HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 October 2011

NUMETAH G13%E, emulsion for infusion
Ten 300 mL bags (CIP code: 416 622-3)

NUMETAH G16%E, emulsion for infusion
Six 500 mL bags (CIP code: 416 624-6)

NUMETAH G19%E, emulsion for infusion
Six 1000 mL bags (CIP code: 416 625-2)

Applicant: BAXTER S.A.S.

Ternary mixture: glucose, amino acids and electrolytes, lipids

ATC code: B05BA10 (solutions for parenteral nutrition)

List I

Date of Marketing Authorisations (decentralised procedure): 18 May 2011

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

NUMETAH G13E

Composition		
Active substance	2 comp.* open (240 mL)	3 comp.** open (300 mL)
Amino acid compartment		
Alanine	0.75 g	0.75 g
Arginine	0.78 g	0.78 g
Aspartic acid	0.56 g	0.56 g
Cysteine	0.18 g	0.18 g
Glutamic acid	0.93 g	0.93 g
Glycine	0.37 g	0.37 g
Histidine	0.35 g	0.35 g
Isoleucine	0.62 g	0.62 g
Leucine	0.93 g	0.93 g
Lysine monohydrate equivalent to Lysine:	1.15 g (1.03 g)	1.15 g (1.03 g)
Methionine	0.22 g	0.22 g
Ornithine hydrochloride equivalent to Ornithine:	0.30 g (0.23 g)	0.30 g (0.23 g)
Phenylalanine	0.39 g	0.39 g
Proline	0.28 g	0.28 g
Serine	0.37 g	0.37 g
Taurine	0.06 g	0.06 g
Threonine	0.35 g	0.35 g
Tryptophan	0.19 g	0.19 g
Tyrosine	0.07 g	0.07 g
Valine	0.71 g	0.71 g
Potassium acetate	0.61 g	0.61 g
Calcium chloride dihydrate	0.55 g	0.55 g
Magnesium acetate tetrahydrate	0.27 g	0.27 g
Sodium glycerophosphate hydrate	0.98 g	0.98 g
Glucose solution compartment		
Glucose monohydrate equivalent to anhydrous glucose:	44.00 g (40.00 g)	44.00 g (40.00 g)
Lipid emulsion compartment		
Refined olive oil (approximately 80%) + refined soybean oil (approximately 20%)	-	7.5 g

* 2 comp = two compartments of the bag, ** 3 comp = three compartments of the bag

NUMETAH G16E

Composition		
Active substance	2 comp.* open (376 mL)	3 comp.** open (500 mL)
Amino acid compartment		
Alanine	1.03 g	1.03 g
Arginine	1.08 g	1.08 g
Aspartic acid	0.77 g	0.77 g
Cysteine	0.24 g	0.24 g
Glutamic acid	1.29 g	1.29 g
Glycine	0.51 g	0.51 g
Histidine	0.49 g	0.49 g
Isoleucine	0.86 g	0.86 g
Leucine	1.29 g	1.29 g
Lysine monohydrate equivalent to Lysine:	1.59 g (1.42 g)	1.59 g (1.42 g)
Methionine	0.31 g	0.31 g
Ornithine hydrochloride equivalent to Ornithine:	0.41 g (0.32 g)	0.41 g (0.32 g)
Phenylalanine	0.54 g	0.54 g
Proline	0.39 g	0.39 g
Serine	0.51 g	0.51 g
Taurine	0.08 g	0.08 g
Threonine	0.48 g	0.48 g
Tryptophan	0.26 g	0.26 g
Tyrosine	0.10 g	0.10 g
Valine	0.98 g	0.98 g
Sodium chloride	0.30 g	0.30 g
Potassium acetate	1.12 g	1.12 g
Calcium chloride dihydrate	0.46 g	0.46 g
Magnesium acetate tetrahydrate	0.33 g	0.33 g
Sodium glycerophosphate hydrate	0.98 g	0.98 g
Glucose solution compartment		
Glucose monohydrate equivalent to anhydrous glucose:	85.25 g (77.50 g)	85.25 g (77.50 g)
Lipid emulsion compartment		
refined olive oil (approximately 80%) + refined soybean oil (approximately 20%)	-	15.5 g

