

## Directions for Use

B. Braun Medical SA · 1023 Crissier, Switzerland

715/12604634/0108



# Combiflex® plus

## Amino Acids + Electrolytes Solution for Infusion

### 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               |                             | After Mixing | Before Mixing                |                             | After Mixing |
|---------------------------------------|-----------------------------|-----------------------------|--------------|------------------------------|-----------------------------|--------------|
|                                       | Lower Compartment<br>600 ml | Upper Compartment<br>400 ml | 1000 ml      | Lower Compartment<br>1200 ml | Upper Compartment<br>800 ml | 2000 ml      |
| Isoleucine                            |                             | 2.82 g                      | 2.82 g       |                              | 5.64 g                      | 5.64 g       |
| Leucine                               |                             | 3.76 g                      | 3.76 g       |                              | 7.52 g                      | 7.52 g       |
| Lysine Hydrochloride                  |                             | 3.41 g                      | 3.41 g       |                              | 6.82 g                      | 6.82 g       |
| △ Lysine                              |                             | (2.73 g)                    | (2.73 g)     |                              | (5.46 g)                    | (5.46 g)     |
| Methionine                            |                             | 2.35 g                      | 2.35 g       |                              | 4.70 g                      | 4.70 g       |
| Phenylalanine                         |                             | 4.21 g                      | 4.21 g       |                              | 8.42 g                      | 8.42 g       |
| Threonine                             |                             | 2.18 g                      | 2.18 g       |                              | 4.36 g                      | 4.36 g       |
| Tryptophan                            |                             | 0.68 g                      | 0.68 g       |                              | 1.36 g                      | 1.36 g       |
| Valine                                |                             | 3.12 g                      | 3.12 g       |                              | 6.24 g                      | 6.24 g       |
| Arginine Monoglutamate                |                             | 5.98 g                      | 5.98 g       |                              | 11.96 g                     | 11.96 g      |
| △ Arginine                            |                             | (3.24 g)                    | (3.24 g)     |                              | (6.48 g)                    | (6.48 g)     |
| △ Glutamic Acid                       |                             | (2.74 g)                    | (2.74 g)     |                              | (5.48 g)                    | (5.48 g)     |
| Histidine Hydrochloride Monohydrate   |                             | 2.03 g                      | 2.03 g       |                              | 4.06 g                      | 4.06 g       |
| △ Histidine                           |                             | (1.50 g)                    | (1.50 g)     |                              | (3.00 g)                    | (3.00 g)     |
| Alanine                               |                             | 5.82 g                      | 5.82 g       |                              | 11.64 g                     | 11.64 g      |
| Aspartic Acid                         |                             | 1.80 g                      | 1.80 g       |                              | 3.60 g                      | 3.60 g       |
| Glutamic Acid                         |                             | 1.47 g                      | 1.47 g       |                              | 2.94 g                      | 2.94 g       |
| Glycine                               |                             | 1.98 g                      | 1.98 g       |                              | 3.96 g                      | 3.96 g       |
| Proline                               |                             | 4.08 g                      | 4.08 g       |                              | 8.16 g                      | 8.16 g       |
| Serine                                |                             | 3.60 g                      | 3.60 g       |                              | 7.20 g                      | 7.20 g       |
| Magnesium Acetate Tetrahydrate        |                             | 1.23 g                      | 1.23 g       |                              | 2.46 g                      | 2.46 g       |
| Sodium Acetate Trihydrate             |                             | 1.56 g                      | 1.56 g       |                              | 3.12 g                      | 3.12 g       |
| Sodium Dihydrogen Phosphate Dihydrate |                             | 3.12 g                      | 3.12 g       |                              | 6.24 g                      | 6.24 g       |
| Potassium Hydroxide                   |                             | 1.40 g                      | 1.40 g       |                              | 2.80 g                      | 2.80 g       |
| Sodium Hydroxide                      |                             | 0.23 g                      | 0.23 g       |                              | 0.46 g                      | 0.46 g       |
| Glucose Monohydrate                   | 165.0 g                     |                             | 165.0 g      | 330.0 g                      |                             | 330.0 g      |
| △ Anhydrous Glucose                   | (150.0 g)                   |                             | (150.0 g)    | (300.0 g)                    |                             | (300.0 g)    |
| Calcium Chloride Dihydrate            | 0.53 g                      |                             | 0.53 g       | 1.06 g                       |                             | 1.06 g       |
| <b>Electrolytes:</b>                  |                             |                             |              |                              |                             |              |
| Sodium                                |                             | 37.2 mmol                   | 37.2 mmol    |                              | 74.4 mmol                   | 74.4 mmol    |
| Potassium                             |                             | 25.0 mmol                   | 25.0 mmol    |                              | 50.0 mmol                   | 50.0 mmol    |
| Calcium                               | 3.6 mmol                    |                             | 3.6 mmol     | 7.2 mmol                     |                             | 7.2 mmol     |
| Magnesium                             |                             | 5.7 mmol                    | 5.7 mmol     |                              | 11.4 mmol                   | 11.4 mmol    |
| Chloride                              | 7.2 mmol                    | 28.3 mmol                   | 35.5 mmol    | 14.4 mmol                    | 56.6 mmol                   | 71.0 mmol    |
| Dihydrogen phosphate                  |                             | 20.0 mmol                   | 20.0 mmol    |                              | 40.0 mmol                   | 40.0 mmol    |
| Acetate                               |                             | 22.9 mmol                   | 22.9 mmol    |                              | 45.8 mmol                   | 45.8 mmol    |
| <b>Total Amino Acids</b>              |                             | 48 g                        | 48 g         |                              | 96 g                        | 96 g         |
| Nitrogen                              |                             | 6.8 g                       | 6.8 g        |                              | 13.6 g                      | 13.6 g       |
| Non-protein energy kJ (kcal)          | 2510 (600)                  |                             | 2510 (600)   | 5025 (1200)                  |                             | 5025 (1200)  |
| kJ (kcal), total                      | 2510 (600)                  | 795 (190)                   | 3310 (790)   | 5025 (1200)                  | 1590 (380)                  | 6615 (1580)  |
| Osmolarity (mOsm/l)                   |                             |                             | 1400         |                              |                             | 1400         |

