Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

ClinOleic® 20%, emulsion for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition per 100 ml

Refined olive oil and refined soybean oil* ..... 20.00 g
corresponding to a content of essential fatty acids ..... 4.00 g
* Mixture of refined olive oil (approximately 80%) and refined soybean oil (approximately 20%)

Energy content ..... 2000 kcal/l (8.36 MJ/l)
Lipid content (olive and soybean oil) ..... 200 g/l
ClinOleic contains 47 milligrams or 1.5 mmol of phosphorus per 100 ml

Excipient with known effect:
Soybean oil-approximately 4g per 100 ml of emulsion.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Emulsion for infusion
Milk-like, homogeneous liquid with odour of non-saturated glycerides

Osmolarity ..... 270 mOsm/l
pH 6-8
Density 0.986

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Source of lipids during parenteral nutrition in situations where oral or enteral feeding 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. and an infusion rate of 0.15g 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 nutritive 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.
The administration flow rate must be adjusted taking into account the dose being administrated, the daily volume intake, and the duration of the infusion (see Section 4.9).
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 benefice/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 hyperlipidaemia and severe disorders of lipid metabolism characterised by hypertriglyceridemia. Lipoid nephrosis and acute pancreatitis if accompanied by hyperlipaemia.

4.4. Special warnings and 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 soybean oil and egg phospholipids. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean 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.

Infection and sepsis complications

Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state. Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral formulations, or poor maintenance of catheters and contaminated solutions. Immunosuppression and hyperglycemia may predispose patients to infectious complications.
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. Careful monitoring of signs, symptoms and laboratory test results (including fever, chills, leukocytosis and hyperglycemia), and frequent checks of the access device for technical complications can help recognize early infections.

Hepatic Insufficiency

Use with caution in patients with hepatic insufficiency. Regular clinical and laboratory tests are required, particularly blood glucose, electrolytes and triglycerides (not exceeding 3 mmol/l during infusion).

Haematologic and thrombophlebitis

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" may be caused by overdose and/or infusion rate higher than recommended. However, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions, e.g. in patients with reduced or limited ability to metabolize the lipids contained in ClinOleic 20%. This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterized by findings such as fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g., coma). The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.
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.
Baxter has not performed any compatibility studies of additions made directly to the ClinOleic 20% emulsion container. Destabilization of the lipid emulsion may result from such additions. If admixture into the ClinOleic 20% emulsion container is deemed necessary, insure that additives are compatible with the emulsion. Any additions to the container should be performed under strict aseptic conditions.
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 microvascular pulmonary emboli.

PRECAUTIONS

As for any parenteral infusion, particular attention should be given on monitoring fluid status, especially in patients with acute oliguria or anuria and in patients with pulmonary oedema 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.
Parenteral nutrition should be used with caution in patients with preexisting liver disease or liver insufficiency. Liver function parameters should be closely monitored in these patients (see below).
Parenteral Nutrition Associated Liver Diseases (PNALD) 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.
Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, ClinOleic 20% should be protected from light until administration is completed (see sections 6.3 and 6.6).

4.5. Interactions with other medicinal products and other forms of interaction

Complete information about interactions is not available.
No interaction studies have been performed with ClinOleic 20%. If it is necessary to introduce medications, verify the compatibility and mix thoroughly before administration to the patient.
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 if the blood sample is taken before the lipids are eliminated.

4.6. Pregnancy and lactation

There is no adequate data from the use of ClinOleic 20% in pregnant and lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing ClinOleic 20%.

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% in clinical trials and those from post-marketing reports are presented. ClinOleic was administered to 274 adult patients in the clinical trials. The most frequent ADRs noted for ClinOleic 20% in clinical trials were nausea/vomiting, which occurred in more than 2% of the patients.
Frequencies of ADRs are presented 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).

