

Application No.:

Product:

NUTRIFLEX LIPID SPECIAL NOVO EMULSION FOR INFUSION

Applicant's Response Document

But in the end, there is no actual volume overfilling of any compartment of the bag, therefore there is also no API overage involved. The filling volume is controlled by calibrated weighing equipment.

Question

C: Particulars of packing

Under Container Type Description:

3. Please clarify if the packaging material is semi permeable or impermeable container. Please justify with supporting documents.

Response

3. It is herewith clarified that the packaging material is defined as semi permeable. Please refer to the descriptions of the packaging material in P.7. The primary foil used for the bag is made of a 3-layer film based on different polymeric sources as declared in the respective dossier part. Any additional supporting justification is deemed unnecessary.

Question

D1-Inner carton label:

- 1. Please declare source of ingredients derived from animal origin (if any).*
- 2. Please include storage condition as per A19 on the label. (To include in-use storage condition)*
- 3. Observed that quantity/content of electrolytes, calories, osmolality, energy, amino acid, carbohydrate and pH information are included. Please provide supporting document to confirm on quantity/content as per declared is correct for this product.*
- 4. Please provide reference on this: peripheral or central venous use.*
- 5. Please clarify what is this MCT/LCT.*

Response:

1. Egg phospholipids: Egg yolk from hens of German origin. LoD is provided.
2. LoD is provided
3. Please refer to the following calculations:

Application No.:

Product:

NUTRIFLEX LIPID SPECIAL NOVO EMULSION FOR INFUSION

Applicant's Response Document

Electrolytes	E in Salts / Amino Acid: Molar Mass (g/mol)	Content g/l	Molarity (mol/l)	1000 ml	625 ml	1250 ml	1875 ml
	NaH ₂ PO ₄ 2H ₂ O	156.02	2.496	0.016			
Sodium	NaOH	40	1.171	0.029			
	NaCl	58.44	0.378	0.006			
	Na(CH ₃ COO) 3H ₂ O	136.08	0.25	0.002	53	33.5	67
Potassium	K(CH ₃ COO)	98.15	3.689	0.038	38	23.5	47
Magnesium	Mg(CH ₃ COO) ₂ 4H ₂ O	214.46	0.91	0.004	4	2.65	5.3
Calcium	CaCl ₂ 2H ₂ O	147.02	0.623	0.004	4	2.65	5.3
Zinc	Zn(CH ₃ COO) ₂ 2H ₂ O	219.5	0.007	0.00003	0.03	0.02	0.04
Chloride	Lysine HCl	182.65	3.98	0.023			
	Histidine HCl H ₂ O	209.63	2.368	0.012			
	NaCl	58.44	0.378	0.007			
Acetate	CaCl ₂ 2H ₂ O	147.02	0.623	0.005	47	30	60
	Na(CH ₃ COO) 3H ₂ O	219.5	0.25	0.002			
	K(CH ₃ COO)	136.08	3.689	0.038			
	Mg(CH ₃ COO) ₂ 4H ₂ O	98.15	0.91	0.004			
	Zn(CH ₃ COO) ₂ 2H ₂ O	214.46	7.024	0.00003	47	30	60
Phosphate	NaH ₂ PO ₄ 2H ₂ O	156.02	2.496	0.016	16	10	20

Calculation Formula:

Molarity Electrolytes [mmol/L] = (Content [g/L] / Molar Mass [g/mol]) x 1000

Example NaH₂PO₄ * H₂O: (2.496 g/L / 156,02 g/mol) x 1000 = 16 mmol / L

Sum of Electrolytes [mmol] = Molarity Electrolytes [mmol/L] x volume

Example **Sodium**: 16 mmol/L + 29 mmol/L + 6 mmol/L + 2 mmol/L = **53 mmol/L**

For 1875 mL = 53 mmol/L x 2,5 = 100.5 mmol/L

For 1250 mL = 53 mmol/L x 1,875 = 67 mmol/L

For 625 mL = 53 mmol/L x 1,25 = 33.5 mmol/L

Calculation of Energy (caloric values for amino acid, glucose and lipids)

Following approx. values are stated on the label for Nutriflex Omega Peri

Compartment		625 mL Bag	1250 ml Bag	1875 mL Bag
Amino	kcal	140	280	420
Glucose	kcal	360	720	1080
Lipids	kcal	240	475	715
Total caloric values	kcal	740	1475	2215

The calculations for the caloric values are mainly based on literature known values or theoretical assumptions, specifically for nature-based ingredients like fatty acids.

