HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

19 March 2008

INTRALIPIDE 20 PER CENT, emulsion for infusion
100 ml in Excel® container (PE/PP) – (CIP: 355 096-5)
250 ml in Excel® container (PE/PP) – (CIP: 355 097-1)

Applicant : FRESENIUS KABI FRANCE

ATC code : B05BA02

Purified soy-bean oil (essential fatty acids)

Date of the Marketing Authorisation (national procedure): 18 December 1997

This medicinal product has already been **approved for hospital use** (Official Bulletin of 24 December 2000, Order of 15 December 2000).

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance for home parenteral nutrition (HPN) of adults and children.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Purified soy-bean oil (essential fatty acids)

Intralipide concentration	20%
Lipid energy value	2 000 kcal/l or 8.4 MJ
Essential fatty acid content	120 g/l (20%)
Osmolarity	260 mOsm/l (20%)
Osmolality	350 mOsm/kg (20%)

- 5 ml of Intralipide 20% supplies 1 g of triglycerides.
- The phospholipids supply 47 mg or 1.5 mmol of phosphorus per 100 ml.

INTRALIPIDE is a soy bean oil based fat emulsion composed of long-chain triglycerides. Triglycerides are hydrolysed by the lipoprotein lipase into essential or non-essential saturated and polyunsaturated fatty acids, which are involved in energy metabolism and cell membrane structure. Long-chain triglycerides help prevent essential fatty acid deficiency syndrome and excessive glucose use. This fat emulsion has biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, however, it does not contain cholesterol esters or apoprotein, and its phospholipid content is significantly higher. This fat emulsion allows a large energy intake, as required for better protein sparing, within a limited volume.

1.2. Indications

Intralipide 20%:
- “Source of lipid energy for patients requiring parenteral nutrition, when oral or enteral nutrition is impossible, inadequate or contraindicated.”
- “Source of essential fatty acids.”

1.3. Dosage

The dosage should be adjusted to the patient’s ability to eliminate fat emulsion.

- Adults: 2-3 g/kg/24 hours, or 10-15 ml/kg/24 h of Intralipide 20%.
- Children and newborn infants (Intralipide 10% and 20% only): 0.5-4 g/kg/24 hours, or 2.5-20 ml/kg/24 h of Intralipide 20%.

Mode of administration: intravenously by slow, progressive infusion via a central or peripheral vein, depending on the final osmolarity of the emulsion in cases where a nutrient mixture is used (with the addition of amino acids and/or electrolytes and/or oligoelements).

- In adults: the volume of one bag (500 ml for Intralipide 20%) should not be administered in less than 5 hours.
- In children and newborn infants (Intralipide 10% and 20% only):
    - In premature and low-weight newborn infants, the infusion should preferably be administered continuously over 24 hours.
    - For any dose between 2 g/kg/day and the maximum dose of 4 g/kg/day, which do not be exceeded, administration should be monitored of serum triglyceride concentration, liver function and oxygen saturation levels.

Use in nutrient mixtures: this fat emulsion may be used in nutrient mixtures combining carbohydrates, amino acids, electrolytes and/or oligoelements, provided that their compatibility and the stability of the final mixture have been verified and the final osmolarity is known.

Reminder of warnings (SPC): Any signs as fever, dyspnea, shivering, rash or general malaise should lead to immediate interruption of the infusion.

Reminder of precautions for use (SPC):

Adults:

- Biological monitoring of liver function is recommended.
- Monitoring of serum triglycerides concentrations is required for high dosages and where treatment duration exceeds one week. The purpose of this monitoring is to verify the patient's ability to eliminate this fat emulsion..
- Close monitoring of the serum triglyceride concentration is mandatory in conditions of impaired metabolism such as renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertriglyceridemic) and sepsis.
- Determination of serum triglyceride concentration and a serum lactescence test (albeit less precise) should be performed within 6 hours after the end of the infusion.

Newborn and premature infants (Intralipide 10% and 20%):

- The ability to eliminate the infused fat is not fully developed in the newborn infant, particularly in pre-term and very low birth weight infants.
- If hyperbilirubinemia appears or pulmonary hypertension may be suspected, monitoring of platelets, liver function, serum triglycerides and serum fatty acid levels should be performed.
- Close monitoring of serum triglyceride levels is required in newborn infants with suspected sepsis and high C-reactive protein levels.

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

Other fat emulsions indicated for parenteral nutrition (not reimbursed under National Insurance):[1]

Based on soya long-chain triglycerides:
INTRALIPIDE 10%, emulsion for infusion (500 ml bags)
(Children and newborn infants: Intralipide 10% and 20% only)
- ENDOLIPIDE 20%, emulsion for infusion (100, 250 and 500 ml bottles)
- IVELIP 20%, emulsion for infusion (100, 250, 500 and 1000 ml bags)
- IVELIP 10% and 20%, emulsions for infusion (100, 250, 500 and 1000 ml bottles)
- LIPIDEM 20%, emulsion for infusion (250 ml bottles)
(Children: Safety and efficacy have not been demonstrated in children and adolescents.)
- INTRALIPIDE 30%, emulsion for infusion (333 ml bags)

Based on soya and olive oil long-chain triglycerides:
- CLINOLEIC 20%, emulsion for infusion (100, 250, 350, 500 and 1000 ml bags)
- CLINOLEIC 20%, emulsion for infusion (100, 250, 500 and 1000 ml bottles)
(Clinoleic 20% is reserved for pre-term infants at a gestational age of at least 28 weeks.)

