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Directions for Use

B. Braun Melsungen AG · 34209 Melsungen, Germany

NuTRIflex® Lipid peri emulsion for infusion

Composition

The ready-for-use emulsion for intravenous infusion contains after mixing the chamber contents:

from the upper, left-hand chamber (glucose solution)	in 1000 ml	in 1250 ml	in 1875 ml	in 2500 ml
Glucose monohydrate	70.4 g	88.0 g	132.0 g	176.0 g
equivalent to anhydrous glucose	64.0 g	80.0 g	120.0 g	160.0 g
Sodium dihydrogen phosphate dihydrate	0.936 g	1.170 g	1.755 g	2.340 g
Zinc acetate dihydrate	5.30 mg	6.625 mg	9.938 mg	13.250 mg
from the upper, right-hand chamber (fat emulsion)	in 1000 ml	in 1250 ml	in 1875 ml	in 2500 ml
Soya-bean oil, refined	20.0 g	25.0 g	37.5 g	50.0 g
Medium-chain triglycerides	20.0 g	25.0 g	37.5 g	50.0 g
from the lower chamber (amino acid solution)	in 1000 ml	in 1250 ml	in 1875 ml	in 2500 ml
Isoleucine	1.87 g	2.34 g	3.51 g	4.68 g
Leucine	2.50 g	3.13 g	4.70 g	6.26 g
Lysine hydrochloride	2.27 g	2.84 g	4.26 g	5.68 g
equivalent to lysine	1.81 g	2.26 g	3.39 g	4.52 g
Methionine	1.57 g	1.96 g	2.94 g	3.92 g
Phenylalanine	2.81 g	3.51 g	5.27 g	7.02 g
Threonine	1.46 g	1.82 g	2.73 g	3.64 g
Tryptophan	0.46 g	0.57 g	0.86 g	1.14 g
Valine	2.08 g	2.60 g	3.90 g	5.20 g
Arginine	2.16 g	2.70 g	4.05 g	5.40 g
Histidine hydrochloride monohydrate	1.35 g	1.69 g	2.54 g	3.38 g
equivalent to histidine	1.00 g	1.25 g	1.88 g	2.50 g
Alanine	3.88 g	4.85 g	7.28 g	9.70 g
Aspartic acid	1.20 g	1.50 g	2.25 g	3.00 g
Glutamic acid	2.80 g	3.50 g	5.25 g	7.00 g
Glycine	1.32 g	1.65 g	2.48 g	3.30 g
Proline	2.72 g	3.40 g	5.10 g	6.80 g
Serine	2.40 g	3.00 g	4.50 g	6.00 g
Sodium hydroxide	0.640 g	0.800 g	1.200 g	1.600 g
Sodium chloride	0.865 g	1.081 g	1.622 g	2.162 g
Sodium acetate trihydrate	0.435 g	0.544 g	0.816 g	1.088 g
Potassium acetate	2.354 g	2.943 g	4.415 g	5.886 g
Magnesium acetate tetrahydrate	0.515 g	0.644 g	0.966 g	1.288 g
Calcium chloride dihydrate	0.353 g	0.441 g	0.662 g	0.882 g
Electrolytes [mmol]	in 1000 ml	in 1250 ml	in 1875 ml	in 2500 ml
Sodium	40	50	75	100
Potassium	24	30	45	60
Magnesium	2.4	3.0	4.5	6.0
Calcium	2.4	3.0	4.5	6.0
Zinc	0.024	0.03	0.045	0.06
Chloride	38.4	48	72	96
Acetate	32	40	60	80
Phosphate	6	7.5	11.25	15
	in 1000 ml	in 1250 ml	in 1875 ml	in 2500 ml
Amino acid content [g]	32	40	60	80
Nitrogen content [g]	4.6	5.7	8.6	11.4
Carbohydrate content [g]	64	80	120	160
Lipid content [g]	40	50	75	100

Excipients :
Citric acid monohydrate (for pH adjustment)
Egg lecithin
Glycerol
Sodium oleate
Water for injections

