Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

Commercial Name : *Combiflex® Lipid peri emulsion for infusion.*

1.2 Strength

Combiflex® Lipid peri has two packing sizes, 1440 ml and 1920 ml. Both contain the same components, Glucose 11 % solution, Amino acid 11.3 % with electrolytes solution and Lipid emulsion 20 %. The composition of the solutions is the same and only the fill volume differs.

1.3 Pharmaceutical Dosage Form

Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Combiflex® Lipid peri is available in a three chamber bag system. Each bag contains the following different volumes depending on the two pack sizes.

Package Unit / Composition	***Combiflex® Lipid peri***	
	1920 ml	**1440 ml**
Glucose (Glucose 11%)	1180 ml	885 ml
Amino acids and electrolytes (11.3%)	400 ml	300 ml
Fat emulsion (Lipid emulsion 20%)	340 ml	255 ml

Each bag contains :

	Combiflex® Lipid peri	
Active ingredients	**1920 ml**	**1440 ml**
Purified soybean oil	68 g	51 g
Glucose monohydrate	143 g	107g
- corresponding to Glucose (anhydrous)	130 g	97 g
Alanine	6.4 g	4.8 g
Arginine	4.5 g	3.4g
Aspartic acid	1.4 g	1.0 g
Glutamic acid	2.2 g	1.7 g
Glycine	3.2 g	2.4 g
Histidine	2.7 g	2.0 g
Isoleucine	2.2 g	1.7 g
Leucine	3.2 g	2.4 g
Lysine hydrochloride	4.5 g	3.4 g
- corresponding to Lysine	3.6 g	2.7 g
Methionine	2.2 g	1.7 g
Phenylalanine	3.2 g	2.4 g
Proline	2.7 g	2.0 g
Serine	1.8 g	1.4 g
Threonine	2.2 g	1.7 g
Tryptophan	0.76 g	0.57 g
Tyrosine	0.092 g	0.069 g
Valine	2.9 g	2.2 g
Calcium chloride 2 H_2O	0.39 g	0.29 g
- corresponding to Calcium chloride	0.30 g	0.22 g
Sodium glycerophosphate (anhydrous)	2.0 g	1.5 g
Magnesium sulphate 7 H_2O	1.3 g	0.99 g
- corresponding to Magnesium sulphate	0.64 g	0.48 g
Potassium chloride	2.4 g	1.8 g
Sodium acetate 3 H_20	3.3 g	2.5 g
- corresponding to Sodium acetate	2.0 g	1.5 g

Corresponding to :

	Combiflex® Lipid peri	
	1920 ml	**1440 ml**
Amino acids	45 g	34 g
Nitrogen	7.2 g	5.4 g
Fat	68 g	51 g
Carbohydrates - Glucose (dextrose)	130 g	97 g
Energy content - total - non protein	1400 kcal 1200 kcal	1000 kcal 900 kcal
Electrolytes - sodium - potassium - magnesium - calcium - phosphate - sulphate - chloride - acetate	43 mmol 32 mmol 5.3 mmol 2.7 mmol 14 mmol 5.3 mmol 62 mmol 52 mmol	32 mmol 24 mmol 4.0 mmol 2.0 mmol 11 mmol 4.0 mmol 47 mmol 39 mmol
Osmolality	approx. 830 mosm/kg water approx. 750 mosmol/l	
pH	approx. 5.6	

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Emulsion for infusion.
Combiflex® Lipid peri consists of a three chamber bag and an over-pouch. An oxygen absorber is placed between the inner bag and the over-pouch. The inner bag is separated into three chambers by peelable seals. The individual chambers contain glucose and amino acid solutions, and fat emulsion, respectively. Glucose and amino acid solutions are clear and almost colourless or slightly yellowish and the fat emulsion is white and homogenous.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The ability to eliminate fat and metabolize glucose should govern the dosage and infusion rate. The dose should be individualized and the choice of bag size should be made with regard to the patient's clinical condition, body weight and nutritional requirements.

