

NON-ESSENTIAL AMINO ACIDS CONTAINING PHARMACEUTICAL COMPOSITION AND USES THEREOF

[0001] The present invention relates to non-essential amino acids
5 containing pharmaceutical composition, to a method of preparing the
pharmaceutical composition as well as to various medical and therapeutic uses
of this composition. In particular, the invention relates to a pharmaceutical
composition and the use thereof in parental nutrition, for example, for the
treatment of hypercatabolic state.

10 [0002] Amino acids containing compositions are widely applied for
parental nutrition, see for example US Patent 6,337,094 which discloses
aqueous solution containing numerous amino acids including all essential amino
acids and other amino acids such as ornithine or taurine. Other examples of
compositions used for parental applications are the ones described in the PCT
15 application WO 02/02902 and US Patent Application 2004/0102504. According
to these two patent publications, the amino acid compositions that contain up to
75% of the branched essential amino acids leucine, isoleucine and valine are
suitable for improving muscle performance and the treatment of heart failure.

[0003] For examples of compositions that contain amino acids and that
20 are used for parenteral nutrition are commercially available solutions such as
Aminofusin®, Intrafusin®, Pan Amin®, Amiparin® and Aminovel®. All of these
solution can the essential amino acids L-lysine, L-valine, L-leucine, L-isoleucine,
L-methonine, L-phenylalanine, L-tryptophan, and L-threonine. Aminofusin®
additionally comprises the non-essential amino acids alanine, glutamate, glycine,
25 proline and arginine as well as L-malic acid (all in their L-form). Intrafusin®
additionally comprises the non-essential amino acids alanine, aspartate,
glutamate, glycine, proline, arginine, cysteine, tyrosine and serine (all in their L-
form) as well as L-malic acid. The solution Pan Amin® further contains L-
histidine, L-arginine and glycine. The product Amiparen additionally contains L-
30 cysteine, alanine, proline, glycine, proline and arginine, all in their L-form. Finally,
the product Aminonovel® contains proline, alanine, tryrosine, arginine, histidine,
and glycine, all in the L-form.

[0004] Optimal protein synthesis in the body requires very adequate free amino acid composition in the intracellular space. Since some amino acids can compete with each other optimal competition means that each excess or deficit in the intracellular space might affect the efficiency of protein synthesis. When
5 proteins are delivered by the oral route, the gut and the liver are responsible for delivering the best optimal composition into the blood stream. However, this is not the case for parenteral nutrition. Therefore, finding a suitable, and if possible, even better composition for an amino acid solution for parenteral use is still necessary. Accordingly, it is an object of the invention to provide such a
10 composition.

[0005] This object is solved among others by the pharmaceutical composition as defined in the independent claims.

[0006] In one embodiment such a composition is a pharmaceutical composition containing

15 at least one of the essential amino acids selected from the group consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methionine, L-phenylalanine, L-tryptophan, and L-threonine,

at least six non-essential amino acids selected from the group consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine, and
20

wherein the composition does not contain an organic carboxylic acid as electrolyte.

[0007] In another embodiment such a composition is a pharmaceutical composition containing

25 at least one of the essential amino acids selected from the group consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methionine, L-phenylalanine, L-tryptophan, and L-threonine,

at least six non-essential amino acids selected from the group consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine, and
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wherein the composition does not contain alanine as amino acid.

[0008] As used in the present invention the expression that the "composition does not contain an organic carboxylic acid as electrolyte" means that the composition of the invention is free of carboxylic acids (present in free form) such as citric acid, lactic acid, acetic acid, ascorbic acid, lactic acid, maleic acid, fumaric acid, malic, tartaric acid to name a few of such organic acids. Such acids are usually used as buffer or as energy source (i.e. active ingredients in compositions used for parenteral or oral nutrition).

[0009] In preferred embodiments of the invention the composition, contains all seven non-essential amino acids selected from the group consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine. In further preferred embodiments, there are no additional non-essential amino acids present in the composition of the invention. In one of these embodiments, the composition does not contain L-alanine. In other embodiments, the composition may be free of at least one of L-cysteine, L-aspartate, L-glutamate, or L-glutamine. In still further embodiments, the composition may be free of at least two, three or four of the amino acids of the group consisting of L-alanine, L-cysteine, L-aspartate, L-glutamate, and L-glutamine. In one of these embodiments, the composition is free of L-alanine and L-Glutamine. In a further embodiment, all of these five non-essential amino acids are absent, meaning the composition than contains only L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine as non-essential amino acids.