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Dokument = 210 x 297 mm (bxh)  
2 Seiten

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Combiflex plus

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### Excipients

Citric acid, water for injections.

### Pharmaceutical form

Solution for infusion.

### Indications

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

### Contraindications

This product must not be administered in the following conditions

- inborn errors of amino acid metabolism,
- pathologically elevated serum electrolyte values,
- unstable metabolism (e.g. decompensated diabetes mellitus, metabolic acidosis),
- coma of unknown origin,

- hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour,
- severe hepatic insufficiency,
- severe renal insufficiency without renal replacement therapy,
- known hypersensitivity 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.

General contra-indications to parenteral nutrition are:

- unstable circulatory status with vital threat (states of collapse and shock),
- cellular hypoxia,
- 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 Combiflex® plus should be administered with caution to patients with impaired cardiac or renal function.



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Disturbances of the fluid and electrolyte metabolism (e.g. hypotonic dehydration, hyponatremia) should be corrected prior to the administration of Combiflex® plus. Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration and pulmonary oedema.

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 hepatic insufficiency the dose must be carefully adjusted according to individual needs and the severity of organ insufficiency. As with all solutions containing carbohydrates the administration of Combiflex® plus 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 section "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.

Combiflex® plus should not be given simultaneously with blood in the same infusion set due to the risk of pseudoagglutination.

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.

Substitution of additional energy in the form of lipids may be necessary as well as adequate supply of essential fatty acids, electrolytes, vitamins and trace elements. As with all intravenous solutions strict aseptic precautions are necessary for the infusion of Combiflex® plus.

Combiflex® plus is a preparation of complex composition. If the product is mixed with other solutions or emulsions, compatibility must be ensured.

#### Interactions

None known.

#### Pregnancy and lactation

For Combiflex® plus 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 Combiflex plus. The prescriber should consider the benefit/risk relationship before administering Combiflex® plus to pregnant women. Breast-feeding is not recommended if women need parenteral nutrition in that time.

#### Dosage

The dosage is adapted to the patients' individual requirements.

The maximum daily dose amounts to 40 ml/kg body weight, corresponding to

– 1.92 g amino acids/kg body weight per day

– 6.0 g glucose/kg body weight per day

It is recommended that Combiflex® plus be administered continuously.

The maximum rate of infusion is 2.0 ml/kg body weight per hour, corresponding to

– 0.096 g amino acids/kg body weight per hour

– 0.3 g glucose/kg body weight per hour.

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 6.72 g/hour and of glucose 21.0 g/hour.

An individual adjustment of the dosage is necessary in liver and renal insufficiency (see also section "Special warnings and precautions for use").

If the oxidative metabolism of glucose is impaired, which may be the case in the post-operative or post-traumatic phase or in the presence of hypoxia or organ failure, glucose intake should be limited to 2–4 g of glucose/kg body weight/day. The blood glucose level should not exceed 6.1 mmol/l (110 mg/100 ml).

An additional fluid requirement of children should be met with appropriate replacement fluids since a maximum daily dosage of Combiflex® plus above 40 ml/kg body weight/d could exceed the maximum daily dosage for amino acids in this population (1.5–2.5 g/kg body weight/d).

#### Duration of use

The duration of treatment for the indications stated is not limited. During long-term administration of Combiflex® plus it is necessary to provide for appropriate supply of additional energy in the form of lipids, essential fatty acids, trace elements and vitamins.

#### Method of administration

For intravenous use. Administer via central venous catheter.

#### Instructions for use/handling

Immediately before use the internal peel 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.

After infusion, any remaining solution should never be stored for later use. Only completely clear solutions from undamaged containers are to be used.

The construction of the dual chamber bag permits the mixing of amino acids, glucose and optional fat in the lower chamber. The addition of further electrolytes is possible if required. Conventional aseptic precautions during the admixing of solutions or fat emulsions to Combiflex® plus must be strictly observed. Fat emulsions can be easily admixed by means of a special transfer set.

#### Overdose

Overdose of Combiflex® plus 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.

#### Treatment:

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 effects with the components of Combiflex® plus are rare and usually related to inadequate dosage and/or infusion rate. Those that do occur are usually reversible and regress when therapy is discontinued. Nausea or vomiting may occasionally occur. In the event of a forced infusion an 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.

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". Abrupt discontinuation of high glucose infusion rates during PN may lead to hypoglycaemia, especially in children less than 3 years of age and in patients with disturbed glucose metabolism.

#### Note:

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

#### 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

To protect from light, keep containers in the outer carton.

Ideally after mixing the two solutions, Combiflex® plus 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).

#### Date of last revision

11.2005

#### Presentation:

Combiflex® plus 1000 ml, 2000 ml bags

Reg. No.: DK19996900349A1

Harus dengan resep dokter

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1023 Crissier

Switzerland

Imported by:

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