Package Insert

SCHEDULING STATUS:

S3

PROPRIETARY NAME (and dosage form):

NUTRIFLEX® LIPID SPECIAL (Intravenous infusion)

COMPOSITION:			
	In 1250 ml	**In 1875 ml**	**In 2500 ml**
From upper left compartment			
Glucose H_2O *equivalent to glucose*	180,0 g *198,0 g*	270,0 g *297,0 g*	360,0 g *396,0 g*
Sodium dihydrogen phosphate. $2H_2O$	3,12 g	4,68 g	6,24 g
Zinc acetate. $2H_2O$	8,78 mg	13,17 mg	17,56 mg
From upper right compartment			
Medium chain triglycerides	25,00 g	37,50 g	50,00 g
Soya oil	25,00 g	37, 50 g	50,00 g
From lower compartment			
Isoleucine	4,11 g	6,16 g	8,21 g
Leucine	5,48 g	8,22 g	10,96 g
Lysine HCl *equivalent to lysine*	4,98 g *3,98 g*	7,46 g *5,96 g*	9,95 g *7,95 g*
Methionine	3,42 g	5,13 g	6,84 g
Phenylalanine	6,15 g	9,22 g	12,29 g
Threonine	3,18 g	4,76 g	6,35 g
Tryptophan	1,00 g	1,50 g	2,00 g
Valine	4,51 g	6,76 g	9,01 g

Arginine	4,73 g	7,09 g	9,45 g
Histidine HCl. $2H_2O$ *equivalent to histidine*	2,96 g *2,19 g*	4,44 g *3,29 g*	5,92 g *4,38 g*
Alanine	8,49 g	12,73 g	16,98 g
Aspartic acid	2,63 g	3,94 g	5,25 g
Glutamic acid	6,14 g	9,20 g	12,27 g
Glycine	2,89 g	4,33 g	5,78 g
Proline	5,95 g	8,93 g	11,90 g
Serine	5,25 g	7,88 g	10,50 g
Sodium hydroxide	1,464 g	2,196 g	2,928 g
Sodium chloride	0,473 g	0,710 g	0,946 g
Sodium acetate. $3H_2O$	0,313 g	0,470 g	0,626 g
Potassium acetate	4,611 g	6,917 g	9,222 g
Magnesium acetate. $4H_2O$	1,137 g	1,706 g	2,274 g
Calcium chloride. $2H_2O$	0,779 g	1,168 g	1,558 g
Amino acid content	71,8 g	107,7 g	143,6 g
Total nitrogen content	10 g	15 g	20 g
Carbohydrate content	180,0 g	270,0 g	360,0 g
Lipid content	50,0 g	75,0 g	100,0 g
Energy in the form of lipid [kJ/(kcal)]	1990 (475)	2985 (715)	3980 (950)
Energy in the form of carbohydrate [kJ/(kcal)]	3015 (720)	4520 (1080)	6030 (1440)
Energy in the form of amino acids [kJ/(kcal)]	1170 (280)	1755 (420)	2340 (560)
Non-protein energy [kJ/(kcal)]	5005 (1195)	7510 (1795)	10010 (2390)
Total energy [kJ/(kcal)]	6176 (1475)	9265 (2215)	12350 (2950)
Osmolarity [mOsm/kg]	2090	2090	2090
pH	5,0 – 6,0	5,0 – 6,0	5,0 – 6,0
Electrolyte content (mmol)	In 1250 ml	In 1875 ml	In 2500 ml

Sodium	67,0	100,5	134,0
Potassium	47,0	70,5	94,0
Magnesium	5,3	7,95	10,6
Calcium	5,3	7,95	10,6
Zinc	0,04	0,06	0,08
Chloride	60	90	120
Acetate	60	90	120
Phosphate	20	30	40

PHARMACOLOGICAL CLASSIFICATION:

A. 25 Special Foods

PHARMACOLOGICAL ACTION:

Pharmacodynamics

Lipids

The lipid component of **Nutriflex® Lipid Special** contains equal quantities of soybean oil (long-chain triglycerides, LCT) and medium-chain triglycerides (MCT). Soybean oil consists of more than 50 % of the polyunsaturated fatty acids linoleic acid and α-linolenic acid. MCT are included as a high calorie source.

