Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nutriflex basal Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amounts of active substances in both the 1000 ml and 2000 ml sizes of the product are given below.

Composition	**in 1000 ml**	**in 2000 ml**
	from the upper chamber (400 ml)	**from the upper chamber (800 ml)**
Isoleucine	1.88 g	3.76 g
Leucine	2.50 g	5.00 g
Lysine hydrochloride (equivalent to lysine:)	2.27 g (1.82 g)	4.54 g (3.64 g)
Methionine	1.56 g	3.12 g
Phenylalanine	2.81 g	5.62 g
Threonine	1.45 g	2.90 g
Tryptophan	0.46 g	0.92 g
Valine	2.08 g	4.16 g
Arginine monoglutamate (equivalent to arginine:) (equivalent to glutamic acid:)	3.98 g (2.16 g) (1.82 g)	7.96 g (4.32 g) (3.64 g)
Histidine hydrochloride monohydrate (equivalent to histidine:)	1.35 g (1.00 g)	2.70 g (2.00 g)
Alanine	3.88 g	7.76 g
Aspartic acid	1.20 g	2.40 g
Glutamic acid	0.98 g	1.96 g
Glycine	1.32 g	2.64 g
Proline	2.72 g	5.44 g
Serine	2.40 g	4.80 g
Magnesium acetate tetrahydrate	1.23 g	2.46 g
Sodium acetate trihydrate	3.20 g	6.40 g
Potassium dihydrogen phosphate	1.74 g	3.48 g
Potassium hydroxide	0.96 g	1.92 g
Sodium hydroxide	0.10 g	0.20 g
	from the lower chamber (600 ml)	**from the lower chamber (1200 ml)**
Glucose monohydrate (equivalent to glucose:)	137.5 g (125.0 g)	275.0 g (250.0 g)
Sodium chloride	1.40 g	2.80 g
Calcium chloride dihydrate	0.53 g	1.06 g

Electrolytes:	**in 1000 ml**	**in 2000 ml**
Sodium	49.9 mmol	99.8 mmol
Potassium	30.0 mmol	60.0 mmol
Magnesium	5.7 mmol	11.4 mmol
Phosphate	12.8 mmol	25.6 mmol
Acetate	35.0 mmol	70.0 mmol
Chloride	50.0 mmol	100.0 mmol

Calcium	3.6 mmol	7.2 mmol
	in 1000 ml	**in 2000 ml**
Amino acid content	32 g	64 g
Nitrogen content	4.6 g	9.2 g
Carbohydrate content	125 g	250 g
	in 1000 ml	**in 2000 ml**
Energy in the form of amino acids [kJ (kcal)]	536 (128)	1071 (256)
Energy in the form of carbohydrates [kJ (kcal)]	2092 (500)	4184 (1000)
Total energy [kJ (kcal)]	2628 (628)	5255 (1256)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Infusion bag with two compartments
Amino acids and glucose solutions: clear, colourless or slightly yellowish aqueous solution

	in 1000 ml	**in 2000 ml**
Theoretical osmolarity [mOsm/l]	1150	1150
pH	4.8 – 6.0	4.8 – 6.0

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Supply of amino acids, glucose, electrolytes and fluid in the parenteral nutrition of patients in states of mild to moderate catabolism when oral or enteral nutrition is impossible, insufficient or contraindicated.

Nutriflex basal is indicated in adults and children aged 2 to 17 years.

4.2 Posology and method of administration

Posology

Nutriflex basal is suitable for patients with normal tolerance for both glucose and fluid.

Adults
The dosage and infusion rate have to be adjusted individually according to the clinical status of the patients and their requirements of amino acids, glucose, energy, electrolytes and fluid. If necessary, additional fluid, amino acid, glucose or lipid infusions may be given. In special clinical settings, e.g. parenteral nutrition during haemodialysis to compensate for dialysis related nutrients losses, higher infusion rates may have to be used.
It is recommended that Nutriflex basal be administered continuously. A stepwise increase of the infusion rate over the first 30 minutes up to the desired infusion rate prevents possible complications.

