SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

Kabiven® Peripheral

Emulsion for infusion

COMPOSITION

Kabiven Peripheral is a sterile emulsion for infusion available in a three chamber bag system. Each bag contains the following different volumes depending on the three pack sizes.

	2 400 ml	**1 920 ml**	**1 440 ml**
Glucose 11 %	1 475 ml	1 180 ml	885 ml
Vamin 18 Novum	500 ml	400 ml	300 ml
Intralipid 20 %	425 ml	340 ml	255 ml

This corresponds to the following total compositions:

Active ingredients per:	**2 400 ml**	**1 920 ml**	**1 440 ml**
Purified soybean oil	85 g	68 g	51 g
Glucose monohydrate	178 g	143 g	107 g
- corresponding to glucose (anhydrous)	162 g	130 g	97 g
Alanine	8,0 g	6,4 g	4,8 g
Arginine	5,6 g	4,5 g	3,4 g
Aspartic Acid	1,7 g	1,4 g	1,0 g
Glutamic acid	2,8 g	2,2 g	1,7 g
Glycine	4,0 g	3,2 g	2,4 g
Histidine	3,4 g	2,7 g	2,0 g
Isoleucine	2,8 g	2,2 g	1,7 g
Leucine	4,0 g	3,2 g	2,4 g
Lysine hydrochloride	5,6 g	4,5 g	3,4 g
- corresponding to lysine	4,5 g	3,6 g	2,7 g
Methionine	2,8 g	2,2 g	1,7 g
Phenylalanine	4,0 g	3,2 g	2,4 g
Proline	3,4 g	2,7 g	2,0 g
Serine	2,2 g	1,8 g	1,4 g
Threonine	2,8 g	2,2 g	1,7 g
Tryptophan	0,95 g	0,76 g	0,57 g
Tyrosine	0,12 g	0,092 g	0,069 g
Valine	3,6 g	2,9 g	2,2 g
Calcium chloride $2H_2O$	0,49 g	0,39 g	0,29 g
- corresponding to Calcium chloride	0,37 g	0,30 g	0,22 g
Sodium glycerophosphate (anhydrous)	2,5 g	2,0 g	1,5 g
Magnesium sulphate $7H_2O$	1,6 g	1,3 g	0,99 g
- corresponding to Magnesium sulphate	0,8 g	0,64 g	0,48 g
Potassium chloride	3,0 g	2,4 g	1,8 g
Sodium acetate $3H_2O$	4,1 g	3,3 g	2,5 g
- corresponding to Sodium acetate	2,4 g	2,0 g	1,5 g

Corresponding to:	**2 400 ml**	**1 920 ml**	**1 440 ml**
Amino acids	57 g	5 g	34 g

- Nitrogen	9,0 g	7,2 g	5,4 g
Fat	85 g	68 g	51 g
Carbohydrates			
- Glucose (anhydrous)	162 g	130 g	97 g
Energy content:			
- total (kcal) approx.	1 700	1 400	1 000
- non protein (kcal) approx.	1 500	1 200	900
Electrolytes:			
- sodium	53 mmol	43 mmol	32 mmol
- potassium	40 mmol	32 mmol	24 mmol
- magnesium	6,7 mmol	5,3 mmol	4,0 mmol
- calcium	3,3 mmol	2,7 mmol	2,0 mmol
- phosphate[1]	18 mmol	14 mmol	11 mmol
- sulphate	6,7 mmol	5,3 mmol	4,0 mmol
- chloride	78 mmol	62 mmol	47 mmol
- acetate	65 mmol	52 mmol	39 mmol

Osmolality approx. 830 mosm/kg water
Osmolarity approx. 750 mosmol/l
pH approx. 5,6
[1] Contribution is from both Intralipid® and Vamin 18 Novum
Contains sugar (as Glucose 100 g, Glicerol 4,4 g)

PHARMACOLOGICAL CLASSIFICATION

A 25.2 Other nutrients

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Fat emulsion

The fat emulsion provides essential and non-essential long-chain fatty acids for energy metabolism and the structural integrity of cell membranes.

Amino acids and electrolytes

The amino acids, constituents of protein in ordinary food, are utilised for tissue protein synthesis and any surplus is channeled towards gluconeogenesis. Infusions of amino acids are associated with small increases in metabolic rate and thermogenesis.

Pharmacokinetic properties

Fat emulsion

The fat emulsion has biological properties similar to those of endogenous chylomicrons.

The fat emulsion does not contain cholesterol esters or apolipoproteins, while its phospholipid content is significantly higher.

The fat emulsion is eliminated from the circulation via a pathway similar to that of endogenous chylomicrons. The exogenous fat particle is primarily hydrolysed in the circulation and taken up by LDL receptors peripherally and by 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 the 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 patient's clinical condition; elimination is faster and oxidation rates increased in septic states and following trauma, while patients with renal failure and hypertriglyceridaemia have lower rates of elimination and oxidation.

