2. Please refer to LoD-0739-844-846-labels-carton-animal-origin-in-use attached in this section.
3. Please refer to the following calculations:

Calculation of Molar Composition

					Label Information			
					1000 mL	Bag volume: 2500 mL	Bag volume: 1875 mL	Bag volume: 1250 mL
Electrolytes (E)	E in Salts / Amino Acids	Molar Mass (g/mol)	Content (g/L)	Molarity Electrolytes (mmol/L)	Sum of Electrolytes (mmol)	Sum of Electrolytes (mmol)	Sum of Electrolytes (mmol)	Sum of Electrolytes (mmol)
Sodium	NaH2PO4 2*H2O	156,02	0,936	5,999	40	100	75	50
	NaOH	40,00	0,640	16,000				
	NaCl	58,44	0,865	14,802				
	Na(CH3COO) 3*H2O	136,08	0,435	3,197				
Potassium	K(CH3COO)	98,15	2,354	23,984	24	60	45	30
Magnesium	Mg(CH3COO)2 4*H2O	214,46	0,515	2,401	2,4	6,0	4,5	3,0
Calcium	CaCl2 2*H2O	147,02	0,353	2,401	2,4	6,0	4,5	3,0
Zinc	Zn(CH3COO)2	219,50	0,00528	0,024	0,024	0,06	0,045	0,03
Chloride	Lysine HCl	182,65	2,272	12,439	38	96	72	48
	Histidine HCl H2O	209,63	1,352	6,449				
	NaCl	58,44	0,865	14,802				
	CaCl2 2*H2O	147,02	0,353	4,802				
Acetate	Zn(CH3COO)2	219,50	0,00528	0,0481	32	80	60	40
	Na(CH3COO) 3*H2O	136,08	0,435	3,197				
	K(CH3COO)	98,15	2,354	23,984				
	Mg(CH3COO)2 4*H2O	214,46	0,515	4,803				
Phosphate	NaH2PO4 2*H2O	156,02	0,936	5,999	6,0	15,0	11,25	7,5

Calculation Formula:

Molarity Electrolytes [mmol/L) = (Content [g/L] / Molar Mass [g/mol]) x 1000
Example NaH2PO4 * H2O: (0,936 g/L / 156,02 g/mol) x 1000 = 5,999 mmol / L

Sum of Electrolytes [mmol] = Molarity Electrolytes [mmol/L] x volume
Example **Sodium**: 5,999 mmol/L + 16,000 mmol/L + 14,802 mmol/L + 3,197 mmol/L = 39,998 mmol/L
= 40 mmol/L

For 2500 mL = 40 mmol/L x 2,5 = 100 mmol/L
For 1875 mL = 40 mmol/L x 1,875 = 75 mmol/L
For 1250 mL = 40 mmol/L x 1,25 = 50 mmol/L

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

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

Compartment		**1250 mL Bag**	**1875 ml Bag**	**2500 mL Bag**
Amino	kcal	**160**	240	320
Glucose	kcal	**320**	480	640
Lipids	kcal	**475**	715	950
Total caloric values	kcal	**955**	1435	1910

The calculations for the caloric values are mainly based on literature known values or theoretical assumptions,

specifically for nature-based ingredients like fatty acids.

Calculations for Amino Compartment:

Amount of amino acids per Liter: 80 g/L

Volume of amino acid solution per Bag: 500 mL / 750 mL / 1000 mL

Caloric value for Amino acids solutions: 4 kcal / g[1]

Caloric value calculated (example 1250 mL bag with 500 mL amino acid solution):

In 500 mL Amino Acid Solution are 40 g amino acids, thus, approx. **160 kcal** are supplied with the 1250 mL bag.