Adult patients

The nitrogen requirements for maintenance of body protein mass depend on the patient's condition (e.g. nutritional state and degree of catabolic stress). The requirements are 0.10-0.15 g nitrogen/kg body weight/day in the normal nutritional state or in conditions with mild metabolic stress. In patients with moderate to high metabolic stress with or without malnutrition, the requirements are in the range of 0.15-0.30 g nitrogen/kg body weight/day (1.0-2.0 g amino acid/kg body weight/day). The corresponding commonly accepted requirements are 2.0-6.0 g for glucose and 1.0-2.0 g for fat.

The dose range of 0.10-0.15g N/kg body weight/day (0.7-1.0 g amino acid/kg body weigh/day) and a total energy of 20-30 kcal body weight/day corresponds to approx. 27-40 ml *Combiflex® Lipid peri*/kg body weight /day. The total energy requirement depends on the patient's clinical condition and is often between 20-30 kcal/kg body weight/day. In obese patients the dose should be based on the estimated ideal weight. *Combiflex® Lipid peri* is produced in two sizes intended for patients with moderately increased, basal or low nutritional requirements. To provide total parenteral nutrition, the addition of trace elements, vitamins and supplemental electrolytes may be required.

Children

The ability to metabolize individual nutrients must determine the dosage. In general the infusion for small children (2-10 years) should start with a low dose i.e. 14-28 ml/kg (corresponding to 0.49-0.98 g fat/kg/day, 0.34-0.67 g amino acids/kg/day and 0.95-1.9 g glucose/kg/day) and increased by 10-15 ml/kg/day up to maximum dosage of 40 ml/kg/day. For children over 10 years of age the dosage for adults can be applied. The use of *Combiflex® Lipid peri* is not recommended in children under 2 years of age in whom the amino acid cysteine may be considered conditionally essential.

Infusion rate

The maximum infusion rate for glucose is 0.25 g/ kg body weight/h. Amino acid dosage should not exceed 0.1 g/ kg body weight /h. Fat dosage should not provide more than 0.15 g/ kg body weight/h. The infusion rate should not exceed 3.7 ml/kg body weight/h (corresponding to 0.25 g glucose, 0.09 g amino acids, 0.13 g fat per kg body weight). The recommended infusion period for individual bags of *Combiflex® Lipid peri* is 12-24 hours.

Maximum daily dose

40 ml/kg body weight/day. This is equal to one bag (largest size) to a 48 kg-patient and will provide 0.94 g amino acids/ kg body weight/day (0.15 g N/ kg body weight/day), 25 kcal/ kg body weight/day nonprotein energy (2.7 g glucose/ kg body weight/day and 1.4 g fat/ kg body weight/day). The maximum daily dose varies with the clinical condition of the patient and may even change from day to

day.

Method and duration of administration

Intravenous infusion only into a peripheral vein. Infusion may be continued for as long as required by the patient's clinical condition. In order to minimize the risk of thrombophlebitis for peripheral application, daily rotation of infusion site is recommended.

4.3 Contraindications

- Hypersensitivity to egg-, soya- or peanut protein or to any of the active substances or excipients.
- Severe hyperlipaemia.
- Severe liver insufficiency.
- Severe blood coagulation disorders.
- Inborn errors of amino acid metabolism.
- Severe renal insufficiency without access to hemofiltration or dialysis.
- Acute shock.
- Hyperglycemia, which requires more than 6 units insulin/h.
- Pathologically elevated serum levels of any of the included electrolytes.
- General contraindications to infusion therapy: acute pulmonary edema, hyper hydration and decompensated cardiac insufficiency and hypotonic dehydration.
- Haemophagocytotic syndrome.
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes, acute myocardial infarction, metabolic acidosis, severe sepsis and hyperosmolar coma).
- Infants and children under 2 years of age.

