HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 October 2011

PEDIAVEN AP-HP G15, solution for infusion
1000 ml of solution in two chamber bag, B/4 (CIP code: 419 999-0)

PEDIAVEN AP-HP G20, solution for infusion
1000 ml of solution in two chamber bag, B/4 (CIP code: 419 957-6)

PEDIAVEN AP-HP G25, solution for infusion
1000 ml of solution in two chamber bag, B/4 (CIP code: 216 036-3)

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 the Marketing Authorisation (national procedure): 28 September 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

Nutritional value for 1000 ml	PEDIAVEN AP-HP **G15**	PEDIAVEN AP-HP **G20**	PEDIAVEN AP-HP **G25**
Glucose	150 g	200 g	250 g
Amino acids	15 g	20 g	25 g
Total nitrogen	2.14 g	2.85 g	3.56 g
Total energy	660 kcal	880 kcal	1100 kcal
Non protein-energy	600 kcal	800 kcal	1000 kcal
Sodium	30 mmol	30 mmol	40 mmol
Potassium	25 mmol	25 mmol	40 mmol
Calcium	6 mmol	6 mmol	8 mmol
Magnesium	4 mmol	4 mmol	6 mmol
Chloride	39 mmol	39 mmol	60 mmol
Phosphorus	8 mmol	8 mmol	10 mmol
Chromium	20 µg	20 µg	40 µg
Cobalt	150 µg	150 µg	300 µg
Copper	300 µg	300 µg	600 µg
Iron	500 µg	500 µg	1000 µg
Fluoride	500 µg	500 µg	1000 µg
Iodine	50 µg	50 µg	100 µg
Manganese	100 µg	100 µg	200 µg
Molybdenum	50 µg	50 µg	100 µg
Selenium	50 µg	50 µg	100 µg
Zinc	2000 µg	2000 µg	4000 µg

1.2. Background

PEDIAVEN AP-HP G15, G20 and G25 are parenteral nutrition binary solutions intended for infants, children and adolescents. Their compositions comply with recommendations.

1.3. Indication

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

PEDIAVEN AP-HP G15, G20 and G25 are indicated to meet the daily requirements of nitrogen (amino acids of the L series), glucose, electrolytes, trace elements and fluid intake in infants, children and adolescents in a stable condition, notably without excessive gastrointestinal losses and without severe malnutrition ".

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

NUMETAH G16%E is a ternary mixture indicated for children under 2 years and NUMETAH G19%E for children over 2 years. The lipid chamber of these medicinal products may not be given, if required.
There is a binary nutritional solution indicated for children: NP2 ENFANTS AP-HP.
These medicinal products do not contain trace elements.

2.3. Medicines with a similar therapeutic aim

There are solutions, presented individually, that can be used for parenteral nutrition in infants, children and adolescents. These solutions are based on amino acids, glucose, electrolytes, lipids 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 G15, G20 and G25 have not undergone specific clinical trials.

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

The PEDIAVEN range includes the following components:

Amino acids
The amino acid composition of PEDIAVEN AP-HP G15, G20 and G25 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
These medicinal products provide glucose at a concentration of 15%, 20% or 25%.
It is the only carbohydrate energy source in these mixtures.

Electrolytes
The electrolytes provided are different depending on the different PEDIAVEN AP-HP G15, G20 and G25 medicinal product. The electrolyte compositions meet European guidelines.[2]

Trace elements
Trace element compositions, quantitatively different for PEDIAVEN AP-HP G15/G20 and G25, meet these guidelines. They provide intake in chromium, cobalt, copper, iron, fluoride, iodine, manganese, molybdenum, selenium and zinc.

No lipids
PEDIAVEN AP-HP G15, G20 and G25 are binary solutions and thus do 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 at the latest from the third day), not only to provide essential fatty acids, but also to give enough energy intake with no carbohydrate overload.[2]
The absence of lipid in PEDIAVEN AP-HP G15, G20 and G25 means that amino acids, glucose and electrolytes can be administered independently from lipids, the volume can be

[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.