Calculations for Glucose Compartment:

Amount of glucose per Liter: 160.02 g/L (based on glucose without monohydrate)

Volume of glucose solution per Bag: 500 mL / 750 mL / 1000 mL

Caloric value for Glucose solutions: 4 kcal / g[2]

Caloric value calculated (example 1250 mL bag with 500 mL glucose solution):

In 500 mL Glucose Solution are 80 g glucose, thus, approx. **320 kcal** are supplied with the 1250 mL bag.

Calculations for Lipids Compartment:

Volume of lipid emulsion per Bag: 250 mL / 375 mL / 500 mL

The caloric values are calculated with literature-based assumptions for the ingredients of the fat emulsion[3]:

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: 1930 kcal/L

Caloric value calculated (example 1250 mL bag with 250 mL lipid emulsion):

1930 kcal/L x 0,25 L = approx. **475 kcal**

[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.

Calculations for total caloric value (example 1250 mL bag):

Caloric value for amino acid solution: 160 kcal

Caloric value for glucose solution: 320 kcal

Caloric value for lipid emulsion: 475 kcal

Total: **955 kcal**

Amino acid chamber	g/l	MW (g/mol)	Content mol/l	Amount of ions	Ions (mol/l)
Isoleucine	4.68	131.17	0.036	1	0.036
Leucine	6.26	131.17	0.048	1	0.048
Valine	5.2	117,15	0.044	1	0.044
Lysine Hydrochloride	5.68	182.65	0.031	3	0.093
Threonine	3.64	119.12	0.031	1	0.031
Tryptophan	1.14	204.22	0.006	1	0.006
Methionine	3.92	149.21	0.026	1	0.026
Phenylalanine	7.02	165.19	0.042	1	0.042
Histidine Hydrochloride Monohydrate	3.38	209.63	0.016	3	0.048
Arginine	5.4	174.2	0.031	1	0.031
Alanine	9.7	89.09	0.109	1	0.109
Glycine	3.3	75.07	0.044	1	0.044
Serine	6	105.09	0.057	1	0.057
Proline	6.8	115.13	0.059	1	0.059
Glutamic Acid	7	147.13	0.048	1	0.048
Aspartic Acid	3	133.1	0.023	1	0.023
Sodium Hydroxide	1.6	40	0.04	2	0.08
Sodium Chloride	2.162	58.44	0.037	2	0.074
Sodium Acetate Trihydrate	1.088	136.08	0.008	2	0.016
Potassium Acetate	5.886	98.15	0.06	2	0.12
Magnesium Acetate Tetrahydrate	1.288	214.45	0.006	3	0.018
Calcium Chloride Dihydrate	0.882	147.01	0.006	3	0.018
Citric Acid Monohydrate to adjust the pH	0.42	210.14	0.002	1	0.002
Theor. Osmolarity (mOsmol/l) 1073					

Glucose chamber	g/l	MW (g/mol)	Content mol/l	Amount of ions	Ions (mol/l)
Glucose Monohydrate	176	198.17	0.888	1	0.888
Sodium Dihydrogen Phosphate Dihydrate	2.345	156	0.015	2	0.03
Zinc Acetate Dihydrate	0.0132	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) 920					

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	0.4
Proportional volume of Glucose	0.4
Proportional volume of Lipids	0.2

Theor. Osmolarity (mOsmol/l)

round - 840

Calculation Formula

Content [mol/L] = Content [g/L] / MW [g/mol]
Example (Isoleucine)
4,68 g/L / 131,17 g/mol = 0,036 mol/L

Ions [mol/L] = Content [mol/L] x Amount of Ions
Example (Isoleucine)
0,036 mol/L x 1 = 0,036 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 840 mOsmol/L.

pH Limit

The 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

D2-Outer 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.
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.
6. Please clarify what is this REF XXX XXXX

Response

1: Same answer as D1-Inner carton label

2: Same answer as D1-Inner carton label

3: Same answer as D1-Inner carton label

4: Same answer as D1-Inner carton label

5: Same answer as D1-Inner carton label

6: REF = finished good article number and xxx is a place holder for the article number which will be added after coding