Carbohydrates

In order to ensure optimal utilization of the amino acids delivered with the nutrient solution, and to improve the emulsion triglyceride utilization, an energy source is required. This can be partly fulfilled by carbohydrates namely glucose monohydrate

Amino acids

Nutriflex® Lipid Special contains all essential amino acids and the non-essential amino acids.

Electrolytes

Nutriflex® Lipid Special contains all the essential electrolytes, i.e. sodium, potassium, magnesium, calcium and phosphate. It also contains the trace element zinc.

INDICATIONS:

Supply of the daily requirement of energy, essential fatty acids, amino acids, electrolytes and fluids during parenteral nutrition for patients with mild to moderately severe catabolism when oral or enteral nutrition is impossible, insufficient or contraindicated.

CONTRA-INDICATIONS:

This product must not be administered in the following conditions:

- Disturbances of amino acid metabolism
- Disturbances of lipid metabolism
- Hypokalaemia; hyponatraemia
- Unstable metabolism e.g. severe post aggression syndrome (an endocrine imbalance with glucose intolerance and peripheral resistance to insulin, which can result in persistent hyperglycaemic states with increased lipolysis and progressive proteolysis), unstabilised diabetes mellitus coma of unknown origin)
- Hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour
- Acidosis
- Intrahepatic cholestasis
- Severe hepatic insufficiency
- Severe renal insufficiency
- Manifest cardiac insufficiency
- Aggravating haemorrhagic diatheses
- Acute myocardial infarction and stroke
- Acute event of thromboembolism, lipid embolism
- Know hypersensitivity to egg or soy-bean protein or to any of the ingredients

On account of its composition **Nutriflex® Lipid Special** should not be used for neonates, infants and children under 2 years of age.

General contra-indications to parenteral nutrition are:

- Unstable circulatory status

- Inadequate cellular oxygen supply
- Fluid overload/overhydration
- Disturbances of the electrolyte and fluid balance
- Acute pulmonary oedema, decompensated cardiac insufficiency

INTERACTIONS:

Some medication, 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 agents.

Solutions containing amino acids, carbohydrate and lipids should not be mixed with other solutions due to the risk for incompatibilities or microbial contamination. Concomitant infusion with other medicines should also be avoided due to the risk of incompatibilities.

PREGNANCY AND LACTATION:

Safety and efficacy have not yet been established. **Nutriflex® Lipid Special** is manufactured with soy-bean oil that contains phytosterols in concentrations that could lead to disturbances of fertility.

Breastfeeding is not recommended if women need parenteral nutrition.

DOSAGE AND DIRECTIONS FOR USE:

The dosage is adjusted according to the patients' individual requirements.

The maximum daily dose is 35 ml/kg body weight, corresponding to

- 2,0 g amino acids/kg body weight per day
- 5,04 g glucose/kg body weight per day
- 1,4 g fat/kg body weight per day

It is recommended that **Nutriflex® Lipid Special** be administered continuously. A stepwise increase of the infusion rate over the first 30 minutes up to the desired infusion rate avoids possible complications.

The maximum rate of infusion is 1,7 ml/kg body weight per hour, corresponding to

- 0,1 g amino acids/kg body weight per hour
- 0,24 g glucose/kg body weight per hour
- 0,07 g fat/kg body weight per hour

For a patient weighing 70 kg this corresponds to an infusion rate of 119 ml/kg body weight per hour. The amount of amino acid administered is then 6,8 g/hour, of glucose 17,1g /hour and of lipid 4,8 g/hour.

In general, it is recommended that the maximum amount of energy should not exceed 40 kcal/ BW per day. If specially indicated e.g. for burned patients higher dosage is possible.