Application No.:

Product:

NUTRIFLEX LIPID SPECIAL NOVO EMULSION FOR INFUSION

Applicant's Response Document

Calculations for Amino Compartment:

Amount of amino acids per Liter: 140 g/L

Volume of amino acid solution per Bag: 250 mL / 500 mL / 750 mL

Caloric value for Amino acids solutions: 4 kcal / g¹Caloric value calculated (example 625 mL bag with 250 mL amino acid solution):

In 250 mL Amino Acid Solution are 35 g amino acids, thus, approx. **140 kcal** are supplied with the 625 mL bag.

Calculations for Glucose Compartment:

Amount of glucose per Liter: 360 g/L (based on glucose without monohydrate)

Volume of glucose solution per Bag: 250 mL / 500 mL / 750 mL

Caloric value for Glucose solutions: 4 kcal / g²Caloric value calculated (example 625 mL bag with 250 mL glucose solution):

In 250 mL Glucose Solution are 90 g glucose, thus, approx. **360 kcal** are supplied with the 625 mL bag.

Calculations for Lipids Compartment:

Volume of lipid emulsion per Bag: 125 mL / 250 mL / 375 mL

The caloric values are calculated with literature-based assumptions for the ingredients of the fat emulsion³:

MCT: 100 g/L x 8,3 kcal/g = 830 kcal/L

LCT: 100 g/L x 9,2 kcal/g = 920 kcal/L

Glycerol: 25 g/L x 4,3 kcal/g = 108 kcal/L

Egg Phospholipids for Injection: 12 g/L x 9,2 kcal/g x 0.67 = 74 kcal/L (based on approx. 2/3 of phospholipids are contributing)

Sodium Oleate: 0,3 g/L x 9,2 kcal/g = 3 kcal/L

Alpha-Tocopherol: 0,2 g/L x 7,1 kcal/g = 1 kcal/L

Total of kcal/L rounded to the nearest 5: 1910 kcal/L

Caloric value calculated (example 625 mL bag with 125 mL lipid emulsion):

1910 kcal/L x 0,125 L = **240 kcal** (rounded)

¹ M E May, J O Hill, The American Journal of Clinical Nutrition, Volume 52, Issue 5, November 1990, Pages 770–776

² Jeevanandam, 1995; Bolder et al., 2009; Butte et al., 2014

³ Johnson RC, Cotter R. Metabolism of medium-chain triglyceride lipid emulsion. Nutr Int 1986 May/Jun;2(3):150-8. Mirtallo JM. Parenteral formulas. In: Rombeau JL, Rolandelli RH, editors. Clinical nutrition: parenteral nutrition. Third ed. Philadelphia. PA: W. B. Saunders Company; 2001. p. 118-39.

Application No.:

Product:

NUTRIFLEX LIPID SPECIAL NOVO EMULSION FOR
INFUSION

Applicant's Response Document

Calculations for total caloric value (example 625 mL bag):