Pharmaceutical form

Emulsion for infusion

Amino acids and glucose solutions: clear, colourless up to straw-coloured solutions
Lipid emulsion: oil-in-water emulsion, milky white

	in 1000 ml	in 1250 ml	in 1875 ml	in 2500 ml
Energy in the form of lipid [kJ (kcal)]	1590 (380)	1990 (475)	2985 (715)	3980 (950)
Energy in the form of carbohydrate [kJ (kcal)]	1075 (255)	1340 (320)	2010 (480)	2680 (640)
Energy in the form of amino acids [kJ (kcal)]	535 (130)	670 (160)	1005 (240)	1340 (320)
Non-protein energy [kJ (kcal)]	2665 (635)	3330 (795)	4995 (1195)	6660 (1590)
Total energy [kJ (kcal)]	3200 (765)	4000 (955)	6000 (1435)	8000 (1910)
Osmolality [mOsm/kg]	950	950	950	950
Theoretical osmolarity [mOsm/l]	840	840	840	840
pH	5.0 - 6.0	5.0 - 6.0	5.0 - 6.0	5.0 - 6.0

Therapeutic indications

Supply of energy, essential fatty acids, amino acids, electrolytes and fluids in the setting of parenteral nutrition of patients in states of mild to moderately severe catabolism when oral or enteral nutrition is impossible, insufficient or contraindicated.

Posology and method of administration

Posology

The dosage is adapted to the patients' individual requirements.
It is recommended that Nutriflex Lipid peri be administered continuously. A stepwise increase of the infusion rate over the first 30 minutes up to the desired infusion rate avoids possible complications.

Adolescents from 14 years of age and adults

The maximum daily dose amounts to 40 ml/kg body weight, corresponding to:
1.28 g amino acids/kg body weight per day
2.56 g glucose/kg body weight per day
1.6 g lipid/kg body weight per day.

The maximum rate of infusion is 2.5 ml/kg body weight per hour, corresponding to:
0.08 g amino acids/kg body weight per hour
0.16 g glucose/kg body weight per hour
0.1 g lipid/kg body weight per hour.

For a patient weighing 70 kg this corresponds to a maximum infusion rate of 175 ml per hour. The amount of substrate administered is then 5.6 g of amino acids per hour, 11.2 g of glucose per hour and 7 g of lipids per hour.

Paediatric population

Newborn infants, infants and toddlers less than two years of age

Nutriflex Lipid peri is contraindicated in newborn infants, infants and toddlers < 2 years of age (see section"Contraindications").

Children from 2 to 13 years of age

The given dosage recommendations are guiding data based on average requirements. The dosage should be individually adapted according to age, developmental stage and illness. For calculation of dosage account must be taken of the hydration status of the paediatric patient.

For children, it might be necessary to start the nutritional therapy with half of the target dosage. The dosage should be increased stepwise according to the individual metabolic capacity up the maximum dosage.

Daily dose for 2 – 4 years of age: 45 ml/kg body weight, corresponding to:
1.44 g amino acids/kg body weight per day
2.88 g glucose/kg body weight per day
1.8 g lipid/kg body weight per day.

Daily dose for 5 – 13 years of age: 30 ml/kg body weight, corresponding to:
0.96 g amino acids/kg body weight per day
1.92 g glucose/kg body weight per day
1.2 g lipid/kg body weight per day.

The maximum rate of infusion is 2.5 ml/kg body weight per hour, corresponding to:
0.08 g amino acids/kg body weight per hour
0.16 g glucose/kg body weight per hour
0.1 g lipid/kg body weight per hour.

Due to the individual needs of paediatric patients, Nutriflex Lipid peri may not cover sufficiently the total energy and fluid requirements. In such cases carbohydrates and/or lipids and/or fluids must be provided in addition, as appropriate.

Patients with renal/hepatic impairment

The doses should be adjusted individually in patients with hepatic or renal insufficiency (see also section "Special warnings and precautions for use").

Duration of treatment

The duration of treatment for the indications stated should not exceed 7 days.

Method of administration

Intravenous use. Infusion into a peripheral or central vein.

Contraindications

- hypersensitivity to the active substances, to egg, peanut or soya protein or to any of the excipients listed
- congenital disorders of amino acid metabolism
- severe hyperlipidaemia
- hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour
- acidosis
- intrahepatic cholestasis
- severe hepatic insufficiency
- severe renal insufficiency in absence of renal replacement therapy
- aggravating haemorrhagic diatheses
- acute thrombo-embolic events, lipid embolism

On account of its composition, Nutriflex Lipid peri must not be used in newborn infants, infants and toddlers under 2 years of age.