* 2 comp = two compartments of the bag, ** 3 comp = three compartments of the bag

NUMETAH G19E

Composition		
Active substance	**2 comp.* open (775 mL)**	**3 comp.** open (1000 ml)**
Amino acid compartment		
Alanine	1.83 g	1.83 g
Arginine	1.92 g	1.92 g
Aspartic acid	1.37 g	1.37 g
Cysteine	0.43 g	0.43 g
Glutamic acid	2.29 g	2.29 g
Glycine	0.91 g	0.91 g
Histidine	0.87 g	0.87 g
Isoleucine	1.53 g	1.53 g
Leucine	2.29 g	2.29 g
Lysine monohydrate equivalent to Lysine:	2.82 g (2.51 g)	2.82 g (2.51 g)
Methionine	0.55 g	0.55 g
Ornithine hydrochloride equivalent to Ornithine:	0.73 g (0.57 g)	0.73 g (0.57 g)
Phenylalanine	0.96 g	0.96 g
Proline	0.69 g	0.69 g
Serine	0.91 g	0.91 g
Taurine	0.14 g	0.14 g
Threonine	0.85 g	0.85 g
Tryptophan	0.46 g	0.46 g
Tyrosine	0.18 g	0.18 g
Valine	1.74 g	1.74 g
Sodium chloride	1.79 g	1.79 g
Potassium acetate	3.14 g	3.14 g
Calcium chloride dihydrate	0.56 g	0.56 g
Magnesium acetate tetrahydrate	0.55 g	0.55 g
Sodium glycerophosphate hydrate	2.21 g	2.21 g
Glucose solution compartment		
Glucose monohydrate equivalent to anhydrous glucose:	210.65 g (191.50 g)	210.65 g (191.50 g)
Lipid emulsion compartment		
Refined olive oil (approximately 80%) + refined soybean oil (approximately 20%)	-	28.1 g

* 2 comp = two compartments of the bag, ** 3 comp = three compartments of the bag

1.2. Background

NUMETAH proprietary medicinal products are the leading ternary mixtures for paediatric parenteral nutrition. They are supplied in a three-compartment bag. Each bag contains a 50% glucose solution, a 5.9% amino acid solution with electrolytes and a 12.5% lipid emulsion. The NUMETAH content can be administered with or without lipids as required.

1.3. Indications

NUMETAH G13E:
“NUMETAH is indicated for parenteral nutrition in premature newborns when oral or enteral nutrition is impossible, insufficient or contraindicated.”

NUMETAH G16E:
“NUMETAH is indicated for parenteral nutrition in full-term newborns and children aged under 2 years when oral or enteral nutrition is impossible, insufficient or contraindicated.”

NUMETAH G19E:
“NUMETAH is indicated for parenteral nutrition in children over 2 years and adolescents between 16 and 18 years when oral or enteral nutrition is impossible, insufficient or contraindicated.”

1.4. Dosage

See SPC

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)

B : Blood and blood forming organs
B05 : Blood substitutes and perfusion solutions
B05B : Intravenous solutions
B05BA : Solutions for parenteral nutrition
B05BA10 : Combinations (solutions for parenteral nutrition)

2.2. Medicines in the same therapeutic category

In newborns
PEDIAVEN AP-HP NOUVEAU-NE 1 is a binary mixture for parenteral nutrition intended for premature infants and newborns in the first 48 hours of life.
PEDIAVEN AP-HP NOUVEAU-NE 2 can be used as a follow-on to PEDIAVEN AP-HP NOUVEAU-NE 1 up to the age of one month.
NP 100 PREMATURES AP-HP is a binary mixture intended for newborns, whether premature or not.

In children and adolescents
There are two binary nutrition solutions indicated for parenteral nutrition in children:
NP2 ENFANTS AP-HP, without trace elements as in the NUMETAH range
PEDIAVEN G15, G20 and G25, which contains trace elements.