[3] Koletzko B et al. Global standard for the composition of infant formula: recommendations of a European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) coordinated international expert group. J Pediatr Gastroenterol Nutr. 2005; 41(5): 584-99.

adapted for each clinical situation and the lipid administration could be temporarily stopped if required.
According to the Marketing Authorisation, compatibility studies performed with the PEDIAVEN AP-HP G15, G20 and G25 solutions and lipid emulsions have shown that it is possible to administer them together through a Y-site.

3.2. Adverse effects

Data from TAU use[4]
PEDIAVEN AP-HP G15, G20 and G25 had a TAU for a cohort granted in March 2007.
Over a period of four years, from 30 April 2007 to 30 April 2011, 18,390 bags of PEDIAVEN AP-HP G15, 18,116 of PEDIAVEN AP-HP G20 and 2,400 of PEDIAVEN AP-HP G25 have been administered. In total, PEDIAVEN AP-HP G15, G20 and G25 bags have been used in 59 hospitals.
For the three PEDIAVEN solutions, 6 adverse reactions were reported during this period, 4 of which were hyperglycaemia that could be attributed to the nutrition.

Information from the SPC
The SmPC states the adverse effects linked to parenteral nutrition in general, and in particular those of metabolism and nutrition disorders (hyperglycaemia, metabolic acidosis, hyperphenylalaninaemia and the 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 G15, G20 and G25 allow to provide the main nutrients at the recommended doses, including trace elements, with the exception of lipids and vitamins.

These medicinal products are ready-to–use solutions, with a composition that provides nutritional intake which meets the guidelines, with the possibility of making changes, depending on the clinical situation. They provide higher quality and pharmaceutical safety than parenteral nutrition admixture prepared in the hospital pharmacy due less handling and a lower risk of microbial contamination.

[4] Periodic summary report for the Temporary Authorisation of Use of a cohort. 30 April 2007 to 30 April 2011.

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 or 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 treatment 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 are also medicinal products that allow parenteral nutrition through a binary or ternary mixture.

Public health benefit

Diseases that require parenteral nutrition are serious clinical situations, and in particular in case of gastrointestinal intolerance. The burden represented by theses disorders can be considered as moderate.
PEDIAVEN AP-HP G15, G20 and G25 appear to provide, especially in emergency situations, 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 can not 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 of these medicinal products is substantial.

4.2. Improvement in actual benefit (IAB)

Given that their compositions meet recommendations, and that their quality and pharmaceutical safety are better than those of hospital-made preparations which are the only other alternatives, PEDIAVEN AP-HP G15, G20 and G25 provide a minor improvement in actual benefit (level IV) in the treatment of infants, children and adolescents in a stable condition, notably without excessive gastrointestinal losses and without severe malnutrition when parenteral nutrition is required.

4.3. Therapeutic use

As for all solutions for parenteral nutrition, PEDIAVEN AP-HP G15, G20 and G25 are indicated for conditions where enteral nutrition is contraindicated or restricted.
Currently the treatments available for paediatric parenteral nutrition are:

- individualised parenteral nutrition adapted to the patient's needs, prescribed and prepared, usually on a daily basis, in the hospital pharmacy
- the use of parenteral nutrition products indicated for adults in children, but with a Marketing Authorisation for children over 2 years old. Such a prescription is dangerous over the medium- to long-term, with a higher risk of metabolic complications, as the solutions are not qualitatively adapted for paediatric use.

PEDIAVEN AP-HP G15, G20 and G25 can be used for paediatric patients and adolescents hospitalised for parenteral nutrition, with a stable clinical situation, especially in hospitals that do not have centralised parenteral nutrition solution making facilities.
Their compositions meet international intake guidelines.[2,3,5,6]

4.4. Target population

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

During a of 4-year period (30 April 2007 to 30 April 2011), TAU monitoring forms for a cohort[3] were created for 1,613 paediatric patients.

The distribution based on the type of PEDIAVEN AP-HP solution is:
- 1,000 paediatric patients received PEDIAVEN AP-HP G15
- 793 paediatric patients received PEDIAVEN AP-HP G20
- 328 paediatric patients received PEDIAVEN AP-HP G25.

Some paediatric patients were receiving several forms of PEDIAVEN.
The mean treatment duration was 10 days, and the median was 5 days.
Approximately 1/3 of the paediatric patients received a lipid emulsion concomitantly.

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 of the Marketing Authorisation.

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.