The daily dose is:

max up to 40 ml per kg body weight per day, corresponding to
up to 1.3 g amino acids per kg body weight per day

up to 5.0 g glucose per kg body weight per day
up to 2800 ml for a 70 kg patient per day

Maximum infusion rate is:

2.0 ml per kg body weight per hour, corresponding to
0.064 g amino acids per kg body weight per hour
0.25 g glucose per kg body weight per hour.
140 ml/hour for a 70 kg patient, corresponding to
4.5 g amino acids per hour and 17.5 g glucose per hour.

Paediatric population

Nutriflex basal is contraindicated in newborn infants, infants and toddlers < 2 years of age (see section 4.3).

The dosage ranges stated below are values for guidance. The exact dosage and infusion rate should be adjusted individually according to clinical status, age, developmental stage and underlying disease. In critically ill and metabolically unstable children, it is advisable to start with lower daily dosages or infusion rates and to increase them according to the patient's condition. If necessary, additional fluid, amino acid, glucose or lipid infusions may be given.

Daily dose (2to 17 years of age)

max up to 63 ml per kg body weight per day, corresponding to
up to 2.0 g amino acids per kg body weight per day
up to 7.9 g glucose per kg body weight per day

Maximum infusion rate (2 to 17 years of age)

2.0 ml per kg body weight per hour, corresponding to
0.064 g amino acids per kg body weight per hour
0.33 g glucose per kg body weight per hour

Patients with impaired glucose metabolism
If the oxidative metabolism of glucose is impaired (e.g. in the early postoperative or posttraumatic period or in the presence of hypoxia or organ failure), the dosage should be adjusted to keep the blood glucose level close to normal values. Close monitoring of blood glucose levels is recommended in order to prevent hyperglycaemia.

Patients with renal/hepatic impairment
The doses should be adjusted individually in patients with hepatic or renal insufficiency (see also section 4.4). Nutriflex basal is contraindicated in severe hepatic insufficiency and in severe renal insufficiency without renal replacement therapy (see section 4.3).

Duration of treatment
The duration of treatment for the indications stated is not limited. During administration appropriate supply of additional energy (preferably in the form of lipids), essential fatty acids, trace elements and vitamins is necessary.

Method of administration
Intravenous use. For infusion into central veins only.

Precautions to be taken before handling or administering the medicinal product
The solution should always be brought to room temperature prior to infusion.
For instructions on aseptic mixing of the chamber contents before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

- Inborn errors of amino acid metabolism
- Hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour
- Intracranial or intraspinal haemorrhage
- Acidosis
- Severe hepatic insufficiency
- Severe renal insufficiency in absence of renal replacement therapy

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

General contraindications to parenteral nutrition include:

- Unstable circulatory status with vital threat (e.g. states of collapse,shock, fluid overload, pulmonary oedema etc.)
- Acute myocardial infarction and stroke
- Unstable metabolic condition (e.g. coma of unknown origin, hypoxia, decompensated diabetes mellitus etc.)

4.4 Special warnings and precautions for use

Caution should be exercised in cases of increased serum osmolarity.

Like all solutions containing carbohydrates the administration of Nutriflex basal 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.

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. In these patient groups, tapering off of glucose administration is recommended. As a precaution it is recommended that patients should be monitored for hypoglycaemia for at least 30 minutes on the first day of abrupt discontinuation of parenteral nutrition.

Refeeding or repletion of malnourished or depleted patients may cause hypokalaemia, hypophosphataemia and hypomagnesaemia. Close monitoring of serum electrolytes is mandatory. Adequate supplementation of electrolytes according to deviations from normal values is necessary.

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. As Nutriflex basal contains magnesium, calcium, and phosphate, care should be taken when it is co-administered with solutions containing these substances.

