Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kabimix 11

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2000 ml of the admixture contains

Active ingredients		
Purified Soybean Oil Ph. Eur.	78.00	g
Glucose monohydrate Ph. Eur	256.00	g
corresponding to		
Glucose (anhydrous)	233.00	g
Alanine Ph. Eur.	9.30	g
Arginine Ph. Eur.	6.50	g
Aspartic acid Ph. Eur.	1.90	g
Cysteine	0.33	g
Glutamic acid Ph. Eur.	3.30	g
Glycine (Aminoacetic acid) Ph. Eur.	4.60	g
Histidine Ph. Eur.	4.00	g
Isoleucine Ph. Eur.	3.30	g
Leucine Ph. Eur.	4.60	g
Lysine acetate USP	7.40	g
corresponding to:		
Lysine	5.30	g
Methionine Ph. Eur.	3.30	g
Phenylalanine Ph. Eur.	4.60	g
Proline Ph. Eur.	4.00	g
Serine Ph. Eur.	2.60	g
Threonine Ph. Eur.	3.30	g
Tryptophan Ph. Eur.	1.10	g
Tyrosine Ph. Eur.	0.13	g
Valine Ph. Eur.	4.30	g
Calcium glycerophosphate Ph. Eur. (anhydrous)	0.81	g
Sodium glycerophosphate F.P. (anhydrous)	2.51	g
Magnesium chloride $6H_2O$ Ph. Eur.	0.79	g
corresponding to:		
Magnesium chloride	0.37	g
Sodium hydroxide (100%) Ph. Eur.	1.60	g
Potassium hydroxide (86.5%) Ph. Eur.	3.01	g
corresponding to		
Potassium hydroxide (100%)	2.61	g

3 PHARMACEUTICAL FORM

Emulsion for infusion; white, opaque.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

KABIMIX 11 is indicated in patients requiring intravenous nutrition to supply energy, essential fatty acids, essential and non-essential amino acids and electrolytes. KABIMIX 11 is particularly suitable for patients with basal or moderately increased nutritional requirements and/or fluid restriction.

4.2 Posology and method of administration

The ability to eliminate fat should govern the dosage and infusion rate. *See Section 4.4, Fat elimination.*

Adults (Including the Elderly)

The contents of one bag of KABIMIX 11 is recommended to be infused intravenously into a central vein. The recommended infusion time for the content of one bag is 12-24 hours, but the infusion time should not be less than 8 hours.

Children

Age (Years)	Dose (ml/kg)
1-6	50-70
6-12	50-60
12-18	30-40

If there is insufficient volume in the KABIMIX II bag to meet the required paediatric dosage, Kabimix 14 with an identical composition per litre but greater bag volume , may be more suitable.

ADMINISTRATION
KABIMIX 11 can be supplemented with trace elements, vitamins and extra electrolytes in certain ranges according toindividual patient requirements and following recommendations on compatibility from the manufacturer *(see section 6.6).*

MONITORING
Electrolyte, fluid, acid base imbalance and shock should be corrected prior to commencement of intravenous nutrition.

In the metabolic and nutritional management of the seriously ill patient, specific preliminary investigations and continuous monitoring are essential, particularly of electrolyte levels.

Monitoring of vitamin and trace element levels should be included, especially in patients receiving long term intravenous nutrition.

INFUSION OF KABIMIX
1. Use an infusion line without an air filter.
2. Remove protective cap on the infusion port. Insert the infusion spike.
3. Fill the drip chamber as described in manufacturers literature and fill the line with liquid. Set the drip rate or infusion pump.

It is advisable to gradually increase the infusion rate to the desired level over approximately 30 minutes. This prevents metabolic complications. The infusion should be gradually slowed before stopping it, to prevent the patient from developing hypoglycaemia.

4.3 Contraindications

KABIMIX 11 is contraindicated in patients with acute shock and severe disturbances in lipid metabolism such as

pathological hyperlipaemia, inborn errors of amino acid metabolism, irreversible liver damage, severe uraemia when dialysis facilities are not available and hyperosmolar nonketotic diabetic coma.

KABIMIX 11 is contraindicated in patients known to be allergic to soya protein.

4.4 Special warnings and precautions for use

KABIMIX 11 should be given with caution in conditions of impaired lipid metabolism, such as in renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertriglyceridaemic) and sepsis. If KABIMIX 11 is given to patients with these conditions, visual inspection of plasma samples and/or close monitoring of serum triglycerides and liver function is recommended.

KABIMIX 11 may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, Hb, etc.) if blood is sampled before fat has been adequately cleared from the bloodstream. Fat is normally cleared after a fat-free interval of 4-6 hours in most patients.

Intravenous infusion of amino acids is accompanied by increased urinary excretion of the trace elements copper and, in particular, zinc. These losses should be considered and possibly compensated for, particularly during long-term intravenous nutrition.

