B BRAUN

APPLICANT'S RESPONSE DOCUMENT

to questions listed in the Request for Further Information raised by Health Sciences Authority in Malaysia dated 16.08.2024

The details are as follows:

Procedure	New registration
Application Number	557318

Medicinal Product concerned	NUTRIFLEX OMEGA PERI NOVO EMULSION FOR INFUSION
ATC code	B05BA10
Pharmaceutical form and strength(s)	Emulsion for infusion

Applicant	B. Braun Medical Industries Sdn. Bhd. (Company Reg: 197401001922 (19051-M) Registered Office: B. Braun 8, No 140 Lebuh Sungai Tiram 1, Taman Perindustrian Bebas Bayan Lepas Fasa 2, 11900 Bayan Lepas, Pulau Pinang, Malaysia. Correspondence Address: P.O Box 880, 10810 Pulau Pinang, Malaysia.
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Question

D2. Outer carton label

1. Noted on the calculation of osmolality of the theoretical osmolalilty provided in document. NutriflexOmegaPeri(0739)-1stDL-response document-2024-02-04, pages: 3 - 7. Please provide the reference of the claim "Total amount is calculated based on the proportional volumes of the three chambers. This results by round up to 840 mOsmol/L.".
2. In- use and shelf life will be evaluated once the stability data is satisfactory

Response

1. The applicant wishes to clarify that Osmolality is a measure of osmoles of solute per kilogram of solvent (Osm/kg) and the **O**smolarity is the measure of osmoles of solute per liter of solution (Osm/L).

Please consider that the determination of Osmolality/Osmolarity in the Quality Control laboratory, is done according to the monograph 2.2.35. OSMOLALITY, of the European Pharmacopoeia, therefore according to an instrumental analytical method (measurement of the depression of freezing point with an Osmometer). Please find the monograph attached to this response letter. Please find the monograph attached to this response letter and also the US Pharmacopoeia monograph Osmolality / Osmolarity <785>. The values are measured in the mixtures of the chambers (ready-to-use product).

The measurement of the number of solutes in the solution allows the direct determination of the osmolality of the solution with units of moles of solutes per kilogram of solvent. This osmolality result can be converted into a value for osmolarity with units of moles of solutes per liter of solvent, typically water.

Please also consider that in the SmPC / DfU, there are stated mean (average) values of the Osmolarity / Osmolality – 840 mOsm/L / 950 mOsm/L.

In the response to the first NoD, the applicant provided the theoretical calculation for the **Osmolarity**.

[*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.***]**

Osmolarity of a solution is a theoretical quantity expressed in osmoles per L (Osmol per L) of a solution and is widely used in clinical practice because it expresses osmoles as a function of volume. Osmolarity (c) can be calculated theoretically from the sum molar concentrations:

$$\xi_c = \Sigma^{\nu}{}_i c_i$$

where ν_i is as defined above, and ci is the molar concentration of the i^{th} solute in solution.

The ready-to-use product will be a mixture of the 3 chambers and the 3 chambers will have a same theoretical contributivity to the final volume (independent of the bag volume which can be 1250 ml, 1875 ml or 2500 ml) and this contributivity is 40% of the final volume (amino acids solution) / 40% (glucose solution) / 20% (fat emulsion). That is why in every bag volume, the osmolarity / osmolality values will remain the same.

Total bag volume	**AA solution volume**	**Glucose solution volume**	**LE volume**	**Proportion / Contributivity to final total volume**
1250 ml	500 ml	500 ml	250 ml	0.4
1875 ml	750 ml	750 ml	375 ml	0.4
2500 ml	1000 ml	1000 ml	500 ml	0.2

The term **Osmolality** expresses concentrations relative to the mass of the solvent.

Please find below a theoretical calculation for osmolality based on the ion-formation behaviour of the APIs and excipients in water (the solvent).