4.4 Special warnings and precautions for use

- The ability to eliminate fat should be monitored. It is recommended that this is done by measuring serum triglycerides after a fat-free period of 5-6 hours.
- The serum concentration of triglycerides should not exceed 3 mmol/l during infusion.
- The bag size, specially the volume and the quantitative composition, should be carefully chosen. These volumes should be adjusted according to the hydration and nutritional status of the children. One reconstituted bag is for single use.
- Disturbances of the electrolyte and fluid balance (e.g. abnormally high or low serum levels of the electrolytes) should be corrected before starting the infusion.
- Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormal sign occur, the infusion must be stopped. Since an increased risk of infection is associated with the use of any central vein, strict aseptic precautions should be taken to avoid any contamination during catheter insertion and manipulation.
- *Combiflex® Lipid peri* should be given with caution in conditions of impaired lipid metabolism due to renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (with hypertriglyceri - daemia) or sepsis. If *Combiflex® Lipid peri* is given to patients with these conditions, close monitoring of serum triglyceride concentrations is mandatory.

- Serum glucose, electrolytes and osmolarity as well as fluid balance, acid-base status and liver enzyme tests (alkaline phosphatase, ALT, AST) should be regularly monitored.
- Blood cell count and coagulation should be monitored when fat is given for a longer period.
- In patients with renal insufficiency, the phosphate and potassium intake should be carefully controlled to prevent hyperphosphataemia and hyperkalemia.
- The amount of indivisaul electrolytes to be added is governed by the clinical condition of the patient and by frequent monitoring of serum levels.
- This emulsion is free of vitamins and trace-elements. The addition of trace elements and vitamins is always required.
- Parenteral nutrition should be given with caution to patients with metabolic acidosis (e.g. lactic acidosis), increased serum osmolarity or those in need of fluid resuscitation.
- *Combiflex® Lipid peri* should be given with caution to patients with a tendency towards electrolyte retention.
- Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should be lead to immediate interruption of the infusion.
- The fat content of *Combiflex® Lipid peri* may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, Hb) if blood is sampled before fat has been adequately cleared from the bloodstream. Fat is cleared after a fat-free interval of 5-6 hours in most patients.
- This medicinal product contains soya-bean oil and egg phospholipids, which may rarely cause allergic reactions. Cross allergic reaction has been observed between soy-bean and peanut.
- Intravenous infusion of amino acids may be accompanied by increased urinary excretion of trace elements, particularly zinc. Additional supplements of trace elements may be required in patients requiring long-term intravenous nutrition.
- In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary edema and congestive heart failure. In addition, decreases in the serum concentrations of potassium, phosphorus, magnesium and water soluble vitamins may occur within 24 to 48 hours. Careful and slow initiation of parenteral nutrition is recommended together with close monitoring and appropriate adjustments of fluid, electrolytes, minerals and vitamins.
- *Combiflex® Lipid peri* should not be given simultaneously with blood or blood products in the same infusion set due to the risk of pseudoagglutination.
- In patients with hyperglycaemia, administration of exogenous insulin might be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Some drugs, like insulin, may interfere with the body's lipase system. This kind of interaction seems, however, to be of only limited clinical importance. Heparin given in clinical doses causes a transient release of lipoprotein lipase into the circulation. This may result initially in increased plasma lipolysis followed by a transient decrease in triglyceride clearance. Soya-bean oil has a natural content of vitamin K_1. This may interfere with the therapeutic effect of coumarin derivatives which should be closely monitored in patients treated with such drugs. There are no clinical data to show that any of the above mentioned interactions are of definite

clinical relevance.