2.3. Medicines with a similar therapeutic aim

There are solutions supplied separately that can be used for parenteral nutrition in newborns. They are based on amino acids, glucose and solutions of electrolytes, lipids and trace elements. These various nutrients and micronutrients are first reconstituted in a nutrition bag or administered together by a drip.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

- **Data on the composition of NUMETAH**

Glucose
NUMETAH provides glucose in concentrated form, in a 50% glucose solution.
Carbohydrates, provided in the form of glucose, must form 60 to 70% of expected total calories (110 to 120 kcal/kg/day in premature infants, and 90 to 100 kcal/kg/day in newborns). This glucose intake is essential, particularly since premature infants and low-birth-weight newborns are at a high risk of hypoglycaemia because of inadequate glycogen reserves, deficient gluconeogenic substrates and the immaturity of certain gluconeogenesis enzymes.

Amino acids
NUMETAH has a compartment for 5.9% paediatric amino acid solution containing electrolytes. This is a dilute solution of PRIMENE 10%, a proprietary medicinal product intended for parenteral nutrition in full-term or premature newborns, infants and children.
This is in line with international guidelines on intake.

Lipids
One compartment of NUMETAH contains a 12.5% lipid emulsion. This is a dilute solution of CLINOLEIC 20%, a proprietary medicinal product intended for parenteral nutrition at any age. This lipid compartment may be left unused if necessary.
European recommendations[1] do not set out any choice as to the use of binary or ternary mixtures. However, lipids form an integral part of paediatric parenteral nutrition and are recommended for all patients, including premature newborns from the first day of life (and no later than the third day), both to provide essential fatty acids and to ensure a sufficient energy intake without a carbohydrate overload.[2]

Electrolytes
NUMETAH contains calcium, magnesium and phosphorus. NUMETAH G16 contains 0.3 g sodium, and NUMETAH G19 1.79 g sodium.
A calcium intake right from birth helps prevent both a postnatal fall in blood calcium levels and early neonatal hypocalcaemia. The electrolyte content, which varies from one form of NUMETAH to another, is in line with European guidelines.[2]

- **PedMCB study**

NUMETAH was assessed in an open-label non-comparative observational study including 159 patients aged under 18 years.

[1] Koletzko B et al. Global standard for the composition of infant formula: recommendations of an European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) coordinated international expert group. J Pediatr Gastroenterol Nutr. 2005; 41 (5): 584-99.
[2] Koletzko B et al. Parenteral Nutrition Guidelines Working Group; European Society for Clinical Nutrition and Metabolism; European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005; 41: Suppl 2: S33-38.

The main inclusion criteria were:

- premature or full-term infant or child up to the age of 18 years, requiring parenteral nutrition for at least five days.
- parenteral nutrition should represent at least 80% of estimated nutritional requirements in premature newborns and at least 50% of estimated requirements in the other groups (full-term infants and young children aged under two years, children and adolescents).

Efficacy endpoints
This study did not have a primary endpoint.
Its efficacy endpoints included:

- activation types (two or three compartments),
- volume infused,
- body weight,
- any supplements administered.

Results:

Characteristics of the patients included:
Patients were treated with the NUMETAH bag appropriate for their age:

- 300 mL for premature infants (NUMETAH G13E)
- 500 mL for full-term infants and children aged under 2 years (NUMETAH G16E)
- 1000 mL for children and adolescents (NUMETAH G19E).

The following population was treated:
Table 1: age and weight of population at inclusion

NUMETAH	No. of patients treated	Mean weight	Mean age	Median age
300 mL	113	1373 ± 501 g	7.4 ± 10.5 days	3 days
500 mL	28	3325 ± 1261 g	1.3 ± 2.3 months	5.5 days
1000 mL	18	31.0 ± 14.7 kg	9.6 ± 4.3 years	9.1 years

Results for activation type
During the study 1,217 bags of NUMETAH were administered by drip.

Table 2: distribution by type of NUMETAH bag

Activation method	Number of bags administered	Number of three-compartment bags administered	Number of two-compartment bags administered
300 mL	934	894	40 (4.3%)
500 mL	147	118	29 (19.7%)
1000 mL	136	116	20 (14.8%)
Total	1217	1128 (93%)	89 (7%)

Around 77% of bags were the 300 mL size.

A majority (93%) of the 1217 bags administered were the three-compartment type (amino acids/electrolytes, glucose solution and lipids).