Method of administration

The ready-for-use emulsion is infused into a central vein.

The emulsion should always be brought to room temperature prior to infusion.

Only intact containers, with homogenous fat emulsions after gentle shaking, and clear solutions, are to be used.

Preparation of mixed solution

Remove the bag from its protective pack and proceed as follows:

- Open out the bag and lay on a solid surface
- Open the peel seals to the two upper chambers by using pressure with both hands
- Briefly mix the contents of the bag together

Preparation for infusion

- Fold the two empty chambers backwards
- Hang the mixing bag on the infusion stand by the centre hanging loop

- Remove the protective cap from the run-out port and carry out infusion using the normal technique

Duration of use

The duration of treatment for the indications stated in not limited. During long-term administration of Nutriflex® Lipid Special it is necessary to supply appropriate replacement of trace elements and vitamins.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

Nervous system disorders:

Less frequent: Flushing.

The following side effects have been reported but the frequency is unknown:

Slight increase in temperature, cold feeling, shivering, headache.

Metabolic and nutritional disorders:

The following side effects have been reported but the frequency is unknown:

Loss of appetite; hyperglycaemia.

Blood disorders:

The following side effects have been reported but the frequency is unknown:

Hypokalaemia, hypophosphataemia, hypomagnesaemia, hypermagnesaemia.

Gastrointestinal disorders:

Less frequent: Nausea, vomiting.

Respiratory disorders:

The following side effects have been reported but the frequency is unknown:

Respiratory distress.

Musculoskeletal and bone disorders:

Less frequent: Back ache, pain in the chest.

The following side effects have been reported but the frequency is unknown:

Bone pain and pain in the lumbar area.

Cardiac disorders:

The following side effects have been reported but the frequency is unknown:

Fall or increase in blood pressure.

Immune system disorders:

The following side effects have been reported but the frequency is unknown:

Hypersensitivity reactions (anaphylactic reactions, dermal eruptions).

Skin disorders:

The following side effects have been reported but the frequency is unknown:

Bluish discoloration of the skin due to reduced oxygen content of the blood (cyanosis).

General disorders and administration site conditions:

Frequent: Thrombophlebitis.

The following side effects have been reported but the frequency is unknown:

Infection of the injection site which can lead to septicaemia; irritation at the injection site.

If any of the above mentioned side-effects occur the infusion should be discontinued or, if appropriate, the infusion should be continued at a lower dose level.

Overloading syndrome is associate with the following symptoms: enlargement of the liver with or without jaundice, enlargement of the spleen, fatty infiltration of organs, pathological hepatic function parameters, anaemia, reduction of white cell count, reduction of platelet count, a tendency to haemorrhage and haemorrhages, alterations or reduction in blood coagulation factors, fever, hyperlipaemia, headache, abdominal pain, fatigue.

Special precautions:

Caution should be exercised in cases of increased serum osmolarity.

Nutriflex® Lipid Special should be administered with caution to patient with impaired cardiac or renal function. Disturbances of the fluid, electrolyte or acid-base balance, e.g. hyperhydration, hyperkalaemia, acidosis, should be corrected before the start of infusion. Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration and pulmonary oedema.

The serum triglyceride concentration should be monitored when infusing **Nutriflex® Lipid Special**. Fasting lipaemia should be excluded in patients with suspected disturbances of lipid metabolism before starting infusion. The administration of lipids is contraindicated if there is fasting lipaemia. The presence of hypertriglyceridaemia 12 hours after lipid administration also indicates a disturbance of lipid metabolism.

Nutriflex® Lipid Special should be administered cautiously to patient with disturbances of lipid metabolism, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (with hypertriglyceridaemia) and sepsis. If **Nutriflex® Lipid Special** is given to patients with these conditions, close monitoring of serum triglycerides is mandatory.

Any sign of symptoms of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.