4.6 Pregnancy and lactation

No specific studies have been performed to assess the safety of *Combiflex® Lipid peri* in pregnancy and lactation. The prescriber should consider the benefit/risk relationship before administering *Combiflex® Lipid peri* to pregnant or breast feeding women.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The infusion may cause a rise in body temperature (incidence <3%) and, less frequently, shivering, chills and nausea/vomiting (incidence <1%). Transient increases in liver enzymes during intravenous nutrition have also been reported. As with all hypertonic solutions for infusion, thrombophlebitis may occur if peripheral veins are used. Reports of other undesirable effects in conjunction with the included components are extremely rare. Hypersensitivity reactions (anaphylactic reaction, skin rash, urticaria), respiratory symptoms (e.g. tachypnoea) and hyper/hypotension have been described. Haemolysis, reticulocytosis, abdominal pain, headache, nausea, vomiting, tiredness and priapism have been reported.

Fat overload syndrome
An impaired capacity to eliminate the fat component in *Combiflex® Lipid peri* may lead to the fat overload syndrome. This may occur as a result of overdosage, but also at recommended rates of infusion, in association with a sudden change in the patient's clinical condition resulting in severe renal or hepatic impairment. The fat overload syndrome is characterized by hyperlipidaemia, fever, fat infiltration, hepatosplenomegaly, splenomegaly, anaemia, leucopenia, thrombocytopenia, blood coagulation disorders and coma. These changes are invariably reversible on discontinuation of the fat infusion.

4.9 Overdose

See 4.8, "Fat overload syndrome".
Nausea, vomiting and sweating have been observed during infusion of amino acids at rates exceeding the recommended maximum rate. If symptoms of overdose occur, the infusion should be slowed down or discontinued. Additionally, overdose might cause fluid overload, electrolyte imbalances, hyperglycemia, and hyperosmolality. In some rare serious cases, haemodialysis, haemofiltration or haemo-diafiltration may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code : B05BA10

Fat emulsion

The fat emulsion used in *Combiflex*® *Lipid peri*, provides essential and nonessential long-chain fatty acids for energy metabolism and the structural integrity of cell membranes. The fat emulsion in the recommended dosage does not cause haemodynamic changes. No clinically significant changes in pulmonary function have been described when FAT EMULSION is used at appropriate infusion rates. The transient increase in liver enzymes observed in some patients on parenteral nutrition is reversible and disappears when parenteral nutrition is discontinued. Similar changes are also seen in parenteral nutrition without fat emulsions.

Amino acids and electrolytes

Amino acids are constituents of protein in ordinary food. They are utilized for tissue protein synthesis and any surplus is channeled to a number of metabolic pathways. Studies have shown a thermogenic effect of amino acid infusion.

Glucose

Glucose has no pharmacodynamic effects apart from contributing to maintain or replete the normal status.

5.2 Pharmacokinetic properties

Fat emulsion

Fat emulsion has biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, Fat emulsion, does not contain cholesterol esters or apolipoproteins, while its phospholipid content is significantly higher. Fat emulsion is eliminated from the circulation by a pathway similar to that of endogenous chylomicrons. The exogenous fat particle is primarily hydrolysed in the circulation and taken up by LDL receptors both peripherally and in the liver. The elimination rate is determined by the composition of the fat particles, the patient's nutritional and clinical status, and the rate of infusion. In healthy volunteers, the maximum clearance rate of Fat emulsion after fasting overnight is equivalent to 3.8 +1.5 g of triglycerides per kg body weight per 24 hours. Both the elimination and the oxidation rates are dependent on the patients clinical condition; elimination is faster and oxidation rates increased in septic states and following trauma, while patients with renal failure or hypertriglyceridaemia have lower rates of elimination and oxidation.

Amino acids and elextrolytes

The principal pharmacokinetic properties of the infused amino acids and electrolytes are essentially the same as for amino acids and electrolytes supplied by ordinary food. However, the amino acids of dietary protein first enter the portal vein and then the systemic circulation, while intravenously infused amino acids reach the systemic circulation directly.

Glucose
The pharmacokinetic properties of infused glucose are essentially the same as those of glucose supplied by ordinary food.