[0010] The essential as well as the non-essential amino acids can be present in any suitable form in the composition of the invention, for example as monomeric amino acids or as dipeptides, tripeptides or oligopeptides. Examples of dipeptides include Gly-L-Tyr, Gly-L-Ile, Gly-L-Leu, Lys-L-Lys, Gly-L-Trp, Gly-L-His, Lys-L-Glu, to name only a few. Other examples of such multimeric forms include the dipeptide L-arginyl-L-arginine, the tripeptide (Arg)₃ or the tetrapeptide (Arg)₄. In one embodiment all the amino acids are present in monomeric form. If present in monomeric form, the amino acids may be present as such or, if wished, in a modified form, for example, an acetylated form as lysine acetate. This modified form may provide advantages in the handling of the composition or

more convenient chemical or physiological properties of the amino acid. For example, tyrosine may be used as N-acetyl-L-tyrosine as this acetylated form has a higher solubility in aqueous solutions. The amino acids may be used in the free acid form acid or as salt, for example, hydrochloride or chloride.

5 **[0011]** In this connection, it is noted that the amino acids are usually present in the composition in their respective L-form. However, they can also be (additionally) present in the D-form as long as (the amount of) the D-form does not have an adverse or even toxic effect on the patient to be treated.

10 **[0012]** The ratio between non-essential amino acids to essential amino acids can vary over a wide range. In typical embodiments, the range of non-essential amino acids to essential amino acids is from 0.80:1 to 1.50:1. In some embodiments the range is between 0.90:1 (non-essential amino acids): (essential amino acids) to 1.30:1 and preferably between 1:1 to 1.10:1. In one embodiment the ratio is 1:1.

15 **[0013]** The non-essential amino acids mentioned above may be present, independently from each other and independently from the total number of essential and non-essential amino acids, in the composition in a concentration of
about 0.01 mmol to about 0.03 mmol L-tyrosine,
about 0.02 mmol to about 0.07 mmol L-asparagine,
20 about 0.03 mmol to about 0.05 mmol L-arginine,
about 0.02 mmol to about 0.05 mmol L-histidine,
about 0.08 mmol to about 0.12 mmol L-glycine,
about 0.05 mmol to about 0.10 mmol L-proline, and
about 0.01 mmol to about 0.05 mmol L-serine.

25 **[0014]** The essential amino acids mentioned above may be present, independently from each other and independently from the total number of essential and non-essential amino acids, in the composition in a concentration of
about 0.08 mmol to about 0.13 mmol L-lysine,
30 about 0.03 mmol to about 0.08 mmol L-valine,
about 0.02 mmol to about 0.07 about mmol L-leucine,
about 0.01 mmol to about 0.05 mmol L-isoleucine,

about 0.005 mmol to about 0.02 mmol L-methionine,
 about 0.01 mmol to about 0.05 mmol L-phenylalanine,
 about 0.005 mmol to about 0.20 mmol L-tryptophan, and
 about 0.05 mmol to about 0.1 mmol L-threonine.

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[0015] The composition of the invention typically has an osmolarity of between about 500 mOsmol/l to about 1500 mmol Osmol/l. In some embodiments, the osmolarity is between about 600 mOsmol/l to about 1200 mOsmol/l, for example about 800 mOsmol/l. The total amino acid (protein)
 10 content is typically about 50 to 200 grams per 1 l solution. In some embodiments, the total amino acid content is about 100 g per 1 l, i.e. 10 % (w/v).

[0016] As mentioned above, the concentration of the essential and non-essential amino acids can in principle be chosen independently from another. However, if for example, an optimisation of the effect of the composition effect is
 15 wanted, the amounts of specific amino acids may be chosen in a special ratio to one another. In one of such embodiments, the amounts of tyrosine and phenylalanine are chosen in relation to each other such that the molar ratio between tyrosine and phenylalanine is 0.8:0.7 (tyr:phe). In another embodiment, the molar ratio of tyrosine to phenylalanine is about 1.