Depending on the patient's metabolic condition, occasional hypertriglyceridaemia or increases of the blood glucose concentration may occur. If the plasma triglyceride concentration rises to more than 3 mmol/L during administration of lipid it is recommended that the infusion rate should be reduced. Should the plasma triglyceride concentration remain above 3 mmol/L the administration should be stopped until the level normalises.

A dose reduction or interruption of administration is also indicated if the blood glucose concentration rises to more than 14 mmol/L (250 mg/dl) when administering the lipid.

The administration of **Nutriflex® Lipid Special** can lead to hyperglycaemia. The blood glucose level should be monitored. If there is hyperglycaemia the rate of infusion should be reduced or insulin should be administered.
Intravenous infusion of amino acids is accompanied by increased urinary excretion of the trace elements, especially copper and, in particular zinc. This should be considered in the dosing of trace elements, especially during long-term intravenous nutrition.

Nutriflex® Lipid Special should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

Moreover monitoring of the serum electrolytes, fluid balance, acid-base balance of blood cell counts, coagulation status and hepatic function are necessary.

The fat content may interfere with certain laboratory measurements (e.g. bilirubin, lactate dehydrogenase, oxygen saturation) if blood is sampled before fat has been adequately cleared from the blood stream.

Substitution of electrolytes, vitamins and trace elements may be necessary as required.

As **Nutriflex® Lipid Special** contains zinc and magnesium, care should be taken when it is co-administered with solutions containing these elements.

As with all intravenous solutions strict aseptic precautions are necessary for the infusion of **Nutriflex® Lipid Special**.

Nutriflex® Lipid Special is a preparation of complex composition. It is, therefore, strongly advisable not to add other solutions.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdose of **Nutriflex® Lipid Special** is not to be expected on proper administration.

Symptoms of fluid and electrolyte overdose

Hypertonic hyperhydration, electrolyte imbalance and pulmonary oedema.

Symptoms of amino acid overdose:

Renal amino acid losses with consecutive amino acid imbalances, sickness, vomiting and shivering.

Symptoms of glucose overdose:

Hyperglycaemia, glycosuria, dehydration, hyperosmolality, hyperglycaemic and hyperosmolar coma.

Symptoms of fat overdose:

Lipid overdose may lead to the overload syndrome, characterised (for example) by fever, headache, abdominal pain, fatigue, hyperlipaemia, hepatomegaly with or without jaundice, splenomegaly, pathological disturbances of liver function, anaemia, reduction if platelet count, reduction in white cell count, hemorrhagic diathesis and haemorrhage, alternation of depression of blood coagulation factors (bleeding time, coagulation time, prothrombin time, etc.). The plasma triglyceride concentration should not exceed 3 mmol/L during infusion.

Emergency treatment, antidotes

Immediate cessation of infusion is indicated in the case of overdose. Further therapeutic measures depend on the particular symptoms and their severity. When infusion is recommenced after the symptoms have declined it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals.

IDENTIFICATION:

Amino acid chamber: Clear, colourless up to faintly straw coloured solution, practically free from part

Glucose chamber: Clear, colourless up to faintly straw coloured solution, practically free from particles.

Fat emulsion chamber: A white, milky oil-in-water emulsion.

PRESENTATION:

Nutriflex® Lipid Special will be manufactured as a transparent colourless, three chamber bag. The two upper compartments of this bag are connected with the lower compartment by peel seams. The bag is

made of a co-extruded film of Polyamide 11 and Polypropylene (V90 film) and is available in the following pack sizes:

625 ml, 1250 ml, 1875 ml and 2500 ml, or

5 x 625 ml, 5 x 1250 ml, 5 x 1875 ml and 5 x 2500 ml packed in a carton.

STORAGE INSTRUCTIONS:

Protect from light and store at or below 25 °C.

Do not freeze. If accidentally frozen, discard the bag.

The emulsion is to be used immediately after mixing. It can be stored for 4 days at 2 – 8 °C and for 48 hours at 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

41/25/0759

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

B Braun Medical (Pty) Ltd.

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2194

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