HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

19 October 2011

PEDIAVEN AP-HP NOUVEAU-NE 1, solution for infusion
250 ml of solution in two chamber bag, B/10 (CIP code: 417 806-0)

PEDIAVEN AP-HP NOUVEAU-NE 2, solution for infusion
250 ml of solution in two chamber bag, B/10 (CIP code: 417 807-7)

Applicant: FRESENIUS KABI FRANCE

Binary solution: glucose, amino acids, electrolytes and trace elements

ATC Code: B05BA10 (solutions for parenteral nutrition)

List I
Medicine for initial hospital prescription

Date of Marketing Authorisation (national procedure): 2 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 ingredient

PEDIAVEN AP-HP NOUVEAU-NE 1

	Amino acids chamber 125 ml	Glucose chamber 125 ml	Mixed solution, ready to use	
			250 ml	1000 ml
Alanine	0.36 g		0.36 g	1.44 g
Arginine	0.24 g		0.24 g	0.96 g
Aspartic acid	0.24 g		0.24 g	0.96 g
Acetylcysteine Equivalent to cysteine	0.08 g 0.06 g		0.08 g 0.06 g	0.32 g 0.24 g
Glutamic acid	0.41 g		0.41 g	1.64 g
Glycine	0.12 g		0.12 g	0.48 g
Histidine	0.12 g		0.12 g	0.48 g
Isoleucine	0.18 g		0.18 g	0.72 g
Leucine	0.40 g		0.40 g	1.60 g
Lysine monohydrate Equivalent to anhydrous lysine	0.36 g 0.32 g		0.36 g 0.32 g	1.44 g 1.28 g
Methionine	0.07 g		0.07 g	0.28 g
Phenylalanine	0.16 g		0.16 g	0.64 g
Proline	0.32 g		0.32 g	1.28 g
Serine	0.22 g		0.22 g	0.88 g
Taurine	0.02 g		0.02 g	0.08 g
Threonine	0.21 g		0.21 g	0.84 g
Tryptophane	0.08 g		0.08 g	0.32 g
Tyrosine	0.03 g		0.03 g	0.12 g
Valine	0.21 g		0.21 g	0.84 g
Glucose monohydrate Equivalent to anhydrous glucose		27.5 g 25.0 g	27.5 g 25.0 g	110.0 g 100.0 g
Calcium gluconate monohydrate		1.05 g	1.05 g	4.20 g
Magnesium lactate dihydrate		0.12 g	0.12 g	0.48 g
Zinc acetate dihydrate		1.70 mg	1.70 mg	6.80 mg
Copper sulfate pentahydrate		0.23 mg	0.23 mg	0.92 mg
Sodium fluoride		44.2 µg	44.2 µg	0.18 mg
Selenium dioxide		6.7 µg	6.7 µg	0.03 mg
Manganese chloride tetrahydrate		5.4 µg	5.4 µg	0.02 mg
Potassium iodide		3.3 µg	3.3 µg	0.01 mg
Chromium chloride hexahydrate		2.6 µg	2.6 µg	0.01 mg

PEDIAVEN AP-HP NOUVEAU-NE 2

Active ingredients	Amino acids chamber 125 ml	Glucose chamber 125 ml	Mixed solution, ready to use 250 ml	Mixed solution, ready to use 1000 ml
Alanine	0.41 g		0.41 g	1.64 g
Arginine	0.27 g		0.27 g	1.08 g
Aspartic acid	0.27 g		0.27 g	1.08 g
Acetylcysteine Equivalent to cysteine	0.094 g 0.07 g		0.094 g 0.07 g	0.38 g 0.28 g
Glutamic acid	0.46 g		0.46 g	1.84 g
Glycine	0.14 g		0.14 g	0.56 g
Histidine	0.14 g		0.14 g	0.56 g
Isoleucine	0.20 g		0.20 g	0.80 g
Leucine	0.46 g		0.46 g	1.84 g
Lysine monohydrate Equivalent to anhydrous lysine	0.40 g 0.36 g		0.40 g 0.36 g	1.60 g 1.44 g
Methionine	0.08 g		0.08 g	0.32 g
Phenylalanine	0.18 g		0.18 g	0.72 g
Proline	0.36 g		0.36 g	1.44 g
Serine	0.25 g		0.25 g	1.00 g
Taurine	0.02 g		0.02 g	0.08 g
Threonine	0.23 g		0.23 g	0.92 g
Tryptophane	0.09 g		0.09 g	0.36 g
Tyrosine	0.03 g		0.03 g	0.12 g
Valine	0.23 g		0.23 g	0.92 g
Monopotassium phosphate	0.31 g		0.31 g	1.24 g
Potassium hydroxide	0.11 g		0.11 g	0.44 g
Glucose monohydrate Equivalent to anhydrous glucose		27.5 g 25.0 g	27.5 g 25.0 g	110.0 g 100.0 g
Calcium gluconate monohydrate		0.86 g	0.86 g	3.44 g
Magnesium lactate dihydrate		0.098 g	0.098 g	0.39 g
Sodium chloride		0.29 g	0.29 g	1.16 g
Zinc acetate dihydrate		1.93 mg	1.93 mg	7.72 mg
Copper sulfate pentahydrate		0.26 mg	0.26 mg	1.04 mg
Sodium fluoride		49.7 µg	49.7 µg	0.20 mg
Selenium dioxide		7.4 µg	7.4 µg	0.03 mg
Manganese chloride tetrahydrate		5.4 µg	5.4 µg	0.02 mg
Potassium iodide		3.3 µg	3.3 µg	0.01 mg
Chromium chloride hexahydrate		3.8 µg	3.8 µg	0.02 mg