[0017] In one presently particularly preferred embodiment, 1000 ml of the
 20 composition of the invention contains the above-mentioned ingredients in the following concentrations:

	L-Threonine	8.98 g	(0.075 mol/l)
	L-Serine	3.52 g	(0.033 mol/l)
25	L-Asparagine	6.55 g	(0.049 mol/l)
	L-Proline	8.77 g	(0.077 mol/l)
	L-Glycine	7.69 g	(0.102 mol/l)
	L-Valine	6.09 g	(0.053 mol/l)
	L-Methionine	1.76 g	(0.012 mol/l)
30	L-Isoleucine	3.45 g	(0.026 mol/l)
	L-Leucine	6.17 g	(0.047 mol/l)
	N-Acetyl-L-Tyrosine	5.88 g	(0.021 mol/l)

	L-Phenylalanine	4.69 g	(0.028 mol/l)
	L-Lysine-Acetate	20.49 g	(0.108 mol/l)
	L-Histidine-HCl	6.82 g	(0.044 mol/l)
	L-Arginine	6.99 g	(0.040 mol/l)
5	L-Tryptophan	2.12 g	(0.010 mol/l)

This composition has an osmolarity of 808 mOsmol/l and a total protein concentration of 99.91g /1000 ml, i.e. about 10 % (w/v). It is further preferred that no other amino acids or proteinaceous moieties or compounds are present in this composition.

[0018] The composition may further contain other ingredients, for example, further physiologically relevant cations such as magnesium or zinc. Magnesium may be present in a concentration of up to about 3 or 4 mmol/litre. The composition may also contain phosphate, in addition to such physiologically relevant cations or independent from their presence. The phosphate may be added in any suitable form, for example, as monohydrogen or dihydrogen phosphate. Examples of suitable phosphate salts are NaH_2PO_4 and Na_2HPO_4 . If present, the phosphate is typically employed in a concentration up to 5 mmol/liter. A further compound that may also be added to the composition of the invention in a concentration of up to about 5 mmol/liter is ATP. ATP may be used in the form of its magnesium salt.

[0019] Other suitable additives that may be included in the composition are agents that exert an osmotic effect (osmolytes and oncotic agents) and thus can further increase the osmotic effect of the composition of the invention. Examples of such osmolytes and oncotic agents include carbohydrate compounds, gelatine, serum proteins such as albumin or mixtures thereof. Examples of suitable carbohydrate compounds are sorbitol, xylitol, dextrose, polydextrose, modified and unmodified starch such as hydroxyethyl starch (HES) or mixtures of these carbohydrate compounds. These carbohydrates may usually be present in a concentration of up to about 10 % (w/v). For example, a typical concentration of hydroxyethyl starch is 6 % (w/v). If another oncotic agent such

as gelatine is chosen as additive, it is typically present in an amount up to about 3.5 % or 4 %.

[0020] The composition of the invention can be used for parenteral nutrition, but is not limited thereto. If employed for parenteral nutrition, the composition is preferably administered for the treatment of hypercatabolic state, including but not limited sepsis, trauma, malignant disease, inflammatory diseases, aggressive treatments, chemotherapy, post operative treatment, and undernutrition status (which occurs, but is not limited to chronic diseases). The hypercatabolic state that is treated can be associated or caused by a disease or condition selected from the group consisting of cardiovascular diseases, brain disorders, organ failure, post-operative stress, acute hemodynamic distress due to medical surgery, as well as in undernutrition state. The composition of the invention can thus be used in emergency cases, as an agent in intensive care units (ICU) as well as parenteral food supplement for obese or hypercatabolic patients.

[0021] In accordance with the above disclosure, the composition disclosed here is usually administered as a fluid. For this purpose, any suitable way of administering a fluid to a patient can be used. Preferably, the composition is administered parenterally by infusion or injection, for example by intravenous, intramuscular or subcutaneous administration.

[0022] The invention further relates to a method of preparing a pharmaceutical composition containing

at least one of the essential amino acids selected from the group consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methionine, L-phenylalanine, L-tryptophan, and L-threonine,

at least six non-essential amino acids selected from the group consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine, and

wherein the composition does not contain an organic carboxylic acid as electrolyte, and

wherein the method comprises providing respective amounts of the amino acids and dissolving the amino acids in a pharmaceutically acceptable solvent.