In patients with renal insufficiency, the phosphate intake should be carefully controlled to prevent accumulation of phosphate in the circulation.

KABIMIX 11 should be given with caution to patients with electrolyte retention.

Severely malnourished patients and patients exposed to a long period of starvation should be given KABIMIX 11 with caution.

Care should be taken in the administration of amino acids to patients with disturbances in protein metabolism.

As with all infusions, care should be taken to avoid complications of catheterisation including air embolism and central venous thrombosis. Strict asepsis should be maintained especially in the immunosuppressed patient.

Care should be exercised in the administration of large volume infusion fluids to patients with cardiac insufficiency.

Potassium replacement therapy should be controlled as plasma potassium levels may not be directly related to tissue levels

FAT ELIMINATION
The ability to eliminate fat should be closely monitored in patients with conditions mentioned in *section 4.4, "Special warnings and precautions for use",* and in patients given KABIMIX 11 for more than one week. This is done by collecting a blood sample after a fat-free clearance period of 4-6 hours. Blood cells are then separated from plasma by centrifugation (1200-1500 rotations per minute, rpm). If the plasma is opalescent, the infusion should be postponed.

The sensitivity of this method is such that hypertriglyceridaemia can pass undetected. Therefore, it is recommended that serum triglyceride concentrations should be measured in patients who are likely to have impaired fat tolerance.

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 in clinical doses causes a transient increase in lipolysis in plasma, resulting in a transient decrease in triglyceride clearance owing to depletion of lipoprotein lipase.

Soybean oil has a natural content of vitamin K_1. This is considered important only for patients treated with coumarin

derivatives which interfere with vitamin K1.

Amino acid solutions may precipitate acute folate deficiency, and folic acid should be given daily.

4.6 Pregnancy and lactation

Animal reproduction studies have not been performed with KABIMIX 11.

There are however published reports of the successful and safe administration of Intralipid, glucose, amino acids and electrolytes during pregnancy in humans.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and operate machines are to be expected.

4.8 Undesirable effects

Undesirable effects with the components of KabiMix are rare. Those that do occur are usually reversible and regress when therapy is discontinued.

Intralipid may cause a rise in body temperature (incidence < 3%) and, less frequently, shivering, chills and nausea/vomiting (incidence < 1%). Nausea, vomiting, flushing and sweating have been observed during infusion of amino acids at rates exceeding the recommended maximal rate.

As with all hypertonic solutions for infusion, thrombophlebitis may occur when peripheral veins are used. Therefore, KABIMIX 11 should not be infused peripherally.

Increased levels of transaminases, alkaline phosphatase and bilirubin have been observed in patients receiving intravenous nutrition. Cholestasis has also been reported. These changes are reversible and usually return to normal when intravenous nutrition is interrupted.

Reports of other adverse events in conjunction with Intralipid infusions are extremely rare; less than one adverse event per million infusions.

Immediate or early adverse events. Hypersensitivity reactions (anaphylactic reaction, skin rash, urticaria), respiratory symptoms (e.g. tachypnoea) and circulatory effects (e.g. hypertension, hypotension) have been described. Haemolysis, reticulocytosis, abdominal pain, headache, tiredness and priapism have been reported.

Delayed adverse events. Thrombocytopenia has been reported if the fat elimination capacity is exceeded. Transient increases in liver tests after prolonged intravenous nutrition have also been noted. The reasons are not clear at present.

Fat overload syndrome. An impaired capacity to eliminate Intralipid may lead to the fat overload syndrome as a result of overdosage, but also at recommended rates of infusion in association with a sudden change in the patients clinical condition, such as renal function impairment or infection.

The fat overload syndrome is characterised by hyperlipaemia, fever, fat infiltration, disorders in various organs and coma. All symptoms are usually reversible if the infusion of Intralipid is discontinued.

4.9 Overdose

In general, significant overdose with KabiMix is unlikely to occur.

If the solution is administered at a rate exceeding that recommended, there is an augmented risk of nausea and vomiting as well as of thrombophlebitis.

See 4.8, "Fat overload syndrome".

There are no specific antidotes for overdosage. In case of suspicion of overdosage the infusion should be stopped.

Emergency procedures should be general supportive measures, respiratory and cardiovascular. Close biochemical monitoring would be essential and specific abnormalities treated appropriately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

INTRALIPID
Intralipid provides essential and non-essential long-chain fatty acids for energy metabolism and apposition in cell membranes.

Intralipid in the recommended dosage does not cause haemodynamic changes. No clinically significant changes in pulmonary function have been described when Intralipid is infused at appropriate rates. The transient increase in liver enzymes seen in some patients on parenteral nutrition including Intralipid is reversible and disappears when parenteral nutrition is discontinued. Similar changes are also seen in parenteral nutrition without fat emulsions.

AMINO ACIDS
The amino acids are utilised for tissue protein synthesis, any surplus being channelled towards hepatic gluconeogenesis. Apart from their nutritive properties, the amino acids should have no specific pharmacodynamic effects when administered at the recommended rates.