Patients with organ impairments

Like all large-volume infusion solutions, Nutriflex basal should be administered with caution to patients with impaired cardiac or renal function.

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.

Application of hyperosmolar glucose solutions in patients with damaged haematoencephalic barrier may lead to increase of intracranial/intraspinal pressure.

There is only limited experience of its use in patients with diabetes mellitus or renal failure.

Patients with metabolic disturbances

Disturbances of the fluid, electrolyte or acid-base balance must be corrected before the start of infusion.

Solutions containing sodium salts should be used with caution in patients with sodium retention (see section 4.5).

Monitoring of clinical parameters

Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and renal function are necessary.

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.

During long-term administration also blood cell counts and blood coagulation should be monitored carefully.

Warnings and precautions concerning intravenous administration

Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration, pulmonary oedema and polyuria.

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

As with all intravenous solutions, especially for parenteral nutrition, strict aseptic precautions are necessary for the infusion of Nutriflex basal.

Nutriflex basal is a preparation of complex composition. It is, therefore, strongly advisable not to add other solutions or emulsions (as long as compatibility is not proven – see section 6.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Corticosteroids and ACTH are associated with sodium and fluid retention.

Potassium-containing solutions should be used with caution in patients receiving medicinal products that increase the serum potassium concentration, such as potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), ACE inhibitors (e.g. captopril, enalapril), angiotensin-II-receptor antagonists (e.g. losartan, valsartan), cyclosporine and tacrolimus.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Nutriflex basal in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).
Nutriflex basal should not be used during pregnancy unless the clinical condition of the woman requires treatment with parenteral nutrition.

Breast-feeding
Components/metabolites of Nutriflex basal 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.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Nutriflex basal has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Undesirable systemic effects with the components of Nutriflex basal 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.

Listing of undesirable effects 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)

Gastrointestinal disorders
Rare: Nausea, vomiting, decreased appetite

Information on particular undesirable effects
If nausea, vomiting or decreased appetite occur, the infusion should be discontinued or, if appropriate, the infusion should be continued at a lower dose level.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Overdose of Nutriflex basal is not to be expected on proper administration.

Symptoms of fluid and electrolyte overdose
Hyperhydration, polyuria, electrolyte imbalance and pulmonary oedema

Symptoms of amino acid overdose
Renal amino acid losses with consecutive amino acid imbalances, sickness, vomiting, shivering, headache, metabolic acidosis, and hyperammonaemia.

Symptoms of glucose overdose
Hyperglycaemia, glucosuria, dehydration, hyperosmolality, hyperglycaemic-hyperosmolar coma

Treatment
Immediate cessation of infusion is indicated for overdose.
Further therapeutic measures depend on the particular symptoms and their severity. Disorders of the carbohydrate and electrolyte metabolism are treated by insulin administration and appropriate electrolyte substitution, respectively. When infusion is recommenced after the symptoms have declined, it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition, combinations
ATC code: B05B A10

Mechanism of action
The purpose of parenteral nutrition is to supply all necessary nutrients and energy for growth and regeneration of tissue as well as to maintain all body functions.

Amino acids are the primary building blocks for protein synthesis and the nitrogen source for the body. Some amino acids are of particular importance since they are essential and can not be synthesized by humans. Intravenously administered amino acids are incorporated in the respective intravascular and intracellular amino acid pools where they serve as substrate for the synthesis of functional and structural proteins and as precursors for various functional molecules. However, to prevent the metabolisation of amino acids for energy production, and also to fuel the other energy consuming processes in the organism, simultaneous energy supply in the form of carbohydrate and/or fat is necessary.

Glucose is ubiquitously metabolised within the organism. Some tissues and organs, such as CNS, bone marrow, erythrocytes, tubular epithelium, cover their energy requirement mainly from glucose. In addition, glucose acts as a structural building block for various cell substances.

Additional energy is ideally supplemented in the form of fat.

Electrolytes are administered for the maintenance of metabolic and physiological functions.