[0023] The invention further relates to a method of preparing a pharmaceutical composition containing

at least one of the essential amino acids selected from the group consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methionine, L-phenylalanine, L-tryptophan, and L-threonine,

at least six non-essential amino acids selected from the group consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine, and

wherein the composition does not contain alanine, and

wherein the method comprises providing respective amounts of the amino acids and dissolving the amino acids in a pharmaceutically acceptable solvent.

[0024] In this respect, it is noted that the ingredients necessary for the preparation of a liquid composition of the invention, that means the various amino acids can also be mixed as solids and this mixture is then dissolved in a pharmaceutically acceptable solvent only prior to its administration to a patient in need thereof. Accordingly, a pharmaceutical composition comprising the essential and non-essential amino acids as defined here (and optionally also any additional ingredients such as an osmolytic agent) in solid form is also within the scope of the present invention. In some circumstances, for example, if storage room is limited, it might even be of advantage to prepare a solid mixture of the components of the composition of the invention, and prepare a liquid form thereof, only when needed.

[0025] The solvent can be any suitable pharmaceutical acceptable solvent, for example, water, or a mixture of water with an organic solvent such as ethanol, as long as this solvent is able to dissolve the solid components, in particular of the composition in the specified amounts. Typically, the solvent is deionised, single or double distilled or micro-filtered water the purity of which is acceptable for pharmaceutical applications. The fluid composition so prepared can be treated further, for example, by heat sterilisation or sterile-filtration before administered to a patient. An example of a preferred solvent/pharmaceutical carrier used for the preparation of the composition of the invention is sterile Water for Injection (WFI) as classified by the United States Pharmacopia (USP).

[0026] The invention is further illustrated by the following non-limiting Example.

5 **Example 1: Comparative Study of a pharmaceutical composition of the invention versus amino acid solution with branched chained amino acids (BCAA)**

Patients and methods

[0027] The study was approved by the Ethics Committee of the Faculty of
 10 Medicine, University of Indonesia and informed consent was obtained from each patient. Included in this study were 118 patients who needed parenteral nutrition support after major laparotomy under general anesthesia without regional analgesia. *Their physical status* were ASA class I and II, male and female aged 21-60 years, body weight not exceeded $\pm 20\%$ of ideal body weight. Clinical data
 15 were summarized and table 1,2,3,4 and in graph 1. None of the patients was with pregnancy or hypersensitive to the ingredients, or moderate to severe renal disorders (serum creatinine $>2\text{mg/dL}$), or *liver* disorders with SGOT and SGPT as high as twice of normal values or more, or diabetes mellitus who needed medication *to* control their blood glucose level, or developed shock lasting more
 20 than 30 minutes before parenteral nutrition support, or on corticosteroid therapy for at least 4 weeks. The withdrawal criteria were: sepsis with severe organ dysfunction, shock lasting more than 30 minutes, cardiac arrest, re-operative cases.

[0028] The patients were randomly allocated into two groups. Patients in
 25 Study Group (n=61) received a composition of the invention and those in the Control group (n=57) received BCAA 30%, for 5 days, starting on the first post-operation day. The amino acid solutions were given simultaneously with carbohydrate, main electrolytes (Na, K and Mg) and multivitamin to obtain the optimal results. In any case parenteral nutrition was started after hemodynamic
 30 status had been stabilized. The ingredients of the solutions are as below:

[0029] Each 1000 ml of the solution of the invention contain

L-Threonine	8.98 g	(0.075 mol/l)
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	L-Serine	3.52 g	(0.033 mol/l)
	L-Asparagine	6.55 g	(0.049 mol/l)
	L-Proline	8.77 g	(0.077 mol/l)
	L-Glycine	7.69 g	(0.102 mol/l)
5	L-Valine	6.09 g	(0.053 mol/l)
	L-Methionine	1.76 g	(0.012 mol/l)
	L-Isoleucine	3.45 g	(0.026 mol/l)
	L-Leucine	6.17 g	(0.047 mol/l)
	N-Acetyl-L-Tyrosine	5.88 g	(0.021 mol/l)
10	L-Phenylalanine	4.69 g	(0.028 mol/l)
	L-Lysine-Acetate	20.49 g	(0.108 mol/l)
	L-Histidine-HCl	6.82 g	(0.044 mol/l)
	L-Arginine	6.99 g	(0.040 mol/l)
	L-Tryptophan	2.12 g	(0.010 mol/l)

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The osmolarity of the solution is 808 mOsmol/L

[0030] Each 1000 ml of the enriched BCAA solution contain:

	L-Leucine	14.00 g
20	L-isoleucine	8.00 g
	L-Valine	8.00 g
	L-Lysine Acetat	14.80 g
	(L-Lysine equivalent) (10.5 g)	
	L-Threonine	5.70 g
25	L-Tryptophan	2.00 g
	L- Methionine	3.90 g
	L-Phenylalanine	7.00 g
	L-Cysteine	1.00 g
	L-Tyrosin	0.50 g
30	L-Arginine	10.50 g
	L-Histidine	5.00 g
	L-Alanine	8.00 g

	L-Proline	5.00	g
	L-Serine	3.00	g
	Aminoacetic acid/Glycine	5.90	g
	L-Aspartic acid	1.00	g
5	L-Glutamic acid	1.00	g

The osmolarity of the comparative solution is 932.5 m Osmol/L.

[0031] The parenteral nutrition solutions were administered to central vein. No concomitant injectable medication was allowed through this venous line. The dosing schedule of the infusion given per day depended on the body weight, i.e.

Body weight 35.1 — 45.0 kg = 1.6 L
 Body weight 45.1 — 55.0 kg = 2 L
 Body weight 55.1 — 65.0 kg = 2.4 L
 15 Body weight 65.2 — 75.0 kg = 2.8 L

[0032] Two infusion administration sets were used for each amino acid solution and Dextrose 20% + electrolytes and intravenous multivitamin Cernevit® was connected to Y type connector. Each infusion rate was regulated by infusion pump. Both solutions were given concomitantly every 24 hours.

[0033] Composition of 2 L solution:
 - 500 ml Amino acid
 - 1500 ml *Dextrose* 20% (1200 kcal) with :50 meq, Na⁺ 50 meq, Mg⁺⁺ 10 meq, and multivitamin Cernevit®

25 **[0034]** Composition of 2.4 L solution:
 - 600 ml Amino acid
 - 1800 ml *Dextrose* 20% (1400 kcal) with : K⁺ 60 meq, Na⁺ 60 meq, Mg⁺⁺ 12 meq, and multivitamin Cernevit®

[0035] Composition of 2.8 L solution:
 30 - 700 ml Amino acid
 - 2100 ml *Dextrose* 20% (1680 kcal) with : K⁺ 70 meq, Na⁺ 70 meq, Mg⁺⁺ 14 meq, and multivitamin Cernevit®

[0036] Electrolyte(s) might be added as necessary to the carbohydrate solution.

[0037] Physical examination was performed every day until the 6th post-operative day. Body weight and height of each patient was measured before the operation. Blood sample of 15-20 ml was taken by the hospital trained personal and directly taken care by trained personel of Laboratorium Klinik PRODIA in the respective study sites (Medan, Jakarta. Bandung, Semarang, Yogyakarta and Surabaya). Blood sample was taken just before starting the infusion of parenteral nutrition on day 1, day 3 and day 6 post-operative days respectively. These blood samples were examined for total nitrogen, ureum, creatinine, total amino acid, prealbumin, albumin, lipid (triglyceride, high density lipoprotein-cholesterol and low density lipoprotein-cholesterol), SGOT, SGPT, aminogram and blood glucose. For each blood sample, 1 ml plasma was frozen and kept in at least minus 20°C. This method of storage was also applied for each 3-5 ml urine samples before its examination. Twenty-four hour urine for urea nitrogen, creatine and methyl-histidine were collected starting froth the day before surgery (day 0), until day 6 *postoperative* day. Fluid balance of each patient was recorded. All laboratory examinations were organized by Laboratorium Kilnik PRODIA. Adverse Event (AE)/or Serious Adverse Event (SAE) during the in-study period, if any, was reported in the Case Report Form (CRF). NI concomitant medication and its relevant data including dosages were entered on the Case Report Form. The patients were allowed to take oral intake on day 4 onward, in the form of water or water with sugar (tea with sugar). No protein intake was allowed.

[0038] Prior to randomization subjects are stratified for center. The random assignment of the subjects was provided In numbered sealed envelopes. On each envelope the stratum was clearly marked.