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

System Organ Class (SOC)	*MedDRA Preferred Term*	*Frequency*
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Leukopaenia	Uncommon
	Thrombocytopaenia	Unknown
IMMUNE SYSTEM DISORDERS	Hypersensitivity	Unknown
METABOLISM AND NUTRITION DISORDERS	Hyperglycaemia	Common
	Hypoproteinaemia	Common
	Hyperlipidaemia†	Common
VASCULAR DISORDERS	Mean arterial pressure decreased	Common
	Circulatory collapse	Uncommon
	Hypotension	Uncommon
	Hot flush	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnoea	Uncommon
GASTROINTESTINAL DISORDERS	Nausea/Vomiting	Common
	Abdominal distension	Common
	Abdominal pain	Uncommon
	Epigastric discomfort	Uncommon
HEPATOBILIARY DISORDERS	Cholestasis	Common
	Cytolytic hepatitis	Uncommon
	Cholecystitis	Unknown
	Cholelithiasis	Unknown
MUSCULOSKELETAL AND CONNECTIVE TISSUE AND BONE DISORDERS	Muscle spasms	Common
	Back pain	Uncommon
SKIN AND SUBCUTANEOUS DISORDERS	Pruritus	Unknown
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Chills	Uncommon
INVESTIGATIONS	Blood bilirubin increased**	Common
	Liver function test abnormal‡	Common
	Pancreatic enzyme increased	Uncommon
	Blood triglycerides increased	Common

† 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

Fat overload syndrome (very rare)**:** see section 4.4 for more information.

During long-term parenteral nutrition, the following adverse reactions have been observed:

- increase of alkaline phosphatase, transaminases and bilirubin,
- rarely: hepatomegaly and icterus,
- moderate thrombocytopenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il

4.9. Overdose

In the event of fat overload (severe hyperlipidaemia, hepatosplenomegaly with hepatic dysfunctions, thrombocytopenia and respiratory failure) during therapy, stop or if necessary, continue at a reduced dosage the infusion of ClinOleic 20% until plasma triglyceride concentration has returned to baseline (also see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

LIPID EMULSION FOR PARENTERAL NUTRITION

(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) facilitates their utilisation, enables a correct status of EFA upper derivatives and corrects EFA deficiency. This property has 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

At physiologic doses, the elimination kinetics of serum triglycerides of ClinOleic 20% are comparable to those of natural chylomicrons. Fatty acids generated from triglyceride hydrolysis can be used as an energy source, stored in adipose tissue or incorporated in different types of cell membranes, depending on the individual needs.

5.3. Preclinical safety data

The toxicological evaluation of ClinOleic 20% demonstrates good tolerance and a substantial safety margin.

The undesirable side effects (hypercholesterolemia, transient thrombopenia, thromboembolies and fat and pigment deposits in the liver), observed at high dosage, occur with the same frequency as for soybean oil emulsions and are already described in the literature. The composition of ClinOleic contributes in preclinical studies to reduced lipid peroxidation, improved vitamin E status and better lithogenic index compared to soybean oil emulsion therapy.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

– Glycerol
– Egg phosphatides
– Sodium oleate
– Sodium hydroxide (for pH adjustment)
– 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

The expiry date of the product is indicated on the packaging materials

When used in neonates and children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed (see sections 4.4 and 6.6).

After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion.

6.4. Special precautions for storage

Store at a temperature below 25°C

Do not freeze

Keep the container in the outer carton. Store in protective overwrap

For shelf life after first opening see sec. 6.3.

6.5. Nature and contents of container

The solution is supplied in a bag container.

The bag is a multi-layer plastic bag (EP-SEBS/EVA/EVA2/PCCE) packaged in an oxygen barrier outer packaging. An oxygen absorber can be added inside of the overwrap; discard the sachet after removing the overwrap.

Presentations:

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. Instructions for use / handling and disposal

Before opening the overwrap, check the colour of the oxygen indicator affixed to the oxygen absorber. 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
   For single use only
   After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion. Use of a final filter is recommended during administration of all parenteral nutrition solutions, where possible.
   Do not re-connect partially used-bags.
   Do not connect bags in series in order to avoid the possibility of air embolism due to air contained in the primary bag.
   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. Use of vented intravenous administration set with the vent in the open position could result in air embolism.
   Any unused product or waste material and all necessary devices must be discarded.
   One litre containers are bulk source containers for pharmacy use and should not be used for direct intravenous infusion.
   When used in neonates and children below 2 years, protect from light exposure, until administration is completed. Exposure of ClinOleic 20% to ambient light, especially if admixtures include trace elements and vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure (see sections 4.4 and 6.3).

7. LICENSE HOLDER AND MANUFACTURER

LICENSE HOLDER

Remedix Care Ltd.
8 Haorgim St., Ashdod

MANUFACTURER

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8. REGISTRATION NUMBER

122 09 30186

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