Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

PERIOLIMEL N4E
OLIMEL N5E
OLIMEL N7
OLIMEL N7E
OLIMEL N9
OLIMEL N9E
Emulsion for infusion

(Olive oil and soya bean oil based emulsion
Amino acid solution with or without electrolytes
Glucose solution with or without calcium chloride)

FR/H/419/001-006/MR

Applicant: BAXTER S.A.S

Date of the PAR: March 2010

Information about the initial procedure:

Application/Legal Basis	Full dossier Art 8.3, line-extension
Active substance	Olive oil and soya bean oil based emulsion; amino acid solution with or without electrolytes; glucose solution with or without calcium chloride
Pharmaceutical form	Emulsion for infusion
Applicant	Baxter S.A.S
EU-Procedure number	FR/H/419/001-006/MR
End of procedure	23/10/2009

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for PERIOLIMEL N4E, OLIMEL N5E, OLIMEL N7, OLIMEL N7E, OLIMEL N9 and OLIMEL N9E, emulsion for infusion from Baxter 21 July 2008.
The product is indicated for the parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated

Periolimel/Olimel is a triple chambered bag.
Each bag contains:

- glucose solution with or without calcium,
- lipid emulsion (corresponding to Clinoleic speciality, marketed by the same laboratory, constituted by a mixed olive and soya oil)
- 17 amino-acids solution (alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine)
- electrolytes (sodium, potassium, magnesium, phosphate) for the 4 formulations with a "E" in the denomination.

Olimel was developed on the basis of an extension to Oliclinomel, already marketed in several countries with the following differences:

- use of 2 additional amino-acid: aspartic acid and glutamic acid (and lysine acetate instead of lysine hydrochloride)
- a higher nitrogen concentration,
- updated glucose calories/ lipid calories ratios (decrease of carbohydrate supply).

A comprehensive description of the indications and doses is given in the SPC.

No new preclinical studies were conducted. This is considered acceptable in view of the human experience available with medicinal products similar or close to Periolimel / Olimel and taking into account the nature of the active substances (amino acid solution with or without electrolytes, glucose and lipid emulsion).

During the procedure, no potential serious risk to public health concerns was raised. The procedure was ended positively, the CMSs agreed to recognize the Marketing Authorisation (MA) granted by FR..

2. QUALITY ASPECTS

2.1 Introduction

Periolimel / Olimel is an emulsion for infusion.

Periolimel / Olimel is presented in the form of a three-chamber plastic bag. Each bag contains a solution of 17 amino acids (alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, isoleucine, leucine, lysine (as lysine acetate), methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine) with or without electrolytes (sodium, potassium, magnesium, phosphate), a glucose solution with or without calcium, and a lipid emulsion (ClinOleic containing a mix of refined olive oil and refined soya-bean oil).

The bags to be registered are a full non-PVC container with non-PVC or PVC ports and may include an oxygen indicator.

2.2 Drug substance

The drug substances have either a monograph in the Ph.Eur and the manufacturer holds either a Certificate of Suitability of the monograph (CoS) or an Active Substance Master File (ASMF), or no monograph in the Ph.Eur and in this case, a satisfactory scientific data is provided.

For each, the specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

The retest period of each drug substance is based either on stability studies conducted under ICH conditions or described in the corresponding CoS.

2.3 Medicinal product

All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The development is sufficiently described in accordance with the relevant European guidelines.

The manufacturing process has been sufficiently described and critical steps identified.

Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

The data provided in Module 3 of the application are considered adequate and satisfactory to demonstrate the quality of the proposed drug product.

Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 2 years with a storage condition “Do not freeze”.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

Periolimel / Olimel qualitatively differs from OliClinomel (approved in 17 EU countries in 2001) in the addition of 2 amino acids (aspartic and glutamic acids) in the amino acid solution. The amino acid compartment used in Periolimel / Olimel is identical to that of Clinisol 15% approved in the USA in 1996, which is also a generic equivalent of Novamine 15% marketed in the USA for over 20 years.

Pharmacology

The non-clinical pharmacology dossier submitted by the applicant does not contain any new primary pharmacodynamic study or conventional safety pharmacology study. This is considered acceptable in view of the human experience available with medicinal products similar or close to Periolimel / Olimel.