[0039] Sociodemographic and medical characteristic of the study and control groups were analyzed at the beginning of the treatment to assess its comparability. In assessing the efficacy of the studied Amino acid solution, the efficacy variables were compared between groups. Data on the exposure of study medication were analyzed for the all subject treated group. The amount of

administered solution was summarized. Safety data were analyzed for the all subject treated group comparing the safety variables. The occurrence of any Adverse Event (AE) during the study period was summarized by means of frequency distribution. Appropriate parametric and non-parametric statistical
5 procedures were applied using 95% Confidence Interval. Student t-test was performed to compare quantitative variables. In case of non-normal distribution, log transformation was first be performed. If normality still could not be achieved, Mann-Whitney non parametric test was performed.

[0040] This short period study (5 days) has the main objective to assess
10 the safety of the composition of the invention as compared with another solution. An excellent tolerance was found, which was fully comparable to that of the control group. The study period was too short to see a difference in parameters involve in efficiency (nitrogen balance). However, the concentration of transthyritin (prealbumin) was significantly higher on day 5 indicating an effect of
15 the composition of the invention on protein synthesis.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition containing
at least one of the essential amino acids selected from the group
5 consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methonine, L-phenylalanine, L-tryptophan, and L-threonine,
at least six non-essential amino acids selected from the group
consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine, and
10 wherein the composition does not contain an organic carboxylic acid as electrolyte.
2. The composition of claim 1, containing all seven non-essential
amino acids selected from the group consisting of L-tyrosine, L-
15 asparagine, L-arginine, L-histidine, L-glycine, L-proline and L-serine.
3. The composition of claim 1 or 2, wherein the ratio of non-essential
amino acids to essential amino acids is in the range of 0.80:1 to
20 1.50:1, preferably 0.90:1 to 1.30:1, most preferably 1:1 to 1.10:1.
4. The composition of any of claims 1 to 3, containing any of the
non-essential amino acids in a concentration of
about 0.01 mmol to about 0.03 mmol L-tyrosine,
25 about 0.02 mmol to about 0.07 mmol L-asparagine,
about 0.03 mmol to about 0.05 mmol L-arginine,
about 0.02 mmol to about 0.05 mmol L-histidine,
about 0.08 mmol to about 0.12 mmol L-glycine,
about 0.05 mmol to about 0.10 mmol L-proline, and
30 about 0.01 mmol to about 0.05 mmol L-serine.

5. The composition of any of claims 1 to 4 containing at least three or preferably all of the essential amino acids selected from the group consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methionine, L-phenylalanine, L-tryptophan, and L-threonine.
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6. The composition of any of the claims 1 to 5, wherein the amino acids are all present in monomeric form.
7. The composition of any of claims 1 to 6 containing the essential amino acids in a concentration of
10 about 0.08 mmol to about 0.13 mmol L-lysine,
about 0.03 mmol to about 0.08 mmol L-valine,
about 0.02 mmol to about 0.07 mmol L-leucine,
about 0.01 mmol to about 0.05 mmol L-isoleucine,
15 about 0.005 mmol to about 0.02 mmol L-methionine,
about 0.01 mmol to about 0.05 mmol L-phenylalanine,
about 0.005 mmol to about 0.20 mmol L-tryptophan, and
about 0.05 mmol to about 0.1 mmol L-threonine.
- 20 8. The composition of any of claims 1 to 7 having an osmolarity of between 500 mOsmol/l to 1500 mmol Osmol/l, preferably 600 mOsmol/l to 1200 mOsmol/l.
9. The composition of any of claims 1 to 8 which does not contain at
25 least one non-essential amino acid selected from the group consisting of L-alanine, L-cysteine, L-aspartate, L-glutamate, and L-glutamine.
10. The composition of any of claims 1 to 9 which does not contain L-
30 alanine.

11. The composition of any of claims 1 to 10 which is adapted for parental nutrition.
- 5 12. The use of a pharmaceutical composition of any of claims 1 to 11 for parental nutrition.
13. The use of claim 12, wherein the composition of any of claims 1 to 11 is administered for the treatment of hypercatabolic state.
- 10 14. A pharmaceutical composition containing
at least one of the essential amino acids selected from the group
consisting of L-lysine, L-valine, L-leucine, L-isoleucine, L-methionine, L-
phenylalanine, L-tryptophan, and L-threonine,
at least six non-essential amino acids selected from the group
15 consisting of L-tyrosine, L-asparagine, L-arginine, L-histidine, L-glycine, L-
proline and L-serine, and
wherein the composition does not contain L-alanine.