5.2 Pharmacokinetic properties

Absorption
Nutriflex basal is infused intravenously. Hence, all substrates are available for metabolism immediately. It's bioavailability is 100%.

Distribution
Amino acids are incorporated in a variety of proteins in different organs of the body. In addition each amino acid is maintained as free amino acid in the blood and inside cells.

As glucose is water-soluble, it is distributed with the blood over the whole body. At first, the glucose solution is distributed in the intravascular space and then it is taken up into the intracellular space.

Electrolytes are available in sufficient amounts to sustain the numerous biological processes that they are required for.

Biotransformation
Amino acids that do not enter protein synthesis are utilized by the body as precursors in various metabolic pathways for the biosynthesis of N-containing molecules like nucleotides, haemoglobin, signalling molecules (e.g. thyroxin, dopamine, adrenalin) or co-enzymes (nicotinamide adenine dinucleotide) and energy substrates. The latter metabolism starts with the separation of the amino group from the carbon skeleton by transamination. The remaining carbon chain is then either oxidised directly to CO_2 or utilized as substrate for gluconeogenesis in the liver. The amino group is metabolised in the liver to urea.
Glucose is metabolised to CO_2 and H_2O via the known metabolic routes. Some glucose is utilised for lipid synthesis.

Elimination
Only minor amounts of amino acids are excreted unchanged in urine.
Excess glucose is excreted in urine only if the renal threshold of glucose is reached.

5.3 Preclinical safety data

Non-clinical studies have not been performed with Nutriflex basal.

Toxic effects of mixtures of nutrients given as substitution therapy at the recommended dosage are not to be expected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Water for injections

6.2 Incompatibilities

No additive or other component should be added to the medicinal product unless compatibility has been proven in advance. See also section **6.6**.

6.3 Shelf life

Unopened
2 years

After first opening the container
The product should be administered immediately after connecting to infusion set. Partially used containers must not be stored for later use.

After mixing of the contents
Ideally after mixing the two solutions, Nutriflex basal should be administered immediately, but if immediate administration is not possible it can be stored for up to 7 days at room temperature and up to 14 days if stored in a refrigerator at 2 – 8°C (including administration time).

6.4 Special precautions for storage

Do not store above 25 °C.
Keep bag in the outer carton in order to protect from light.
For storage conditions after mixing the contents see section 6.3.

6.5 Nature and contents of container

Flexible plastic bag made of a dual–layer film consisting of polyamide (external layer) and polypropylene (internal layer). The container is divided into two compartments, separated by an internal peal seam, of either 400 ml and 600 ml or 800 ml and 1200 ml. Opening the peel seam results in an aseptic mixing of the two solutions.

Each bag is packed in a protective plastic bag.
An oxygen absorber is placed between the infusion bag and the outer wrap.

Nutriflex basal is supplied in two-chamber plastic bags containing:
- 1000 ml (400 ml of amino acids solution + 600 ml of glucose solution)
- 2000 ml (800 ml of amino acids solution + 1200 ml of glucose solution)

Pack sizes: 5 × 1000 ml, 5 × 2000 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements are needed for disposal of container, overwrap and oxygen absorber.

Only completely clear solutions from undamaged containers are to be used.

The design of the dual chamber bag permits aseptic mixing of amino acids, glucose and optional fat in the lower chamber. The addition of further electrolytes is possible if required.

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 bag and proceed as follows:
- Open out the bag and lay on a solid surface
- Open the peel seam 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 basal.

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

When admixing other solutions or fat emulsions to Nutriflex basal, aseptic precautions must be strictly observed. Fat emulsions can be easily admixed by means of a special transfer set.

After infusion, any remaining solution should never be stored for later use.

7 MARKETING AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Straße 1
34212 Melsungen
Germany

8 MARKETING AUTHORISATION NUMBER

PA 0736/005/001

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10 DATE OF REVISION OF THE TEXT

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