HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

31 March 2010

SMOFLIPID 200 mg/ml, emulsion for infusion
B/1 100 ml bottle (CIP code: 376 705-0)
B/1 250 ml bottle (CIP code: 376 706-7)
B/1 500 ml bottle (CIP code: 376 707-3)

Applicant: FRESENIUS KABI FRANCE

refined soya-bean oil
medium-chain triglycerides
refined olive oil
fish oil rich in omega-3 fatty acids

ATC Code: B05BA02

Date of the Marketing Authorisation: 04/07/2006
Extension of indication: 20 January 2010

Reason for request: Assessment of the dosage change permitting use in children.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Refined soya-bean oil
Medium-chain triglycerides
Refined olive oil
Fish oil rich in omega-3 fatty acids

1.2. Indications

"Supply of energy and essential fatty acids and omega-3 fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated."

1.3. Dosage

Adults (unchanged ,see SPC)

Paediatric **dosage** appearing in the new SPC

"*Neonates and infants*
The initial dose should be between 0.5 and 1.0 g fat/kg body weight/day followed by a successive increase by 0.5 – 1.0 g fat/kg body weight./day up to 3.0 g fat/kg body weight/day.
It is recommended not to exceed a daily dose of 3 g fat/kg body weight/d, corresponding to 15 ml SMOFLIPID/kg body weight/day. The rate of infusion should not exceed 0.125 g fat/kg body weight /hour. In premature and low birth weight neonates, SMOFLIPID should be infused continuously over about 24 hours.

Children
It is recommended not to exceed a daily dose of 3 g fat/kg body weight /d, corresponding to 15 ml SMOFLIPID/kg body weight /day. The daily dose should be increased gradually during the first week of administration. The infusion rate should not exceed 0.15 g fat/kg body weight /hour."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

B	:	Blood and blood forming organs
B05	:	Blood substitutes and perfusion solutions
B05B	:	I.V. solutions
B05BA	:	Solutions for parenteral nutrition
B05BA02	:	Fat emulsions

2.2. Medicines in the same therapeutic category

These are the other lipid emulsions indicated for parenteral nutrition in paediatric medicine.

Based on soya long-chain triglycerides:
- ENDOLIPIDE 20%, emulsion for infusion
- INTRALIPIDE 10%, 20%, emulsion for infusion
- IVELIP 20%, emulsion for infusion

Based on soya and olive oil long-chain triglycerides:
- CLINOLEIC 20%, emulsion for infusion

TCM/TCL 50/50
- MEDIALIPIDE 20%, emulsion for infusion

2.3. Medicines with a similar therapeutic aim

These are the other medicinal products indicated in paediatric parenteral nutrition.

3 ANALYSIS OF AVAILABLE DATA

Only the phase III studies have been taken into account.

- **00-SMOF-002 study which compared the efficacy and tolerance of SMOFLIPID** *versus* **INTRALIPIDE**

This was a controlled, randomised, double-blind, parallel-group phase III study.
Twenty-eight children between 1 month and 11 years of age were included. The children had gastrointestinal conditions such as short bowel syndrome, severe refractory diarrhoea or chronic intestinal pseudoobstruction syndrome. The patients had been under parenteral nutrition at home for 4-7 days a week for at least 4 consecutive weeks.
The treatment was as follows: an infusion of 2 g lipids (SMOFLIPID or INTRALIPIDE 20%) /kg/day, or 0.125 g lipids/kg/hour, without ever exceeding a dose of 0.15 g lipids/kg/hour. The treatment was administered continuously over a period of 12-24 h, 4-5 days per week with other nutrients (amino acids, glucose, vitamins and electrolytes packaged in binary bags) for at least 4 consecutive weeks.
The primary endpoint was the tolerability of the product.
Results:
The number of patients who experienced at least one adverse event during the study was comparable in the SMOFLIPID group (7/15 patients, or 46.7%) and in the INTRALIPIDE group (6/13 patients - 46.2%).
No serious adverse reactions were observed and no difference was observed between the two treatment groups in terms of serum triglycerides concentration.

- **03-SMOF-005 study which compared the efficacy and tolerance of SMOFLIPID and INTRALIPIDE 20% in premature infants**

This was a controlled, randomised, double-blind, parallel-group phase III study.
In summary, 84 premature infants born before 34 weeks of gestation, between 1 and 7 days old, with a birth weight of between 500 and 2,000 g, were included. All the infants required parenteral nutrition comprising lipids for at least 7 days.
SMOFLIPID or INTRALIPIDE 20% were administered progressively. Between D1 and D3, 1 g lipids/kg weight/day was administered to the patients. This intake was then increased by 1 g/kg on D4 and then on D5. The lipid intake thus rose to 3.5 g lipids/kg/day between D6 and D14. Enteral nutrition represented up to 30% of the total energy intake between D1 and D3 and up to 50% of the total energy intake between D4 and D14.
The assessment of tolerance was based on the serum triglycerides concentration (primary endpoint).
Results:
There was no difference between the two groups in terms of blood triglycerides levels on D8.
No serious adverse reactions were observed.