Results for nutritional intake and volume administered

Nutritional intake can be analysed by the following volumes administered:

Table 3: NUMETAH G13%E, 300 mL bag

Parameters	**Mean ± SD for maximum daily intake of parenteral nutrition**	**ESPEN/ESPGHAN guidelines[3] in stable phase**
Total volume infused (mL/kg/day)	114.3 ± 26.2	100 – 180
Amino acids (g/kg/day)	3.62 ± 0.87	3.5 – 4
Glucose (g/kg/day)	15.40 ± 3.70	12 – 18
Lipids (g/kg/day)	2.74 ± 0.83	2 – 3 (up to 4)
Total calories (kcal/kg/day)	103.7 ± 23.6	100 – 120

Table 4: NUMETAH G16%E, 500 mL bag

Parameters	**Mean ± SD for maximum daily intake of parenteral nutrition**	**ESPEN/ESPGHAN guidelines for stable phase**
Total volume infused (mL/kg/day)	95.3 ± 25.0	80 – 150
Amino acids (g/kg/day)	2.56 ± 0.68	2 – 3
Glucose (g/kg/day)	15.26 ± 4.07	12 – 18
Lipids (g/kg/day)	2.67 ± 1.20	1.5 – 4
Total calories (kcal/kg/day)	97.9 ± 26.0	80 – 100

Table 5: NUMETAH G19%, 1000 mL bag

Parameters	**Mean ± SD for maximum daily intake of parenteral nutrition**	**ESPEN/ESPGHAN guidelines for stable phase**
Total volume infused (mL/kg/day)	39.3 ± 21.9	50 – 100
Amino acids (g/kg/day)	0.93 ± 0.49	1 – 2 (up to 3)
Glucose (g/kg/day)	7.73 ± 4.08	6 – 12
Lipids (g/kg/day)	1.00 ± 0.73	0.5 – 2 (up to 3)
Total calories (kcal/kg/day)	44.6 ± 25.1	30 – 90

Results for weight

The change in weight was measured after 10 days in premature infants and 5 days in other children. These changes can constitute undernourishment markers in newborns but not in older children.

Table 6: changes in weight

NUMETAH	N	Weight before treatment (g)	Weight at end of treatment (g)	Difference between start and end of treatment (g)
300 mL	113	1373 ± 501	1595 ± 523	221 ± 131
500 mL	28	3325 ± 1,261	3483 ± 1,232	163 ± 203
1000 mL	18	31,022 ± 14,774	31,560 ± 15,041	538 ± 774

Supplements

Vitamin supplements were administered to all the subjects included. Trace element supplements were administered to more than 2/3 of children and newborns.

Table 7: rate of administration of trace element supplements

	300 mL N (%)	500 mL N (%)	1000 mL N (%)
Trace elements	105 (93)	20 (71)	12 (67)

3.2. Adverse effects

- **Data from the PedMCB study**

The adverse effects recorded during this study were mainly metabolic disorders (as shown below).

Table 8: number of adverse effects

Adverse effects	Number of cases/number of patients included
Hyperglycaemia	14/159
Hypertriglyceridaemia	8/159
Hyponatraemia	7/159
Hypophosphataemia	5/159
Hypercalcaemia	4/159
Hyperlipidaemia	1/159
Cholestasis	1/159

- **Data from SPC**

The SPC mentions a risk of fat overload. This involves a reduced ability to eliminate the lipids contained in NUMETAH, which can occur in the case of overdose or administration of normal doses. It is generally reversible when infusion of the lipid emulsion is discontinued.

- **Risk management plan**

A risk management plan (RMP) was set up.
The following risks were identified:
- errors in administering the medicinal product
- use in patients who are hypersensitive to one of the ingredients.
- use in patients with severe metabolic disorders
- infection or septicaemia associated with the use of catheters
- refeeding syndrome
- use in patients with disorders of certain organs.

3.3. Conclusion

NUMETAH provides the main nutrients, apart from trace elements and vitamins.
The results of an observational study show that the volumes administered provided an intake of amino acids, glucose and lipids in line with international guidelines.

The use of NUMETAH sometimes has to be combined with the administration of sodium supplements, the requirements of which can vary as a child develops and from one child to another.
Vitamins and trace elements must be systematically added to NUMETAH.

