Directions for Use

B. Braun Medical SA, 1023 Crissier, Switzerland

Nutriflex® peri

Composition
Amounts of active ingredients in both the 1000 ml and 2000 ml sizes of the product before and after mixing of the two chambers are given below.

Composition		Before Mixing Lower Compartment 600 ml	Before Mixing Upper Compartment 400 ml	After Mixing 1000 ml	Before Mixing Lower Compartment 1200 ml	Before Mixing Upper Compartment 800ml	After Mixing 2000 ml
Isoleucine			2.34 g	2.34 g		4.68 g	4.68 g
Leucine			3.13 g	3.13 g		6.26 g	6.26 g
Lysine			2.27 g	2.27 g		4.54 g	4.54 g
(as Lysine Hydrochloride)			(2.84 g)	(2.84 g)		(5.68 g)	(5.68 g)
Methionine			1.96 g	1.96 g		3.92 g	3.92 g
Phenylalanine			3.51 g	3.51 g		7.02 g	7.02 g
Threonine			1.82 g	1.82 g		3.64 g	3.64 g
Tryptophan			0.57 g	0.57 g		1.14 g	1.14 g
Valine			2.60 g	2.60 g		5.20 g	5.20 g
Arginine Monoglutamate			4.98 g	4.98 g		9.96 g	9.96 g
(eq. to Arginine)			(2.70 g)	(2.70 g)		(5.40 g)	(5.40 g)
(eq. to Glutamic Acid)			(2.28 g)	(2.28 g)		(4.56 g)	(4.56 g)
Histidine			1.25 g	1.25 g		2.50 g	2.50 g
(as Histidine Hydrochloride Monohydrate)			(1.69 g)	(1.69 g)		(3.38 g)	(3.38 g)
Alanine			4.85 g	4.85 g		9.70 g	9.70 g
Aspartic Acid			1.50 g	1.50 g		3.00 g	3.00 g
Glutamic Acid			1.22 g	1.22 g		2.44 g	2.44 g
Glycine			1.65 g	1.65 g		3.30 g	3.30 g
Proline			3.40 g	3.40 g		6.80 g	6.80 g
Serine			3.00 g	3.00 g		6.00 g	6.00 g
Magnesium Acetate Tetrahydrate			0.86 g	0.86 g		1.72 g	1.72 g
Sodium Acetate Trihydrate			1.56 g	1.56 g		3.12 g	3.12 g
Potassium Dihydrogen Phosphate			0.78 g	0.78 g		1.56 g	1.56 g
Potassium Hydroxide			0.52 g	0.52 g		1.04 g	1.04 g
Sodium Hydroxide			0.50 g	0.50 g		1.00 g	1.00 g
Glucose		80.0 g		80.0 g	160.0 g		160.0 g
(as Glucose Monohydrate)		(88.0 g)		(88.0 g)	(176.0g)		(176.0g)
Sodium Chloride		0.17 g		0.17 g	0.34 g		0.34 g
Calcium Chloride Dihydrate		0.37 g		0.37 g	0.74 g		0.74 g
Electrolytes:							
Sodium		3.0 mmol	24.0 mmol	27.0 mmol	6.0 mmol	48.0 mmol	54.0 mmol
Potassium			15.0 mmol	15.0 mmol		30.0 mmol	30.0 mmol
Calcium		2.5 mmol		2.5 mmol	5.0 mmol		5.0 mmol
Magnesium			4.0 mmol	4.0 mmol		8.0 mmol	8.0 mmol
Chloride		8.0 mmol	23.6 mmol	31.6 mmol	16.0 mmol	47.2 mmol	63.2 mmol
Dihydrogen phosphate			5.7 mmol	5.7 mmol		11.4 mmol	11.4 mmol
Acetate			19.5 mmol	19.5 mmol		39.0 mmol	39.0 mmol
Total amino acids			40 g	40 g		80 g	80 g
Nitrogen			5.7 g	5.7 g		11.4 g	11.4 g
Non-protein energy	[kJ (kcal)]	1340 (320)		1340 (320)	2680 (640)		2680 (640)
Total energy	[kJ (kcal)]	1340 (320)	670 (160)	2010 (480)	2680 (640)	1340 (320)	4020 (960)

Excipients
Citric acid, water for injections.

Pharmaceutical form
Intravenous infusion solution for parenteral nutrition in two-chamber bags containing 1000 ml or 2000 ml
Clear, colourless or slightly yellowish aqueous solution
Osmolarity: 900 mOsm/l

Pharmaco-therapeutic group
Solutions for parenteral nutrition, combinations
ATC code: B 05B A10

Indications
Supply of the daily requirements of energy, amino acids, electrolytes and fluids during parenteral nutrition to patients in states of mild to moderate catabolism when oral or enteral nutrition is impossible, insufficient or contraindicated.