Amino acids and electrolytes

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.

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to egg-, soy- 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 haemofiltration or dialysis

Acute shock

Hyperglycaemia, which requires more than 6 units insulin/h

Pathologically elevated serum levels of any of the included electrolytes

General contra-indications to infusion therapy: acute pulmonary oedema, hyperhydration, 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.

WARNINGS AND SPECIAL PRECAUTIONS

Fat overload syndrome:

An impaired capacity to eliminate fat may lead to the fat overload syndrome as a result of overdosage, but can also occur 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 characterised by hyperlipidaemia, fever, hepatomegaly, splenomegaly, anaemia, leucopenia, thrombocytopenia, blood coagulation disorders and coma. All symptoms are usually reversible if the infusion is discontinued.

Kabiven Peripheral should be given with caution in conditions of impaired lipid metabolism due to renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (with hypertriglyceridemia) and sepsis. If Kabiven Peripheral is given to patients with these conditions, close monitoring of serum triglyceride concentrations is mandatory.

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, especially the volume and the quantitative composition, should be carefully chosen. These volumes should be adjusted according to the hydration and nutritional status of the child.

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 immediately.

Kabiven Peripheral should be used with caution in patients in whom the amino acid cysteine may be considered as essential or conditionally essential.

Serum glucose, electrolytes and osmolarity as well as fluid balance, acid-base status and liver enzyme tests should be monitored regularly.

Blood cell count and coagulation status should be monitored when fat is given for a period longer than 7 days.

In patients with renal insufficiency, the phosphate and potassium intake should be carefully controlled to prevent hyperphosphataemia and hyperkalaemia.

The amount of individual electrolyte to be added, is decided upon by the clinical condition of the patient and by frequent monitoring of serum levels.

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. Kabiven Peripheral should be given with caution to patients with a tendency towards electrolyte retention.

Any sign or symptom of anaphylactic reaction necessitates interruption of the infusion.

The fat content of Kabiven Peripheral 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 soya-bean and peanut.

Intravenous infusion of amino acids may be accompanied by increased urinary excretion of trace elements, particularly zinc.

In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary oedema and congestive heart failure. In addition, decreases in the serum concentrations of potassium, phosphorous, 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.

Kabiven Peripheral should not be given simultaneously with blood or blood products in the same infusion set.

In patients with hyperglycaemia, administration of exogenous insulin might be necessary.

Peripheral infusion:

Thrombophlebitis does occur if peripheral veins are used for infusions. Several factors contribute to the incidence of thrombophlebitis. These include the type of cannula used and its diameter and length, the duration of infusion, pH and osmolarity of infusates, infection and the number of manipulations. It is recommended that venous access sites for peripheral TPN should not be used for other intravenous additives or solutions.

INTERACTIONS

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.

Soybean oil has a natural content of vitamin K1. This may interfere with the therapeutic effect of coumarin derivatives which should be closely monitored in patients treated with such drugs.

HUMAN REPRODUCTION

No specific studies have been performed to assess the safety of Kabiven Peripheral in pregnancy and lactation. The prescriber should consider the benefit/risk relationship before administering Kabiven Peripheral to pregnant or breast-feeding women. Safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

The ability to eliminate fat and metabolize glucose should govern the dosage and infusion rate (See "Warnings" and "Special precautions").

The dose should be individualised 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. 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 total energy requirement depends on the patient's clinical condition and is most often between 20 – 30 kcal/kg body weight/day. In obese patients the dose should be based on the estimated ideal weight.

Kabiven Peripheral is produced in three 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 is required.

The dose range of 0,10 - 0,15 g nitrogen/kg body weight/day (0,7 - 1,0 g amino acid/kg body weight/day) and a total energy of 20 – 30 kcal/body weight/day correspond to approx. 27 – 35 ml Kabiven Peripheral/kg body weight/day.

It should be borne in mind that the energy and nutrient requirements may not be met by Kabiven Peripheral depending on the metabolic status of the patients.

Children:

The ability to metabolise 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/day (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 a maximum dosage of 35 ml/kg/day.

For children over 10 years of age the dosage for adults can be applied.

The use of Kabiven Peripheral is not recommended in children under 2 years of age in whom the amino acid cystine may be considered conditionally essential.

Infusion rate:

The maximum infusion rate for glucose is 0,25 g/kg body weight/hour.

Amino acid dosage should not exceed 0,1 g/kg body weight/hour.

Fat dosage should not provide more than 0,15 g/kg body weight/hour.

The infusion rate should not exceed 3,7 ml per kg body weight per hour (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 Kabiven Peripheral is 12 – 24 hours.

The maximum daily dose varies with the clinical condition of the patient and may even change from day to day. The maximum daily dose is 35 ml/kg/day. This is equal to one bag (largest size) to a 64 kg-patient.