Urinary excretion of trace elements. Besides the desired effects of amino acid administration, infusion of amino acids is accompanied by certain other effects, although they are of limited clinical importance. Thus, intravenous feeding including amino acids is accompanied by increased excretion of the essential trace elements, copper and, in particular, zinc. In view of the fact that most trace elements either form an integral part of enzymes or are required as cofactors in order to enhance enzyme activity, it is important to supply adequate trace elements and minerals and vitamins to all patients on prolonged (> 5 days) intravenous feeding. No data are available regarding the time limit given above; it has been set arbitrarily on the basis of clinical experience.

5.2 Pharmacokinetic properties

INTRALIPID

Intralipid has biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, Intralipid does not contain cholesterol esters or apolipoproteins, while its phospholipid content is significantly higher.

Intralipid is eliminated from the circulation via the same pathway as endogenous chylomicrons, at least early on in the catabolism. The exogenous fat particle is 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 nutritional status of the patient, the disease and the rate of infusion. In healthy volunteers, the maximum clearance rate of Intralipid 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 utilisation is increased in postoperative patients and in trauma, while patients with renal failure and hypertriglyceridaemia show lower utilisation of exogenous fat emulsions.

AMINO ACIDS AND ELECTROLYTES

The principle 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. Consequently, the ingestion of protein exposes the liver to higher concentrations of amino acids compared to

other tissues, while this is not the case during intravenous amino acid infusions. Another important difference is that the process of absorption places a physiological limit on the rate of entry, whereas during infusion, this is determined by the infusion rate. The latter is associated with a theoretical risk of hyperaminoacidaemia in connection with excessive rates of infusion.

5.3 Preclinical safety data

No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified egg phospholipids Ph. Eur.
Glycerol (anhydrous) Ph. Eur.
Hydrochloric acid Ph. Eur.
Acetic acid, glacial Ph. Eur.
Water for injections Ph. Eur.

6.2 Incompatibilities

Kabimix 11 may only be mixed with other medicinal products for which compatibility has been documented.

See section 6.6, "Instructions for use/handling".

6.3 Shelf Life

Eight months.

6.4 Special precautions for storage

Store at 2 - 8° C in the outer pouch.

6.5 Nature and contents of container

A 3-litre EVA (ethylene vinyl acetate) plastic bag, overwrapped in an aluminium pouch containing 2000 ml of emulsion.

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

Compatibility

Additives
Only medicinal, nutritional or electrolyte solutions for which compatibility has been documented may be added to Kabimix 11.

Admixture guidelines are available on request from Pharmacia & Upjohn Limited.

Vitamins, trace elements and extra electrolytes are added aseptically to the bag before infusion.

Limits for additions to KABIMIX 11 (per bag)

Addition	**Highest possible amount** *Added*		*Total*	
Vitlipid N Adult*	10.00	ml	10.00	ml
Solivito N*	1.00	vial	1.00	vial
Additrace*	10.00	ml	10.00	ml
Sodium	100.00	mmol	162.00	mmol
Potassium	75.00	mmol	121.00	mmol
Magnesium	3.00	mmol	7.00	mmol
Calcium	6.00	mmol	10.00	mmol
Phosphate	9.00	mmol	30.00	mmol

To ensure a homogenous admixture, the bags should be inverted twice immediately before the infusion.

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Vitlipid N Adult - PA 187/31/1
Solivito N - PA 187/30/1
Additrace - PA 187/29/1

STABILITY

Additives
Chemical and physical stability has been demonstrated for the recommended range of admixtures for 6 days at 2-8°C.

At the ward level: It is generally recommended that additions are made in the hospital pharmacy under controlled and validated aseptic conditions. When additions are made at the ward level using aseptic technique, the bag can be stored for up to 3 hours at 2-8°C.

The infusion should be completed within a maximum of 27 hours from preparation to prevent microbiological contamination. (3 hours at 2-8°C, and 24 hours at room temperature).

Hospital pharmacy: In line with good pharmaceutical practice, admixtures prepared aseptically in the hospital pharmacy should normally be stored for a maximum of 24 hours at 2-8°C prior to use. However, where additions are made under *controlled and validated aseptic conditions*, the admixture may be stored for up to 6 days at 2-8°C before being used. Once removed from 2-8°C, the admixture must be used within 24 hours including infusion time. The maximum storage of the admixture (6 days at 2-8°C + 1 day at room temperature) must be within the 180 days shelflife given for the finished product KABIMIX 11. It is the responsibility of the user to ensure that the admixture is adequately stored prior to use and infused within the required timescale.

Any admixture remaining after an infusion must be discarded

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Limited
Melbury Park
Birchwood
Warrington WA3 6FF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0566/008/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 September 1999

10 DATE OF REVISION OF THE TEXT

September 2003