- **00-SMOF-004 study which compared the tolerance of SMOFLIPID and INTRALIPIDE in premature infants**

This was a controlled, randomised, double-blind, parallel-group study. In summary, 60 premature infants born before 34 weeks of gestation, between 1 and 7 days old, with a birth weight between 1,000 and 2,500 g, were included. All the patients were to receive parenteral nutrition containing lipids for at least 7 days.
The treatment was as follows: On D1, 0.5 g lipids/kg (SMOFLIPID or INTRALIPIDE 20%) administered, with an increase of 0.5 g/kg/day between D2 and D4, rising to an intake of 2 g/kg/day between D4 and D14. Lipids represented up to 70% of the parenteral nutrition energy intake. Enteral nutrition represented up to 30% of the total energy intake between D1 and D3 and up to 50% of the total energy intake between D4 and D14.
The primary efficacy endpoint was the serum triglycerides level.
Results:
The characteristics of the patients were comparable on inclusion, with the exception of the number of boys, which was higher in the SMOFLIPID group.
In terms of length, weight and head circumference, no difference was observed between the 2 treatment groups. The clinical parameters were comparable between the 2 treatment groups (number of days of antibiotic therapy, sepsis score, duration of ventilatory assistance).
During the study, 29 adverse events were observed in 13/30 patients (43.3%) in the SMOFLIPID group and 28 adverse events in 14/30 patients (46.7%) in the INTRALIPIDE group. The only difference between the groups concerned the lipid parameters, with an increase in omega-3 levels being observed in the SMOFLIPID group.

Results:
There was no difference between the two groups in terms of the blood triglyceride levels on D8.

Conclusion

The three phase III studies conducted in premature newborns and children enabled tolerance to be evaluated and confirmed that SMOFLIPID is well tolerated.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Parenteral nutrition forms part of the management of patients with serious conditions which are liable to be life-threatening: primarily major gastrointestinal and cancer surgery.
From the youngest age, nutrition influences the health of children and the adults they become. Poor nutrition can have potentially serious consequences in children. The poorly nourished child is at risk of increased morbidity and mortality.
This medicinal product is intended as replacement therapy: SMOFLIPID 20% is a replacement therapy for oral and enteral nutrition.

Treatment alternatives exist.

The efficacy/adverse effects ratio is high.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit (IAB)

The medicinal product SMOFLIPID has the same actual benefit in the paediatric population as previously recognised by the transparency Committee in adults (IAB V).

4.3. Therapeutic use

Parenteral nutrition consists of the intravenous infusion of macronutrients (glucose, amino acids, lipids), electrolytes, micronutrients (vitamins and trace elements).
It is limited to certain conditions which make oral and/or enteral nutrition impossible, insufficient or ineffective, notably in cases of intestinal insufficiency caused by short bowel syndrome or severe intestinal malabsorption, states of chronic intestinal obstruction.
It must be initiated in a hospital setting.
Poor nutrition is common in hospitalised patients[1],[2],[3]. The poorly nourished patient is at risk of increased morbidity and mortality[4],[5],[6].
The lipids in parenteral nutrition are emulsions of triglycerides in aqueous phase stabilised with egg or soya phospholipids. Their low osmolarity enables them to be infused via a peripheral vein.

In qualitative terms, commercially available emulsions are differentiated by their fatty acid composition which can modify their functional characteristics[7]. The choice of parenteral nutrition lipid emulsion depends on the qualitative composition of the product, the patient's condition (chronic or acute) and how well the patient tolerates the product[8].

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[1] Jouquan J, Garre M, Pennec Y, Morin JF, Youinou P, Boles JM*, et al.* Prévalence de la dénutrition protidique à l'admission en médecine interne. Etude de 260 adultes hospitalisés. Presse Med 1983;12(14):877-81
[2] Perrot D, Bouletreau P, Seranne C, Bret M, Meunier J, Balay C*, et al.* Evaluation du degré de malnutrition chez les malades hospitalisés en chirurgie. Nouv Presse Med 1982;11(18):1379-83
[3] Rietsch MP, Picand B, Aby MA, Kuntzmann F. Equilibre alimentaire « apparent » et malnutrition « clinique et biologique » de la personne âgée : à propos d'une étude prospective, effectuée auprès de 283 patients hospitalisés. Med Hyg 1989;47(1794):1488-96
[4] Edington J, Boorman J, Durrant ER, Perkins A, Giffin CV, James R*, et al.* Prevalence of malnutrition on admission to four hospitals in England. The Malnutrition Prevalence Group. Clin Nutr 2000;19(3):191-5
[5] Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. Clin Nutr 2003;22(3):235-9
[6] Reilly JJ, Jr., Hull SF, Albert N, Waller A, Bringardener S. Economic impact of malnutrition: a model system for hospitalized patients. JPEN J Parenter Enteral Nutr 1988;12(4):371-6
[7] Société Française d'Anesthésie et de Réanimation, Hasselmann M, Kummerlen C. Comment faut il nourrir les patients de réanimation? 2000. <http://www.sfar.org/sfar_actu/ca00/html/ca00_31/00_31.htm> .
[8] Hasselmann M, Zazzo J. Pratique de la nutrition parentérale. In: Nutrition artificielle de l'adulte en réanimation. Issy les Moulineaux: Elsevier Masson; 2002. p. 180-201

The lipid emulsions available for paediatric use are all 20% lipid emulsions with an identical triglyceride/phospholipid ratio and proven to be well tolerated. They differ in terms of their fatty acid composition and the different characteristics of the fatty acids they contain[9].
The lipid intake must be selected on the basis not only of quantitative (compliance with recommended dosages) and qualitative (choice of emulsion based on composition) criteria, but also on the basis of the anticipated benefits, depending on the clinical status of the child.
SMOFLIPID is a lipid emulsion intended for parenteral nutrition when the infant's clinical status necessitates a supply of fatty acids, as a source of energy but also as a source of omega-6 and omega-3 fatty acids.

4.4. Transparency Committee recommendations

The transparency Committee approves the changes in the conditions of inclusion on the list of medicines approved for hospital use and various public services following the change in the dosage permitting use in children.

[9] Koletzo B, Goulet O, Shamir R. ESPGHAN ESPEN *Guidelines on Paediatric Parenteral Nutrition*. Journal of Pediatric Gastroenterology and Nutrition, 2005 Vol. 41, Suppl. 2