Caloric value for amino acid solution: 140 kcal

Caloric value for glucose solution: 360 kcal

Caloric value for lipid emulsion: 240 kcal

Total: **740 kcal**

Amino acid chamber	g/l	MW (g/mol)	Content mol/l	Amount of ions	Ions (mol/l)
Isoleucine	8.21	131.17	0.063	1	0.063
Leucine	10.96	131.17	0.084	1	0.084
Valine	9.01	117,15	0.077	1	0.077
Lysine Hydrochloride	9.95	182.65	0.054	3	0.162
Threonine	6.35	119.12	0.053	1	0.053
Tryptophan	2	204.22	0.01	1	0.01
Methionine	6.84	149.21	0.046	1	0.046
Phenylalanine	12.29	165.19	0.074	1	0.074
Histidine Hydrochloride Monohydrate	5.92	209.63	0.028	3	0.084
Arginine	9.45	174.2	0.054	1	0.054
Alanine	16.98	89.09	0.191	1	0.191
Glycine	5.78	75.07	0.077	1	0.077
Serine	10.5	105.09	0.099	1	0.099
Proline	11.9	115.13	0.103	1	0.103
Glutamic Acid	12.27	147.13	0.083	1	0.083
Aspartic Acid	5.25	133.1	0.039	1	0.039
Sodium Hydroxide	2.928	40	0.073	2	0.146
Sodium Chloride	0.946	58.44	0.016	2	0.032
Sodium Acetate Trihydrate	0.626	136.08	0.005	2	0.01
Potassium Acetate	9.222	98.15	0.094	2	0.188
Magnesium Acetate Tetrahydrate	2.274	214.45	0.011	3	0.033

Application No.:

Product:

NUTRIFLEX LIPID SPECIAL NOVO EMULSION FOR INFUSION

Applicant's Response Document

Calcium Chloride Dihydrate	1.558	147.01	0.011	3	0.033
Citric Acid Monohydrate to adjust the pH	0.42	210.14	0.002	1	0.002
Theor. Osmolarity (mOsmol/l) 1743					

Glucose chamber	g/l	MW (g/mol)	Content mol/l	Amount of ions	Ions (mol/l)
Glucose Monohydrate	396	198.17	1.998	1	1.998
Sodium Dihydrogen Phosphate Dihydrate	6.24	156	0.04	2	0.08
Zinc Acetate Dihydrate	0.01756	201.48	0	3	0
Citric Acid Monohydrate to adjust the pH	0.42	210.14	0.002	1	0.002
Theor. Osmolarity (mOsmol/l) 2080					

Lipids chamber	g/l	MW (g/mol)	Content mol/l	Amount of ions	Ions (mol/l)
Medium-chain Triglycerides	100	503			
Soya-Bean Oil, Refined	100	856			
Egg Phospholipids for Injection	12	775			
Alpha-tocopherol	0.2	430.71			
Sodium Oleate	0.3	304.44	0.001	2	0.002
Glycerol	25	92.09			206
Water for Injections	753.5	18			
Theor. Osmolarity (mOsmol/l) 208					

Mixture

Proportional volume of Amino acids

Proportional volume of Glucose

Application No.:

Product:

NUTRIFLEX LIPID SPECIAL NOVO EMULSION FOR INFUSION

Applicant's Response Document

Proportional volume of Lipids

Theor. Osmolarity (mOsmol/l) = round 1545

Calculation Formula

Content [mol/L] = Content [g/L] / MW [g/mol]

Example (Isoleucine)

 $4,68 \text{ g/L} / 131,17 \text{ g/mol} = 0,036 \text{ mol/L}$

Ions [mol/L] = Content [mol/L] x Amount of Ions

Example (Isoleucine)

 $0,036 \text{ mol/L} \times 1 = 0,036 \text{ mol/L}$

Theoretical Osmolarity [mOsmol/L] = Sum of Ions [mol/L] in each of the three chambers (Amino, Glucose, Lipid)

Total amount is calculated based on the proportional volumes of the three chambers. This results by round up to 1545 mOsmol/L.

pH LimitThe pH limit of 5.0 to 6.0 stated in the texts is following P5.1 and the implemented release and shelf life limits for the read-to-**use mixture**.

4. Please see Clinical Overview – pages 9 and 83 / 136. And Bibliographic References

*Jauch KW, Schregel W, Stanga Z, Bischoff SC, Braß P, Hartl W, Muehlebach S etz al,**Working group for developing the guidelines for parenteral nutrition of The German Association for Nutritional Medicine. Access technique and its problems in parenteral nutrition –**Guidelines on Parenteral Nutrition, Chapter 9. Ger Med Sci 2009;*

5. MCT / LCT = abbreviation for Medium-Chain Triglycerides and Long-Chain Triglycerides (Soyabean oil, refined)

Question***E12: Analytical method***

1. Please provide the POA for Assay, dihydrogenphosphate

2. Please provide the calculation for assay zinc.

3. BET: Please provide MVD calculation

4. Please clarify which BET method is used routinely, Method A or D?

Response