Coming from aminoacid chamber	**g/l**	**MW (g/mol)**	**g/kg water**	**mol/kg water**	**Amount of ions**	**Osm/kg**
Isoleucine	4.68	131.17	5	0.038	1	0.038
Leucine	6.26	131.17	6.69	0.051	1	0.051
Lysine HCl	5.68	182.65	6.07	0.033	3	0.099
Methionine	3.92	149.21	4.19	0.028	1	0.028
Phenylalanine	7.02	165.19	7.5	0.045	1	0.045

Threonine	3.64	119.12	3.89	0.033	1	0.033
Tryptophan	1.14	204.22	1.22	0.006	1	0.006
Valine	5.2	117.15	5.55	0.047	1	0.047
Arginine	5.4	174.2	5.77	0.033	1	0.033
(Histidine HCl) H2O	(3.09)3.38	(191.62)209.63	3.3	0.017	3	0.051
Alanine	9.7	89.09	10.36	0.116	1	0.116
Aspartic acid	3	133.1	3.2	0.024	1	0.024
Glutamic acid	7	147.13	7.48	0.051	1	0.051
Glycine	3.3	75.07	3.52	0.046	1	0.046
Proline	6.8	115.13	7.26	0.063	1	0.063
Serine	6	105.09	6.41	0.061	1	0.061
Sodium hydroxide	1.6	40	1.71	0.043	2	0.086
Sodium chloride	2.162	58.44	2.31	0.04	2	0.08
(Sodium acetate) 3H2O	(0.656)1.088	(82.03)136.08	0.7	0.009	2	0.018
Potassium acetate	5.886	98.15	6.29	0.064	2	0.128
(Magnesium acetate) 4H2O	(0.855)1.288	(142.39)214.45	0.91	0.006	3	0.018
(Calcium chloride) 2H2O	(0.666)0.882	(110.98)147.01	0.71	0.006	3	0.018
(Citric acid) H2O	(0.384)0.42	(192.12)210.14	0.41	0.002	1	0.002
						1.142

Water = 935 g + *1.407* (*coming from hydrates*) 0.93641 kg/l

Coming from glucose chamber	**g/l**	**MW (g/mol)**	**g/kg water**	**mol/kg water**	**Amount of ions**	**Osm/kg**
(Glucose) H2O	(160)176	(180.16)198.17	178.26	0.989	1	0.989
(Sodium Dihydrogen Phosphate) 2H2O	(1.804)2.345	(120)156	2.01	0.017	2	0.034
(Zinc Acetate) 2H2O	(0.012)0.0132	(183.48)201.48	0.013	0	3	0
(Citric acid) H2O	(0.384)0.42	(192.12)210.14	0.43	0.002	1	0.002
						1.025

Water = 881 g + *16,578* (*coming from hydrates*) 0.89758 kg/l

Coming from lipid chamber	**g/l**	**MW (g/mol)**	**g/kg water**	**mol/kg water**	**Amount of ions**	**Osm/kg**
Medium-chain Triglycerides						
Soya-Bean Oil, Refined						
Omega-3-acid triglycerides						
Egg Phospholipids for Injection						

Alpha-tocopherol						
Sodium Oleate	0.06	304.44	0.08	0.0002	2	0.0004
Sodium hydroxide	0.012	40	0.02	0.0005	2	0.001
Glycerol	25	92	33.16	0.36	1	0.36
Water for Injections						
						0.361

No contribution

Water = 753.5 0.7535 kg/l

Total osmolality - mOsm/kg = (1142x0.4) + (1025x0.4) + (361x0.2) ~ 950

Please consider that approximations were made. For example, excipients citric acid (glucose and amino acid chambers) or sodium hydroxide (lipid chamber) are added in the manufacturing process within a range and the calculations were made with the maximum value of the range. Also, for the calculus, the coefficients (0.4; 0.4; 0.2) were added as the initial values of concentrations (second column, <g/l>) are concentrations of the API/excipient in solution, in the corresponding chamber, and each chamber has a contributive proportion to the final solution. This can be done as the water is the solvent for each of the three chamber's electrolytes.

Question

P5.1: FP Specifications

Please provide the reference of the limit and limit range of the osmolality of this product.

Own reference:

The difference between osmolality and osmolarity is as follows [1] [2] [3] [4]:

- **Osmolality** refers to the number of osmoles of solute per kilogram of solvent.
- **Osmolarity** refers to the number of osmoles of solute per liter of solution.

Response

Due to the fact that the osmolality is a measurement (of the depression of freezing point with an Osmometer), a range in the specification must be given due to the variability of the production of the solutions/emulsions and the measurement of the osmolality as such. The given ranges describe nearly the normal specification setting plus/minus 5 % of the nominal value.