Pharmacokinetics
No new preclinical pharmacokinetic study was performed with either individual active substances or the admixture to be reconstituted before administration. The applicant provided a comprehensive review of available data for each compartment content. This is acceptable taking into account the kind of active substances contained in Periolimel / Olimel and the human experience available with similar or close medicinal products.

Toxicology
The applicant did not perform any new toxicity studies, which is acceptable taking into account the nature of the active substances (amino acid solution with or without electrolytes, glucose, lipid emulsion), and the previous registration of similar products in the EU and/or USA in the past decades. Available single and repeat-dose toxicity studies were summarized.

The present non-clinical dossier filed to support the Marketing Authorizations of Periolimel and Olimel is acceptable.

4. CLINICAL ASPECTS

4.1 Introduction

Olimel is a new panel of triple chamber bags formulations for parenteral nutrition. Strengths vary from 4 g of nitrogen and 600 non-proteic kilocalories per 1000 ml, to 9 g of nitrogen and 840 non-proteic kilocalories per 1000 ml. Compared to the preceding version, Oliclinomel, the differences bear on three aspects:
- a modified glucose-lipid ratio: this follows the general evolution towards a reduction of the carbohydrates intakes, avoiding hyperglycaemia,
- a more complete amino acids solution: aspartic and glutamic acids are now included, as in most of the amino acids solutions commercialized,
- a more concentrated amino acids solution: 14.2% instead of 12.5% allows higher nitrogen intakes, particularly in hypercatabolic patients.

The efficacy data for Olimel are largely based on studies performed with existing products that are similar to or the same as the individual components of Olimel. Studies are therefore presented on Synthamin, an amino acid solution that contains all the amino acids in Olimel except two (aspartic acid and glutamic acid), and ClinOleic, the lipid emulsion component of Olimel. No studies on the glucose solution are presented, as this is considered to be standard therapy, and similar glucose solutions are commonly used in many types of intravenous fluids. In addition, two non-comparative studies are presented that have been performed with OliClinomel to support the efficacy and safety data obtained with similar premixes. A double-blind comparative study comparing Olimel to the currently marketed product OliClinomel is also reported.

4.2 Discussion on the clinical aspects

Amino acids administered intravenously are directly bioavailable to the body then rapidly removed from blood by absorption in tissues that rapidly metabolise them. Most of them are excreted in the urine.
No new pharmacokinetic studies have been performed for this compartment which is acceptable as Olimel was developed on the basis of an extension to Oliclinomel through the addition of two additional amino-acids (glutamic acid and aspartic acid) which are not intent to modify pharmacokinetic profile of Olimel drug.

As it was said in the introduction, the efficacy data for Olimel are based on studies performed with existing products that are similar to or the same as the individual components of Olimel.

A pivotal double-blind comparative study comparing Olimel to the currently marketed product Oliclinomel is also reported as it was suggested during a Scientific Advice in Afssaps in France (21 may 2003) and in MHRA in the United Kingdom (28 April 2003).

In the clinical safety study with Olimel, the safety of Olimel seems to be comparable to Oliclinomel for short term use and no major unknown risk has appeared. However, number of patients in this study is low. Additionally, long term data on safety for Olimel is lacking.
However, the limited safety data on Olimel on this study must be seen in the context of the already known safety profile of the products containing either identical or very similar components to those included in Olimel. Based on the safety data provided by the MAH containing data from clinical studies, post marketing data and published literature, the safety profile seems to be comparable to Oliclinomel.
As for other parenteral nutrition the main complications awaited with Olimel are metabolic, technical and septic complications. However, an adequate monitoring of the patients and the respect of the precaution for use of this product as mentioned in the proposed SPC is necessary to avoid or reduce these complications.

No specific risk minimisation plan is needed.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Overall, based on the studies performed with similar existing products and on the result of the double-blind comparative study comparing Olimel to the currently marketed product Oliclinomel, and considering that the addition of two non-essential amino-acids is not affecting efficacy, the clinical demonstration of this new triple chambered bag for the parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated, was judged acceptable.

There was no discussion in the CMD(h). Agreement between Member States was reached at the end of the procedure.

The Member States mutually recognised the French evaluation of the marketing authorisation.

The SPC, Package Leaflet and Labelling are in the agreed template and are consistent with the safety and efficacy profile of this product.