1.2. Background

PEDIAVEN AP-HP NOUVEAU-NE 1 is a parenteral nutrition binary solution intended for premature infants and neonates during the first 48 hours of life.

PEDIAVEN AP-HP NOUVEAU-NE 2 allows taking over the parenteral nutrition with PEDIAVEN AP-HP NOUVEAU-NE 1 up to the age of 1 month.

1.3. Indication

PEDIAVEN AP-HP NOUVEAU-NE 1:

"Indicated for parenteral nutrition when enteral nutrition is impossible, insufficient or contraindicated.

PEDIAVEN AP-HP NOUVEAU-NE 1 is indicated to meet the daily requirements of nitrogen (amino acids of the L series), glucose, electrolytes, trace elements and fluid requirements of neonates in the first 24 to 48 hours of life, whether they are premature or not."

PEDIAVEN AP-HP NOUVEAU-NE 2:

"Indicated for parenteral nutrition when enteral nutrition is impossible, insufficient or contraindicated.

PEDIAVEN AP-HP NOUVEAU-NE 2 is indicated to meet the daily requirements of nitrogen (amino acids of the L), glucose, electrolytes, trace elements and fluid requirements of neonates, premature or not, from the 2nd day of life to the age of 1 month (age corrected for premature neonates).. "

1.4. Dosage

See SmPC

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

There is a binary nutritional solution indicated in premature neonates for parenteral nutrition: NP100 PREMATURES AP-HP.
NUMETAH G13%E is ternary mixture indicated for a parenteral nutrition in premature neonates up to one month.
These medicinal products do not contain trace elements.

2.3. Medicines with a similar therapeutic aim

There are solutions available separately that can be used for parenteral nutrition in neonates. These are based on amino acids, glucose, electrolyte, lipid and trace element solutions. These different nutrients and micronutrients are firstly reconstituted in a feeding bag or given jointly intravenously.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

PEDIAVEN AP-HP NOUVEAU-NE has not been the subject of specific clinical trials, especially due to the difficulty in assessing the efficacy of nutrition after a short period of administration (less than 48 hours for PEDIAVEN AP-HP NOUVEAU NE 1 and 1month for PEDIAVEN AP-HP NOUVEAU NE 2).

A TAU[1] (Temporary Authorisation of Use) for a cohort was granted in April 2007.

PEDIAVEN AP-HP NOUVEAU NE includes the following components:

Amino acids
The amino acid composition of PEDIAVEN AP-HP NOUVEAU-NE is similar to that of VAMINOLACT, an amino acid solution with a composition close to that found in breast milk. VAMINOLACT, which has been marketed for nearly 25 years, is indicated for the artificial nutrition of premature infants, neonates at term, infants and paediatric patients.

Glucose
The PEDIAVEN AP-HP NOUVEAU-NE medicinal products provide glucose at a concentration of 10%. Carbohydrates, in the form of glucose, must be provided in the order of 110 to 120 kcal/kg/day in premature infants, and 75 to 90 kcal/kg/day in neonates at term. This glucose intake is essential as premature infants and low birth weight neonates are at a high risk of hypoglycaemia through insufficiency in glycogen reserves, neoglucogenesis substrates deficiency and an immaturity in certain neoglucogenesis enzymes.