Contraindications
Related to the product:
- congenital abnormalities of amino acid metabolism
- unstable metabolism (e.g. decompensated diabetes mellitus, metabolic acidosis)
- hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour
- pathologically elevated serum electrolyte values
- intracranial or intraspinal haemorrhage
- known hypersensivity to any of the ingredients

On account of its composition the product should not be administered to neonates, infants and children under 2 years of age.

Related to parenteral nutrition:
- unstable circulatory status with vital threat (states of collapse and shock)
- cellular hypoxia, acidosis
- coma of unknown origin
- severe hepatic insufficiency
- severe renal insufficiency without renal replacement therapy

Related to infusion therapy in general
- hyperhydration
- acute pulmonary oedema
- decompensated cardiac insufficiency

Special warnings and precautions for use
Caution should be exercised in cases of increased serum osmolarity.
As for all large-volume infusion solutions Nutriflex® peri should be administered with caution to patients with impaired cardiac or renal function.
Disturbances of fluid and electrolyte metabolism (e.g. hypotonic dehydration, hyponatremia, hypokalaemia) should be corrected prior to the administration of Nutriflex® peri.
Sodium salts should be used with caution in patients with sodium retention (see section 'Interactions').
In patients with renal insufficiency, the dose must be carefully adjusted according to individual needs, severity of organ insufficiency and the kind of instituted renal replacement therapy (haemodialysis, haemofiltration etc.).
Likewise in patients with insufficiencies of liver, adrenal glands, heart and lungs the dose must be carefully adjusted according to individual needs and the severity of organ insufficiency.
Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration and pulmonary oedema.
As with all solutions containing carbohydrates the administration of Nutriflex® 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.
To avoid occurrence of a re-feeding syndrome in malnourished or depleted patients (see 'Undesirable effects'), parenteral nutrition should be built up gradually with great caution. Adequate substitution of potassium, magnesium and phosphate must be ensured.
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.
Clinical monitoring should include fluid balance, serum electrolyte concentrations, acid-base balance, blood glucose, BUN. Hepatic function should be monitored as well. Frequency and kind of laboratory testing should be adapted to the overall condition of the patient.
During long-term administration also blood cell counts and blood coagulation should be monitored carefully.
Substitution of additional energy in form of lipids may be necessary, as well an adequate supply of essential fatty acids, electrolytes, vitamins and trace elements.
Nutriflex® peri should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.
As with all intravenous solutions strict aseptic precautions are necessary for the infusion of Nutriflex® peri.

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Nutriflex® peri is a preparation of complex composition. If the product is mixed with other solutions or emulsions, compatibility must be ensured.
When Nutriflex® peri is administered peripherally the state of the veins should be taken into account. It is recommended to change the site of venous access regularly. See section 'Undesirable effects'.

Interactions
Corticosteroids and ACTH are associated with sodium and fluid retention.
Solutions containing potassium should be used with caution in patients receiving medicinal products that increase the serum potassium concentration, such as potassium sparing diuretics (triamterene, amiloride), ACE inhibitors, cyclosporine and tacrolimus.

Pregnancy and lactation
For Nutriflex® peri no clinical data on exposed pregnancies are available. Preclinical studies with respect to effects on pregnancy, embryonal/foetal development, parturition and/or postnatal development have not been performed with Nutriflex® peri. The prescriber should consider the benefit / risk relationship before administering Nutriflex® peri to pregnant women.
Breast-feeding is not recommended if women need parenteral nutrition in that time.

Dosage
The dosage is adjusted individually according to the patients' requirements and clinical status.

Adolescents from 15th year of life onward and adults
Up to 40 ml per kg body weight per day, corresponding to
– 1.6 g amino acids per kg body weight per day
– 3.2 g glucose per kg body weight per day

It is recommended that Nutriflex® peri be administered continuously, if feasible.

The infusion rate should be adjusted individually according to the patient's metabolic and clinical status. It may be:
Up to 2.0 ml per kg body weight per hour, corresponding to
– 0.08 g amino acids per kg body weight per hour
– 0.16 g glucose per kg body weight per hour

Corresponding drop rate: 0.7 drops per kg body weight per min.

For a patient weighing 70 kg this corresponds to an infusion rate of 140 ml per hour. The amount of amino acid administered is then 5.6 g per hour and of glucose 11.2 g per hour. In special clinical settings, e.g. haemodialysis, higher infusion rates may have to be applied.

Paediatric patients
The dosages for this age group as stated below are average values for guidance. The exact dosage should be adjusted individually according to age, developmental stage and prevailing disease. The calorie supply should be adapted individually according to the energy requirements during the respective growth period. If necessary, additional glucose or lipid infusions may be given.

Daily dose for 3rd to 5th year of life:	37.5 ml per kg body weight, corresponding to 1.5 g amino acids per kg body weight and 3.0 g glucose per kg body weight
Daily dose for 6th to 14th year of life:	25 ml per kg body weight, corresponding to 1.0 g amino acids per kg body weight and 2.0 g glucose per kg body weight
Infusion rate:	Up to 2.0 ml per kg body weight per hour, corresponding to 0.08 g amino acids per kg body weight per hour and 0.16 g glucose per kg body weight per hour
Corresponding drop rate:	0.7 drops per kg body weight per min.