MCT/LCT 50/50
- MEDIALIPIDE 10% and 20%, emulsions for infusion (100, 250 and 500 ml bottles)

Structured triglycerides
- STRUCTOLIPIDE 20%, emulsion for infusion
(Safety and efficacy have not been determined in children) (250 and 500 ml bags)

Fish oils
- OMEGAVEN emulsion for infusion (fish oils) (50 and 100 ml bottles)
(Contraindicated in infants, including preterm and newborn, and children: insufficient clinical experience has been acquired with these patients.)

2.3. Medicines with a similar therapeutic aim

For Home parenteral nutrition (HPN) at the patient's home: "industrially prepared" nutrient mixtures for home parenteral nutrition for adults, particularly those known as ternary intravenous solutions for parenteral nutrition, based on carbohydrates, amino acids, glucose and fats (with or without electrolytes), in the form of a three-compartment bag: OLICLINOMEL, NUTRIFLEX. These mixtures need to be supplemented with oligoelements and vitamins.

[1] Products approved for hospital use, to be prescribed only by a doctor practising in a hospital or approved parenteral nutrition centre.

3 ANALYSIS OF AVAILABLE DATA

The efficacy and adverse effects of emulsions of soya-bean oil long-chain triglycerides (LCT) rich in essential fatty acids are well established in parenteral nutrition (PN). The applicant has not submitted any new clinical study.

The efficacy and adverse effects of INTRALIPIDE 20% have not been specifically evaluated in adult or paediatric patients requiring HPN, without the intervention of a specialist parenteral nutrition centre.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

This opinion is issued in the context of the prescription of INTRALIPIDE to patients requiring home parenteral nutrition (outside a hospital and outside an approved nutrition centre).

4.1. Actual benefit

Home parenteral nutrition (HPN) is a treatment for patients with severe, life-threatening disorders. This type of nutrition can, moreover, result in morbidity and mortality (due to thrombosis, infections, metabolic and/or hydroelectrolytic complications, etc.).

INTRALIPIDE 20% is a substitution treatment of oral and enteral nutrition.

<u>Public health benefit:</u>

Patients for whom home parenteral nutrition is justified represent a minor public health burden because of their small numbers.
Improving the management of these patients is an important need in terms of individual health. In public health terms, however, improving the management of these patients is not identified as a priority public health need.
Otherwise, improving parenteral nutrition in an outpatient setting relies above all on the organisation of healthcare in association with alternative medicinal products that are already available ("à la carte" or "formula" mixtures for which a hospital pharmacist is responsible, and industrial ternary mixtures).
No demonstration of any benefit of INTRALIPIDE in terms of morbidity or mortality has been made available. It is not expected to provide any positive public health benefit.
In addition, confirmation is needed that the benefit of INTRALIPIDE that has been observed in hospitals can be transposed to actual practice in the community (in view of the infection risk and the risk of utilisation errors due to the additional handling required at home).

Accordingly, INTRALIPIDE is not expected to benefit public health.

The efficacy/safety ratio of INTRALIPIDE 20% is high in the context of parenteral nutrition where oral or enteral nutrition is impossible, inadequate or contraindicated.

There are alternative medicines that are better adapted to short-term home parenteral nutrition (HPN): à la carte or formula mixtures (magistral formula status) or industrial ternary mixtures.
In view of expert opinion and the current organisation of healthcare, the Committee considers that INTRALIPIDE has no place in the therapeutic strategy for HPN (except in the context of hospitalisation at home).

The actual benefit provided by INTRALIPIDE 20 PER CENT, fat emulsion in 100 and 250 ml bags for short-term (2-3 months) for HPN is therefore insufficient in the context of the treatment of adult and paediatric patients requiring home parenteral nutrition (excluding treatment in the context of hospitalisation at home).

4.2. Improvement in actual benefit

Not applicable.