A 35 ml/kg/day dose will provide approximately 0,96 g amino acids/kg/day (0,16 g N/kg body weight/day) and 25 kcal/kg/day non-protein energy (2,7 g glucose/kg body weight/day and 1,4 g fat/kg body weight/day).

It should be borne in mind that the energy and nutrient requirements may not be met by Kabiven Peripheral depending on the metabolic status of the patients.

Method and duration of administration: Intravenous infusion 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, or cyclic TPN (TPN administered over 12-18 hours instead of continuously over 24 hours) is recommended.

Instructions for use/handling:

Do not use if package is damaged. After inspection of the integrity indicator, the overpouch must be removed. The contents of the three separate chambers must be mixed before use.

To ensure a homogenous admixture, the bag should be inverted repeatedly immediately before the infusion.

Use only if the amino acids and glucose solutions in their separate chambers are clear and colourless or slightly yellow and the fat emulsion is white and homogenous.

Once an infusion is disconnected from the patient, the bag with any remaining emulsion should be discarded.

From a microbiological point of view the product should be used immediately after additions 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 not be longer than 24 hours at 2 - 8°C.

The 24 hour stability period is provisional to the addition of the additives under controlled and validated aseptic conditions. Compatibility with calcium chloride, Soluvit Novum and Vitalipid Novum Adult has been proven.

Shelf life after mixing:

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

SIDE EFFECTS

General disorders:

Common (< 3 %): rise in body temperature.

Uncommon (< 1 %): shivering, chills.

The following side effects have been reported and the frequencies are unknown: hypersensitivity reactions (anaphylactic reaction, skin rash, urticaria), hypertension, hypotension, headache, tiredness.

Injection site disorders:

Common (< 3 %): thrombophlebitis does occur if peripheral veins are used.

Gastrointestinal disorders:

Uncommon (< 1 %): nausea and vomiting

The following side effect has been reported and the frequency is unknown: abdominal pain.

Hepato-biliary disorders:

The following side effect has been reported and the frequency is unknown: transient increases in liver enzymes during intravenous nutrition have been reported.

Respiratory/thoracic and mediastinal disorders:

The following side-effects have been reported and the frequencies are unknown: respiratory symptoms (e.g. tachypnoea).

Disorders of blood and lymphatic system:

The following side-effects have been reported and the frequencies are unknown: haemolysis and reticulocytosis.

Reproductive disorders, male:

The following side effect has been reported and the frequency is unknown: priapism.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See “Fat overload syndrome” under WARNINGS AND SPECIAL PRECAUTIONS.

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 discontinued.

Additionally, overdose might cause fluid overload, electrolyte imbalances, hyperglycemia, and hyperosmolality.

In the case of serious overdose, haemodialysis, haemofiltration or haemo-diafiltration may be necessary.

IDENTIFICATION

The container consists of a multi-chamber inner bag and an overpouch.

The inner bag is made of polypropylene and separated into three chambers by peelable seals. An oxygen absorber and integrity indicator are placed between the inner bag and the overpouch.

Glucose 11 %: Clear almost colourless solution

Vamin 18 Novum: A clear solution, colourless to slight yellow

Intralipid 20 %: A white homogenous emulsion

After mixing: A white homogenous emulsion

If creaming (separation of phases of the emulsion) takes place, it can be easily dispersed by inverting the bag and mixing thoroughly.

PRESENTATION

Clear, colourless bags in the following sizes: 2 400 ml, 1 920 ml and 1 440 ml.

Each bag contains an oxygen absorber consisting of an iron powder in a highly oxygen permeable polymer sachet. The integrity indicator, Oxalert™, consisting of an oxygen indicating transparent aqueous solution will change colour if the integrity of the overpouch is broken. The bags are overpouched with Oxnil™ R 1 375 or HVL 9 003 and consists of three layers.

The inner bag is made of a multilayer polymer film, alternatively Excel or Biofine.

The Excel inner bag consists of three layers. The inner layer consists of poly(propylene/ethylene) copolymer and styrene/ethylene/butylene/styrene thermoplastic elastomer (SEBS). The middle layer consists of SEBS and the outer layer consists of copolyester-ether. The infusion port is equipped with a polyolefine cap. The additive port is equipped with a synthetic polyisoprene (latex-free) stopper.

The Biofine inner bag film consists of poly(propylene-co-ethylene), synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) and synthetic rubber poly(styrene-block-isoprene) (SIS).

The infusion and additive ports are made are made of polypropylene and synthetic rubber poly[styrene-block-(butyl-co-ethylene)] (SEBS) and equipped with synthetic polyisoprene (latex-free) stoppers. The blind port, which is only used during manufacturing, is made of polypropylene equipped with a synthetic polyisoprene (latex-free) stopper.

STORAGE INSTRUCTIONS

Unmixed product: Store at or below 25 °C in overpouch. **Do not freeze**.

Mixed product: Store for 48 hours at or below 25 °C or refrigerate for 6 days at 2 – 8 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

38/25.2/0165

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