If higher doses are necessary, account should be taken of the following limits of the total daily fluid intake:
3rd – 5th year: 80 – 100 ml per kg body weight
6th – 10th year: 60 – 80 ml per kg body weight
11th – 14th year: 50 – 70 ml per kg body weight

Duration of use
Parenteral nutrition with this solution only can be performed for one week max. If used for supplementary parenteral nutrition in combination with oral or enteral food intake or further intravenous nutrients, the duration of its use is not generally limited.

Method of administration
For intravenous use. Suitable for infusion via peripheral veins.

Overdose
Overdose of Nutriflex® peri 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, glucosuria, dehydration, hyperosmolality, hyperglycaemic and hyperosmolar coma.

Emergency treatment, antidotes:
Immediate stop 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

Undesirable effects
Undesirable systemic effects with the components of Nutriflex® peri are rare (≥ 1/10,000 to < 1/1,000) and usually related to inadequate dosage and/or infusion rate. Those that do occur are usually reversible and regress when therapy is discontinued.

Metabolism and nutrition disorders
Parenteral nutrition in malnourished or depleted patients with full doses and infusion rates from the very beginning and without adequate substitution of potassium, magnesium and phosphate may lead to the re-feeding syndrome, characterised by hypokalaemia, hypophosphataemia and hypomagnesaemia. Clinical manifestations may develop within a few days of starting parenteral nutrition and may include haemolytic anaemia due to hypophosphataemia and somnolence. See also section 'Special warnings and precautions for use'.

Gastrointestinal disorders
Nausea or vomiting may occur.

Renal and urinary disorders
In the event of a forced infusion osmotically induced polyuria might occur as a result of the high osmolarity.
If these side effects occur the infusion should be discontinued or, if appropriate, the infusion should be continued at a lower dose level.

General disorders and administration site conditions
Common (1/100 to 1/10):
After a few days, vein irritation, phlebitis or thrombophlebitis may occur. See also section 'Special warnings and precautions for use'.

Undesirable effects after abruptly stopping administration
Abrupt discontinuation of high glucose infusion rates during parenteral nutrition may lead to hypoglycaemia, especially in children less than 3 years of age and in patients with disturbed glucose metabolism. Tapering glucose administration off is recommended.

Note:
Patients are advised to inform their doctor or pharmacist if they notice any adverse effect not mentioned in this leaflet.

Pharmacodynamic properties
Parenteral nutrition must supply the body with all the components necessary for growth and tissue regeneration. The amino acids play a prominent role, being the building blocks for protein synthesis. However, in order to ensure optimal utilisation of the amino acids the administration of an energy source is required. This can be fulfilled partly in the form of carbohydrates. As glucose can be employed directly, it is the carbohydrate of choice. Additional energy, is ideally supplemented in the form of fat. Electrolytes are administered for the maintenance of metabolic and physiological functions.

Pharmacokinetic properties
Following intravenous infusion, the constituents of Nutriflex® peri are immediately available for metabolism. Electrolytes are available in sufficient amounts to sustain the numerous biological processes that they are required for.
A portion of the amino acids is used for protein synthesis, the rest being broken down as follows: the amino groups are separated by transamination and the carbon moiety is either oxidised to CO_2 in the citric acid cycle or utilised in the liver as a substrate for gluconeogenesis. The amino groups resulting from protein breakdown in muscle tissue are transported to the liver, where they are used to synthesise urea or non-essential amino acids.
Glucose is metabolized to CO_2 and H_2O. Some Glucose is utilized for lipid synthesis.

Expiry date
The product must not be used after the expiry date printed on the container.

Instructions for storage / use / handling
Do not store above 25 °C

Keep bag in the outer carton in order to protect from light.

Immediately before use the internal peal seam between the two compartments must be opened allowing the respective contents to be aseptically mixed.

Remove the bag from its protective pack and proceed as follows :
– open out the bag and lay on a solid surface
– open the peel seal by using pressure with both hands
– briefly mix the contents of the bag together

An additive port is provided for admixing of supplements to Nutriflex® peri.

Only mixtures of known compatibility should be prepared. Information on compatibility of specified mixtures is available from the manufacturer.

When admixing other solutions or fat emulsions to Nutriflex® peri, aseptic precautions must be strictly observed. Fat emulsions can be easily admixed by means of a special transfer set.
Ideally after mixing the two solutions, Nutriflex® peri should be administered immediately but in special circumstances it can be stored for up to 7 days at room temperature and up to 14 days if stored in a refrigerator (including administration time).
After infusion, any remaining solution should never be stored for later use. Only completely clear solutions from undamaged containers are to be used. Any unused product or waste material should be disposed of in accordance with local requirements.

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