquid with a milky appearance

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
Do not make any additions directly to the bag.
Lipids present only one component in parenteral nutrition. For a complete parenteral nutrition the concomitant substitution with amino acids, 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.

d. Administration
After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion.
Do not reconnect any partially used – bag.
Do not connect bags in series in order to avoid the possibility of air embolism due to air contained in the primary bag. Any unused product or waste material and all necessary devices must be discarded.

ON MEDICAL PRESCRIPTION ONLY.
HARUS DENGAN RESEP DOKTER.

7. MANUFACTURER ADDRESS
Baxter S.A.
Boulevard René Branquart 80
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Imported and Marketed by:
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Bekasi - Indonesia

8. MARKETING AUTHORISATION HOLDER
PT. Kalbe Farma Tbk
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Jakarta 10510, Indonesia.

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