General contraindications to parenteral nutrition include:

- unstable circulatory status with vital threat (states of collapse and shock)
- acute phases of cardiac infarction and stroke
- unstable metabolic condition (e.g. severe postaggression syndrome, coma of unknown origin)
- inadequate cellular oxygen supply
- disturbances of the electrolyte and fluid balance
- acute pulmonary oedema
- decompensated cardiac insufficiency

Special warnings and precautions for use

Caution should be exercised in cases of increased serum osmolarity.
Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration and pulmonary oedema.
Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.
The serum triglyceride concentration should be monitored when infusing Nutriflex Lipid peri.
Depending on the patient's metabolic condition, occasional hypertriglyceridaemia may occur. If the plasma triglyceride concentration rises to above 3 mmol/l during administration of lipids, it is recommended that the infusion rate be reduced. Should the plasma triglyceride concentration remain above 3 mmol/l, the administration should be stopped until the level normalises.
Like all solutions containing carbohydrates, the administration of Nutriflex Lipid peri 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. If the patient is receiving other intravenous glucose solutions concurrently, the amount of additionally administered glucose has to be taken into account.
An interruption of administration of the emulsion may be indicated if the blood glucose concentration rises to above 14 mmol/l (250 mg/dl) during administration.
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.
Refeeding or repletion of malnourished or depleted patients may cause hypokalaemia, hypophosphataemia and hypomagnesaemia. Adequate supplementation of electrolytes according to deviations from normal values is necessary.
Nutriflex Lipid peri should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

Elderly patients

Basically the same dosage as for adults applies, but caution should be exercised in patients suffering from further diseases like cardiac insufficiency or renal insufficiency that may frequently be associated with advanced age.

Patients with diabetes mellitus, impaired cardiac or renal function

Like all large-volume infusion solutions, Nutriflex Lipid peri should be administered with caution to patients with impaired cardiac or renal function.
There is only limited experience of its use in patients with diabetes mellitus or renal failure.

Patients with impaired lipid metabolism

Nutriflex Lipid peri should be administered cautiously to patients with disturbances of lipid metabolism, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired hepatic function, hypothyroidism (with hypertriglyceridaemia) and sepsis. If Nutriflex Lipid peri is given to patients with these conditions, monitoring of serum triglycerides is necessary. The presence of hypertriglyceridaemia 12 hours after lipid administration also indicates a disturbance of lipid metabolism.
Disturbances of the fluid, electrolyte or acid-base balance, must be corrected before the start of infusion.

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Controls of the serum electrolytes, the water balance, the acid-base balance, and – during long-term administration – of blood cell counts, coagulation status and hepatic function are necessary.
Substitution of electrolytes, vitamins and trace elements may be necessary as required.
As Nutriflex Lipid peri 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 peri.
Nutriflex Lipid peri is a preparation of complex composition. It is, therefore, strongly advisable not to add other solutions (as long as compatibility is not proven – see section "Incompatibilities").

Interference with laboratory tests
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.

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.
Potassium-containing solutions like Nutriflex Lipid peri should be used with caution in patients receiving drugs that increase serum potassium concentration, such as potassium-sparing diuretics (triamterene, amiloride, spironolactone), ACE inhibitors (e.g. captopril, enalapril), angiotensin-II-receptor antagonists (e.g. losartan, valsartan), cyclosporin and tacrolimus.
Corticosteroids and ACTH are associated with sodium and fluid retention.

Pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Nutriflex Lipid peri in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Parenteral nutrition may become necessary during pregnancy. Nutriflex Lipid peri should only be given to pregnant women after careful consideration.

Breast-feeding
Components/metabolites of Nutriflex Lipid peri are excreted in human milk, but at therapeutic doses no effects on the breastfed newborns/infants are anticipated. Nevertheless, breast-feeding is not recommended for mothers on parenteral nutrition.

Effects on ability to drive and use machines
Not relevant.

Undesirable effects
The following listing includes a number of systemic reactions that may be associated with the use of Nutriflex Lipid peri. Under conditions of correct use, in terms of dosing monitoring, observation of safety restrictions and instructions, most of them are rare (≥ 1/10,000 to < 1/1,000).

Undesirable effects are listed according to their frequencies as follows:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (frequency cannot be estimated from the available data)

Blood and lymphatic system disorders
Rare: Hypercoagulation

Immune system disorders
Rare: Allergic reactions (e.g. anaphylactic reactions, dermal eruptions, laryngeal, oral and facial oedema)

Metabolism and nutrition disorders
Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, ketoacidosis
The frequency of these undesirable effects is dose-dependent and may be higher under the condition of absolute or relative lipid overdose.

Nervous system disorders
Rare: Drowsiness

Vascular disorders
Rare: Hypertension or hypotension, flush

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea, cyanosis

Gastrointestinal disorders
Uncommon: Nausea, vomiting, loss of appetite

Skin and subcutaneous tissue disorders
Rare: Erythema

General disorders and administration site conditions
Common: After a few days, vein irritation, phlebitis or thrombophlebitis may occur.