Electrolytes
The electrolytes provided are different depending on the different PEDIAVEN AP-HP NOUVEAU-NE proprietary medicinal products.
PEDIAVEN AP-HP NOUVEAU NE 1 is intended to meet the fluid and metabolic requirements of neonates, premature or not, during the first 24 to 48 hours of life, and contains low amount of sodium (4.5 mmol/l) and chloride (5 mmol/l). It contains calcium (9 mmol/l) and magnesium (2.1 mmol/l) but not phosphorus. Calcium intake from birth helps to prevent post-natal calcaemia drops and early neonatal hypocalcaemia in premature infants. The absence of phosphorus contraindicates the long term use of PEDIAVEN AP-HP NOUVEAU NE 1 after the first 48 hours of life.
PEDIAVEN AP-HP NOUVEAU NE 2 contains 7.6 mmol/l of calcium, 9.1 mmol/l of phosphorus, 1.6 mmol/l of magnesium, 20 mmol/l of sodium, 17 mmol/l of potassium and 26 mmol/l of chloride.
The electrolyte composition meets European guidelines.[2]

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[1] *TAU is a premarket approval for compassionate use. It is an exceptional measure providing access to certain promising new medicinal products that do not have a MA for the treatment of serious or rare diseases/conditions, in the absence of a suitable therapeutic alternative (with a MA), and when there is a presumed positive benefit/risk ratio (www.ansm.sante.fr). The use of a medicinal product in the context of an ATU is subject to regular monitoring by the regulatory agency, mainly focusing on compliance with the indications and analysis of adverse reactions*

[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.

Trace elements
The trace element composition, quantitatively different for PEDIAVEN AP-HP NOUVEAU NE 1 and 2, meets guidelines[2]. These medicinal products provide intake in chromium, copper, iodine, fluoride, manganese, selenium and zinc.

No lipids
PEDIAVEN AP-HP NOUVEAU-NE is a binary solution and thus does not contain lipids. European guidelines[3] do not conclude on the use of binary or ternary mixtures. However, lipid intake is an integral part of paediatric parenteral nutrition and it is recommended for all patients, including premature neonates from the first day of life (and no later than from the third day), to not only provide essential fatty acids, but also give enough energy intake with no carbohydrate overload[2].
The absence of lipid in PEDIAVEN AP-HP NOUVEAU-NE means that lipid intake can be administered independently from other elements, the volume can be adapted for each clinical situation and the lipid administration could be temporarily stopped if required.

Compatibility studies performed with PEDIAVEN AP-HP NOUVEAU-NE solutions and lipid emulsions have shown that it is possible to administer them together with through a Y-site.

3.2. Adverse Effects

Data from TAU use[4]

The PEDIAVEN AP-HP NOUVEAU-NE medicinal products had a TAU for a cohort granted in April 2007.
Over a four year period, from 30 April 2007 to 30 April 2011, 46,563 bags of PEDIAVEN AP-HP NOUVEAU NE 1 and 82,350 bags of PEDIAVEN AP-HP NOUVEAU NE 2 were administered. In total, PEDIAVEN AP-HP NOUVEAU-NE bags have been used in 97 hospitals.

During this four year period, 56 adverse effects possibly attributed to the PEDIAVEN solutions were reported, of which 40 were classified as "General disorders and administration site conditions" and 16 as "Metabolism and nutritional disorders".
The 16 serious adverse effects related to PEDIAVEN are divided as follows:
- 1 hyperkalaemia (due to inadequate usage),
- 3 hypercalcaemias of which one resulted in death not related to hypercalcaemia,
- 1 hyperglycaemia,
- 7 skin necrosis,
- 1 upper limb oedema,
- 1 physiochemical incompatibility considered as severe but with no consequences on the clinical and biological status of the patient
- 1 extravasation (second degree burns),
- 1 multi-organ failure due to substance abuse (PEDIAVEN AP-HP NOUVEAU-NE 2 bag has been completely administered in 1h30 instead of 24 hours).

[3] Koletzko B et al. Global standard for the composition of infant formula: guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) coordinated international expert group. J Pediatr Gastroenterol Nutr. 2005; 41 (5): 584-99.
[4] Periodic summary report for the Temporary Authorisation of Use of a cohort. 30 April 2007 to 30 April 2011.

Information from the SmPC

The SmPC states the adverse effects linked to parenteral nutrition in general, and in particular those of metabolism and nutrition disorders (hyperglycaemia, metabolic acidosis, hyperphenylalaninemia and electrolyte imbalance).
Inadequate usage conditions (excessive or inappropriate intake or too fast infusion rate) can lead to signs of hyperglycaemia, hypercalcaemia or hypovolaemia.