4.3. Therapeutic use

In view of the good practice guide to artificial nutrition at home published by the SFNEP (French Society of Enteral and Parenteral Nutrition) in 2005:

- Parenteral nutrition (PN) is the intravenous infusion of macronutrients (glucose, amino acids and fats), electrolytes and micronutrients (vitamins and oligoelements).
- It is reserved for certain diseases that make oral and/or enteral nutrition impossible, inadequate or ineffective, particularly in cases of intestinal insufficiency due to short bowel syndrome or severe intestinal malabsorption or chronic occlusive conditions.
- It should be commenced in hospital and continued at home at the initiative and under the responsibility of the prescribing centres.
- Home parenteral nutrition (HPN) should only be commenced when the patient is stable (i.e. with a functional catheter, good tolerance and estimated nutritional needs met).
- Patients with permanent intestinal insufficiency (short bowel syndrome) and those expected to require PN for more than 2 months should be managed at an Approved Nutrition Centre because of the difficulties associated with long-term PN.
- Nutrients are administered via a central venous catheter – an external tunnelled catheter or a catheter with an implantable port – with an electric flow regulator to ensure a regular, progressive supply. The peripheral venous route is not suitable for HPN.
- PN is administered in a night cycle (continuous infusion for 8-12 hours) or, more exceptionally, continuously over 24 hours or in a day cycle.
- Macronutrients are supplied in the form of standard composition industrial mixtures or in bags containing a specific composition (personalised mixtures).
- Industrial mixtures are ternary premixes (carbohydrates, fats and proteins) supplied in three-compartment bags and available in **pharmacy**. Some of them include electrolytes, but sometimes in insufficient quantities. They should routinely be supplemented with vitamins and oligoelements.
- The nutrient mixture and the various supplements should be reconstituted immediately before infusion begins.

- Organised nutritional monitoring is essential, requiring close collaboration among the various partners: the doctor at the prescribing centre, the service provider, a private nurse and the primary care doctor.
- HPN should be adaptive (in terms of the nutrients supplied and the timing of the PN), since the aim of this replacement therapy is to improve the patient's quality of life.

Parenteral nutrition can expose patients to severe complications, particularly involving metabolism, the liver and infections (sepsis); monitoring is therefore crucial.

4.3.2 HPN in children: Paediatric parenteral nutrition has been the subject of good clinical practice guidelines.[2]

Industrial mixtures where the composition is fixed in advance are not recommended for use in children. (According to the 2005 guidelines: "no standard formulas are suitable for children on home parenteral nutrition" – chapter 11 Home Parenteral Nutrition in Children, p. S73).

4.3.3 Summary of the Committee's conclusions on medicinal products for parenteral nutrition:

Short-term HPN

Given that:

1. The number of approved HPN centres in France is currently restricted (less than 15 centres have been approved, all of them in major cities and within hospitals);

2. According to expert opinion, certain patients could benefit from parenteral nutrition conducted at home; these are patients who commenced PN in a specialized hospital, whose clinical status is stable, and who can benefit short-term HPN (for between 7 days and 2 months);

3. It is feasible to set up and monitor parenteral nutrition on an ambulatory basis at the patient's home, provided that it is properly supported (expert opinion),

the Transparency Committee agrees that industrial mixtures for short-term HPN in the treatment of adult patients may be listed for non-hospital use. It stresses, however, that HPN is not currently covered by any specific regulatory framework for its implementation, unlike home enteral nutrition.

NB: With regard to "intravenous nutrition support":

- Intravenous nutrition support is intended to supplement inadequate oral or enteral nutrition (less than 1200 kcal non-protein energy per day). It is a transitional solution pending the resumption of adequate oral or enteral nutrition. The Committee considers that bags supplying less than 1500 kcal of energy are suitable for this kind of nutrition support. They need to be supplemented with vitamins, oligoelements and ions.
- Patients requiring nutrition support may be managed in the context of hospitalisation at home.

[2] Koletzko B, Goulet O, Hunt J, Krohn K and Shamir R. for the Parenteral Nutrition Guidelines Working Group. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr. 2005;41 Suppl 2:S1-87.

4.3.4 Use of INTRALIPIDE 20% in short-term HPN (from 7-14 days to 2-3 months):

Two situations may be considered in practice for short-term HPN:
1. The patient's clinical status is stable so that industrial mixtures with standardised proportional compositions may be prescribed. Ternary industrial mixtures are then the most suitable : they reduce the amount of handling and thus limit the risk of infection and bedside (iatrogenic) errors.
In this context, INTRALIPIDE 20% fat emulsion is not suitable for the management of these patients.
2. The patient's clinical status requires an adjusted prescription to his or her nutritional needs, so that an industrial mixture is unsuitable: an "à la carte" or "formula mixture" should then be prepared by and under the responsibility of a hospital pharmacist (magistral formula, hospital use only) and/or by an outside contractor.

In all cases, prescription and monitoring must be overseen by a practitioner working at a public or private hospital specialising in the nutritional treatment of patients.

4.4. Target population

Not applicable.

4.5. Transparency Committee recommendations

The Transparency Committee does not recommend inclusion on the list of medicines reimbursed by National Insurance in the indication and at the dosage given in the Marketing Authorisation.

The Transparency Committee points out that it has requested the opinion of the Committee for the Assessment of Devices and Health Technologies regarding the conditions for the approval of the medical devices and services required for performing total parenteral nutrition out of hospital (according to its opinion of 6 July 2005 for OLICLINOMEL N 6-900 E and OLICLINOMEL N 7-1000 E).