Rare: Headache, elevated body temperature, sweating, feeling cold, chills, pain in the back, bones, chest and lumbar region

Very rare: Fat overload syndrome (details see below)

If signs of vein wall irritation, phlebitis or thrombophlebitis occur, change of the infusion site should be considered.
Should adverse reactions occur or should the triglyceride level rise to above 3 mmol/l during infusion, the infusion should be stopped or, if necessary, continued at a reduced dosage.
If the infusion is restarted, the patient should be carefully monitored, especially at the beginning, and serum triglycerides should be determined at short intervals.

Information on particular undesirable effects
Nausea, vomiting, lack of appetite and hyperglycaemia are symptoms often related to conditions indicating parenteral nutrition or may be associated with parenteral nutrition.

Fat overload syndrome
Impaired capacity to eliminate triglycerides can lead to 'fat overload syndrome' which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient's clinical condition such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipidaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued. Should signs of a fat overload syndrome occur, the infusion of Nutriflex Lipid peri should be discontinued immediately.

Overdose

Symptoms of fluid and electrolyte overdose
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, glucosuria, dehydration, hyperosmolality, hyperglycaemic-hyperosmolar coma.

Symptoms of lipid overdose
See section "Undesirable effects".

Treatment
Immediate cessation of infusion is indicated for 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.

Incompatibilities
Nutriflex Lipid peri must not be used as a carrier solution for pharmaceuticals or be mixed with other infusion solutions without testing, since it is not possible to guarantee adequate stability of the emulsion.
Compatibility data for different additives (e.g. electrolytes, trace elements, vitamins) and the corresponding shelf life of such admixtures can be provided on demand by the manufacturer.

Shelf life
The product must not be used beyond the expiry date stated on the labelling.

After removing the protective overwrap and after mixing of contents of the bag
Chemical and physical in-use stability after mixing the contents has been demonstrated for 7 days at 2-8 °C plus 48 hours at 25 °C.

After admixture of compatible additives
From a microbiological point of view, the product should be used immediately after admixture of additives. If not used immediately after admixture of additives, in-use storage times and conditions prior to use are the responsibility of the user.

After first opening (spiking of the infusion port)
The emulsion is to be used immediately after opening of the container.

Special precautions for storage
Do not store above 25 °C.
Do not freeze. If accidentally frozen discard the bag.
Keep the bag in the outer carton in order to protect from light.

Nature and contents of container
Nutriflex Lipid peri is supplied in flexible multichamber bags of polyamide/polypropylene containing:
- 1250 ml (500 ml of amino acids solution + 250 ml of fat emulsion + 500 ml of glucose solution)
- 1875 ml (750 ml of amino acids solution + 375 ml of fat emulsion + 750 ml of glucose solution)
- 2500 ml (1000 ml of amino acids solution + 500 ml of fat emulsion + 1000 ml of glucose solution)

The multichamber bag is packed in a protective overwrap. An oxygen absorber is placed between the bag and the overwrap; the sachet of inert material contains powdered iron.
The two upper chambers can be connected with the lower chamber by opening the intermediate seam (peel seam).
The design of the bag permits mixing of the amino acids, glucose, lipids and electrolytes in a single chamber. Opening the peel seam results in sterile mixing to form an emulsion.
The different container sizes are presented in cartons containing five bags.
Pack sizes: 5 x 1250 ml, 5 x 1875 ml and 5 x 2500 ml
Not all pack sizes may be marketed.

Special precautions for disposal and other handling
No special requirements for disposal.

Preparation of the mixed emulsion:

Remove inner bag from its protective overwrap and proceed as follows:
- put the bag on a solid, flat surface
- mix glucose with amino acids by pressing the upper left chamber against the peel seam, then add the fat emulsion by pressing the upper right chamber against the peel seam
- mix the contents of the bag thoroughly.

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

Preparation for infusion:
- fold the bag and hang it on the infusion stand by the centre hanging loop
- remove the protective cap from the infusion port and carry out infusion using the standard technique

The mixture is a milky white homogenous oil-in-water emulsion.
Only use bags that are undamaged and in which the amino acid and glucose solutions are clear and colourless up to straw-coloured solutions. Do not use bags where there is a discolouration or discernible phase separation (oil drops) in the chamber containing lipid emulsion.
Nutriflex Lipid peri is supplied in single dose containers. Container and unused residues must be discarded after use.
Do not reconnect partially used containers.
If filters are used they must be lipid-permeable.

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