NUMETAH proprietary medicinal products are ready for use and have a composition that provides an intake of nutrients in line with guidelines, and supplements should be administered according to clinical cases. They provide greater pharmaceutical safety and quality than hospital-prepared products made up to the formula because there is less handling and a lower risk of septic contamination.

Because of their high osmolarity, these proprietary medicinal products are not diluted and must be administered exclusively via a central line. Diluting NUMETAH with water for injections reduces its osmolarity and allows it to be infused via a peripheral vein. This effect of dilution on osmolarity is mentioned in the SPC (see “method of administration”).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The purpose of parenteral nutrition in children with prolonged total or partial digestive intolerance is to prevent the short- and medium-term clinical consequences of malnutrition or undernourishment that might lead to prolonged hospitalisation and sequelae including death.

These proprietary medicinal products fall under the category of curative treatment.

The treatment constitutes a replacement for enteral nutrition. The efficacy/adverse effects ratio of these ternary mixtures is high.

There are treatment alternatives: these include making up nutrition bags at the hospital, particularly using various commercially available solutions. These preparations are administered by Y-type infusion set using an infusion manifold.
There are also proprietary medicinal products available for parenteral nutrition as a binary mixture.

Public health benefit

Disorders requiring parenteral nutrition constitute serious clinical conditions, particularly in premature newborns or in the case of digestive intolerance. The burden represented by these disorders can be considered moderate.
Reducing perinatal mortality is a public health requirement covered by the French Public Health Act of 2004.
NUMETAH proprietary medicinal products appear to provide better, faster access – particularly in an emergency – to high-quality care (composition of solution, aseptic condition). They therefore partly meet this need.
However, in the absence of clinical data, their impact on morbidity and mortality cannot be quantified. These proprietary medicinal products are expected to have a positive impact on the organisation of care but this cannot be quantified at present.
Consequently, these proprietary medicinal products are not expected to offer any public health benefit.

The actual benefit of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

Since the composition of NUMETAH products is in line with guidelines, since their quality and pharmaceutical safety are greater than for hospital-prepared products and since there are no alternatives to these preparations, the improvement in actual benefit (IAB) of NUMETAH G13%E, G16%E and G19%E is minor (level IV) in the provision of care to premature infants, young children aged under 2 years and children aged over 2 years, respectively, when parenteral nutrition is required.

4.3. Therapeutic use

As with any solution intended for parenteral nutrition, NUMETAH proprietary medicinal products are indicated in disorders where use of the enteral route is contraindicated or restricted.
The options currently available for paediatric parenteral nutrition are:

- prescription and making up of customised solutions, i.e. solutions that in theory are suited to the needs of newborns on a day-to-day basis.
- use in children of parenteral nutrition solutions intended for adults but with a Marketing Authorisation for children aged over 2 years. Prescribing these solutions is dangerous in the medium or long term and entails a high risk of metabolic complications since they are qualitatively unsuitable for paediatric use.
- proprietary medicinal products in the form of binary mixtures.

NUMETAH can be used as parenteral nutrition in newborns and hospitalised children, particularly in hospitals that do not have a central unit making up parenteral nutrition solutions.
Because of its composition it provides nutrients in line with international guidelines.[1,2,3 ,4]

4.4. Target population

The target population includes all children with prolonged total or partial digestive intolerance who require parenteral nutrition.

There are no available epidemiological data on which to base an estimate of the number of newborns or children with digestive intolerance who need treatment by prolonged (total or partial) parenteral nutrition.

According to the data collected from the cohort TUA for PEDIAVEN, more than 11,200 newborns received this product over a three-year period, i.e. approximately 3700 per year. These infants would be suitable to receive NUMETAH G13E 300 mL bag.

With respect to NUMETAH G16E and G19E, in view of the multiple disorders that might require treatment by these proprietary medicinal products and in view of the absence of precise epidemiological data, it is difficult to give a very accurate estimate of the target population that might benefit from these 500 mL and 1000 mL bags of NUMETAH.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indications and at the dosages in the Marketing Authorisation.

[3] American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. Clinical Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients, 2009. J Parenter Enteral Nutr. 2009; 33: 255-9.
[4] ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. Section VII: Normal Requirements-Pediatrics. J Parenter Enteral Nutr. 2002; 26 (1 Suppl): 26SA-32SA.