5.3 Preclinical safety data

Preclinical safety studies with *Combiflex® Lipid peri* have not been performed. However, preclinical safety studies with fat emulsion, amino acid solutions and glucose, either individually or mixed in various compositions and concentrations, confirm satisfactory tolerance with minimal adverse effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Purified egg phospholipids.
- Glycerol.
- Sodium hydroxide.
- Acetic acid, glacial.
- Water for injections.

6.2 Incompatibilities

Combiflex® Lipid peri may only be mixed with other medicinal products for which compatibility has been documented. See section 6.6 Instruction for use/handling.

6.3 Shelf life

24 month in the over pouch.

Shelf life after mixing
After breaking the seals, chemical and physical in-use stability of the mixed three chamber bag has been demonstrated for 24 hours at 25°C.

6.4 Special precautions for storage

Do not store above 25°C. Store in over pouch. Do not freeze.

After mixing with Additives
After opening the peelable seals and mixing of the three solutions, additions can be made via medication port. From a microbiological point of view the product should be used immediately when addition have been made. If not used immediately, the in-use storage time and conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2-8°C. If storage can not be avoided and provided that additions are made under controlled and validated aseptic conditions the mixed emulsion may be stored up to 6 days at 2-8°C before being used. After removal from storage at 2-8°C, the admixture should be infused within 24 hours.

6.5 Nature and contents of container

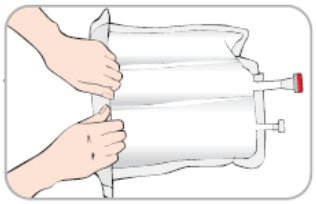
The container consists of a multichamber inner bag and an overpouch. The inner bag is separated into three chambers by peelable seals. An oxygen absorber is placed between the inner bag and the overpouch. The inner bag is made of a multilayer polymer film and it consists of CT-800 film and MT-400 tube. CT-800 film is a three-layered polymer film. The outer layer consists of homo polypropylene. The middle layer consists of soft polypropylene and the inner layer consists of polypropylene, polyethylene and elastomer. MT-400 tube is a three-layer polypropylene/elastomer/polyethylene based tube that is co-extruded with primary bag. It is designed as port tube which is equipped with Infusion, Medication and Close Tip. The infusion and medication tip is equipped with a synthetic isoprene (latex- free) stopper.

Pack sizes : 4 X 1440 ml, 2 X 1920 ml.

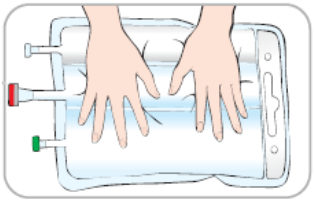
6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only.

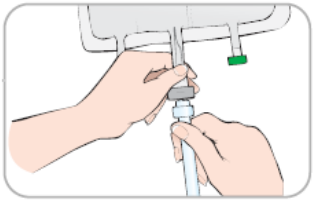
- Preparation: Remove the outer wrap and put the bag flat.



- Squeezing: Break the partition by rolling the hanger part to mix the solutions.



- Mixing: Shake the bag to blend the solution of amino acid, glucose and lipid uniformly.



- Infusion: Before connecting the I.V. set, remove the cap of Infusion Port and infuse the solution into peripheral or central vein.

Do not use if package is damaged. The contents of the three separate chambers have to be mixed before use. After separation of the peelable seals the bag should be inverted on a number of occasions to ensure a homogenous mixture. Use only if the amino acids and glucose solutions are clear and almost colourless or slightly

yellowish and if the fat emulsion is white and homogenous.

Compatibility : Additives

- Only medicinal or nutritional solutions for which compatibility has been documented may be added to *Combiflex® Lipid peri.*
- Addition should be made aseptically.
- Mixing data are delivered upon request.
- Any mixture remaining after infusion must be discarded.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

Not Applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

September 25, 2023