3.3. Conclusion

PEDIAVEN AP-HP NOUVEAU NE 1 (at the dosage of 60 to 120 ml/kg) and PEDIAVEN AP-HP NOUVEAU NE 2 (at the dosage of 80 to 180 ml/kg), according to the average daily fluid requirements of the premature infant and neonate, allow to supply of main nutrients at recommended levels, with the exception of lipids and vitamins.

PEDIAVEN AP-HP NOUVEAU NE 1 and 2 medicinal products are ready-to–use solutions; their compositions meet the guidelines, and supplementations could be made to be adapted with the patient‘s clinical situation. They allow a higher quality and pharmaceutical safety than parenteral nutrition admixture prepared in the hospital pharmacy (hospital-made preparations) due to less handling and a lower risk of microbial contamination.
In addition, their composition could be adapted to many clinical situations during the first 48 hours of life and the first month, in accordance with the nutritional requirements of neonates that change during the first weeks of life.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Parenteral nutrition in paediatric patients with prolonged, total or partial gastrointestinal intolerance aims to restrict the short and medium term clinical consequences of malnutrition, of malnutrition which could increase the length of hospitalisation and, even, the death.

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

They are substitution treatments for enteral feeding. The efficacy/adverse effects ratio for these binary solutions is high.

There are alternative alternatives: hospital-made preparations of nutrition, specifically made from different solutions available on the market. These preparations are given intravenously via a Y-site under ramped infusion.
There is also binary solution intended for neonates: NP 100 PREMATURES, however its composition does not meet international guidelines.

Public health benefit

Diseases that require parenteral nutrition are serious clinical situations, and in particular in premature neonates or in cases of gastrointestinal intolerance. The burden represented by these disorders can be considered as moderate.
The reduction in perinatal mortality is a public health need stated in the public health law of 2004.

PEDIAVEN NOUVEAU NE 1 and 2 medicinal products appear to provide, particularly in emergency situations, a better accessibility in the shortest time possible to quality care (composition of solution and sterility). Therefore, in part, they meet this health need.
However, due to the absence of clinical data, their impact in terms of morbidity and mortality cannot be quantified. A positive impact in the organisation of care is expected, but it can not currently be quantified.
Consequently, it is not expected that these medicinal products will have a public health benefit.

The actual benefit for these proprietary medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

Given that their compositions meet guidelines, their quality and pharmaceutical safety are better than that of hospital-made preparations, the absence of any alternative apart from these, and the specifically appropriate intake from PEDIAVEN AP-HP NOUVEAU NE 1 in the first two days of life, the improvement in actual benefit (IAB) of PEDIAVEN AP-HP NOUVEAU NE 1 is moderate (level III) and the IAB of PEDIAVEN AP-HP NOUVEAU NE 2 is minor (level IV) in the treatment of neonates, even if they are premature, when parenteral nutrition is necessary in the first hours of life and up to the age of one month.

4.3. Therapeutic use

As for all solutions intended for parenteral nutrition, PEDIAVEN AP-HP NOUVEAU-NE is indicated for conditions where enteral nutrition is contraindicated or restricted.
Currently the treatments available for paediatric parenteral nutrition are:

- Individualized parenteral nutrition adapted to the patient's needs, prescribed and prepared, usually on a daily basis, in the hospital pharmacy,
- separate parenteral nutrition solutions.

PEDIAVEN AP-HP NOUVEAU-NE can be used for hospitalised neonates requiring parenteral nutrition, in a stable clinical situation, especially in hospitals that do not have centralised parenteral nutrition solution making facilities.
Their compositions meet international intake guidelines.[1,2,5,6]

4.4. Target population

The target population is all neonates with prolonged, total or partial, gastrointestinal intolerances for which parenteral nutrition is required.

During a 4 year period (30 April 2007 to 30 April 2011), according to the TAU monitoring forms for a cohort[3] more than 14,700 neonates received a PEDIAVEN AP-HP NOUVEAU-NE solution.

In 70% of cases, these children were premature.

[5] 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.
[6] 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.

The distribution based on the type of PEDIAVEN AP-HP NOUVEAU-NE solution is:

- 11,098 neonates received PEDIAVEN AP-HP NOUVEAU-NE 1
- 7,847 neonates received PEDIAVEN AP-HP NOUVEAU-NE 2.

Some neonates received both.

The large majority of the children (90%) did not receive simultaneous lipid administration.

4.5. Transparency Committee recommendations

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