Public Assessment Report

Scientific discussion

Lipoplus
(medium-chain triglycerides, soya-bean oil and omega-3-acid triglycerides)

SE/H/422/02/E01

This module reflects the scientific discussion for the approval of Lipoplus. The procedure was finalised on 2014-06-25. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

B. Braun Melsungen AG has applied for a marketing authorisation for Lipoplus, emulsion for infusion, 200 mg/ml. Lipoplus is a lipid emulsion designed to supply energy and essential fatty acids including essential omega-6 fatty acids and omega-3 fatty acids triglyceride (OAT) as part of parenteral nutrition. Lipoplus was nationally approved in Sweden 2004-01-16. The application was a complete application made according to Article 8(3) of Directive 2001/83/EC. Later the same year, Lipoplus was also approved through the mutual recognition procedure, with AT, BE, CZ, DE, DK, EL, ES, FI, FR, IE, IT, LU, NL, NO, PT, SK and UK as CMS. The MAH has now added EE, HU, PL and SI as CMS via a repeat-use procedure.

For approved indications, see the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

Lipoplus is presented in the form of an oil-in-water emulsion for infusion containing 100 mg/ml of medium-chain triglycerides (MCT), 80 mg/ml long-chain-triglycerides (LCT) from soya-bean oil (refined) and 20 mg/ml omega-3-acid triglycerides (OAT) from fish oil (total fat content of 200 mg/ml). The excipients are egg lecithin, glycerol, sodium oleate, all-rac-α-tocopherol, ascorbyl palmitate, sodium hydroxide (for pH-adjustment) and water for injections. The emulsion for infusion is filled in glass bottles sealed with butyl rubber stoppers.

II.2 Drug Substance

Medium-chain triglycerides, soya-bean oil (refined) and omega-3-acid triglycerides have monographs in the Ph Eur.

The structures of the drug substances have been adequately proven and its physico-chemical properties sufficiently described. The manufacturing processes have been adequately described.

The active substance specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

II.3 Medicinal Product

Lipoplus emulsion for infusion is formulated using excipients described in the current Ph Eur, except for egg lecithin and sodium oleate, which are controlled according to acceptable and validated in-house specifications.

The product development has taken into consideration the physico-chemical characteristics of the active substances.
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.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC, when stored below 25°C and in the original package in order to protect from light. The product should not be frozen.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Relevant safety pharmacology and toxicological studies were performed using a developmental lipid emulsion formulation containing more omega-3-acid triglycerides than that in Lipoplus. The studies showed that the toxicity profile of the developmental lipid emulsion was similar to Lipofundin MCT/LCT / Vasolipid which is marketed in many countries.

In the safety pharmacology studies a treatment-related reduction in blood pH compared with controls (receiving a glycerol solution) was seen. No other significant effects were reported. Mild anaemia was seen at relevant doses in the toxicological studies. In healthy dogs organ changes at clinical relevant dosing were seen after two weeks of treatment (pigment deposits in lung and liver) and additionally minimal to slight inflammation associated with pigment-loaded cells in the liver and fatty changes in different organs (e.g. liver and renal tubuli) after excessive 90 days of treatment. In rat, slight to moderate microgranulomas was observed in liver, lungs and spleen and a generally mild Kupffer’s cell proliferation in liver at high dosing (6-8 x clinical dose) and high infusion rate (36x clinical rate) after 4 weeks of treatment. The special toxicity studies showed that infusion with the test formulation depressed the phagocytic capacity of the mononuclear phagocyte system in the body (-41 and -13% in female and male rats, respectively at 7x clinical maximum infusion rate for 6 h). The Expert Report states that long-term administration of lipid emulsions over 0.13 g lipid/kg/h has led to the deterioration of the mononuclear phagocyte function. This threshold is similar to the maximum infusion rate for Lipoplus (0.15 g/kg/h). To reduce the risk for toxicity associated with lipid overload at prolonged treatment beyond the normal recommended 1 week of therapy, appropriate monitoring of blood lipid levels should be performed as stated in the SmPC (section 4.2).

The test formulation was reported not to be embryotoxic or teratogenic. It was also reported not to have any impact on the in vivo immune reaction against foreign antigens (red blood cells from sheep). The test formulation showed no contact-sensitising potential in the guinea-pig test.

Lysophosphatidylcholine

Because of hydrolytic processes, the amount of lysophosphatidylcholine increases constantly upon storage. This degradation product has been toxicologically qualified at the specified shelf life limit (≤ 2.0 g/L) in a 7-days toxicity test in dog where no toxicological effects were observed after repeated daily dose of 25.5 mg/kg of lysophosphatidylcholine.

III.2 Ecotoxicity/environmental risk assessment

The components of Lipoplus are not expected to pose a risk to the environment.
IV. CLINICAL ASPECTS

IV.1 Introduction
Lipoplus 200 mg/ml is a lipid emulsion designed to supply energy and essential fatty acids including essential omega-6 fatty acids and omega-3 fatty acids as part of parenteral nutrition. The major difference between this product and other lipid emulsions authorised in the European countries is the content of OAT in Lipoplus. OAT are mainly found in marine fats, especially in fat of cold water fishes. The OAT used in Lipoplus are obtained from the body oil of fresh fish according to the monograph OMEGA-3-ACID TRIGLYCERIDES no. 1352 of the European Pharmacopoeia. Lipoplus is a modified form of the lipid emulsion Lipofundin MCT/LCT/Vasolipid marketed by the applicant from which 10% of the total fat content has been replaced by OAT. Lipofundin MCT/LCT/Vasolipid, which is based on a physical 1:1 mixture of MCT and LCT, has been marketed since 1983 and is now authorised in more than 80 countries. Lipoplus consists of MCT, LCT and OAT in a ratio of 5:4:1.

IV.2 Pharmacokinetics
Two pharmacokinetic studies in healthy volunteers have been performed. The clearance of the triglycerides obtained from Lipoplus seems to be similar to the clearance for triglycerides from conventional MCT/LCT emulsions, with approximately 50% of the exogenous triglycerides available in the circulation after 20 minutes.

IV.3 Pharmacodynamics
The Applicant has performed three pharmacodynamic studies demonstrating that the incorporation of omega-3 fatty acids, especially eicosapentaenoic acid (EPA), in phospholipids of erythrocytes, mononuclear cells and in plasma lipids was increased under infusion of Lipoplus in healthy volunteers and in patients undergoing surgery.

IV.4 Clinical efficacy
The applicant has sponsored two studies evaluating Lipoplus as energy source in comparison with conventional lipid emulsions.
In a randomised, double blind cross-over study comparing Lipoplus with Lipofundin MCT/LCT/Vasolipid 28 patients with polytrauma requiring parenteral nutrition and artificial respiration were investigated during two periods, one for each product (12 hours infusion on two subsequent days). The fat dosage was calculated to provide 50% of the individual resting expenditure as measured during a 12-hour period prior to treatment. In this study equivalence was shown with respect to the primary endpoint non-protein respiratory quotient (RQ) as well as for total fat utilisation and total RQ. These three parameters were comparable between the two treatment groups, with mean total RQ values ranging between 0.83 and 0.87 during both nutritional regimens. In conclusion this study has shown that the energetic efficacy of the OAT-containing lipid emulsion Lipoplus is equivalent to that of Lipofundin MCT 20%. In a sub-investigation which was performed as part of a large multicentre safety study fat oxidation was estimated by using indirect calorimetry in surgical patients requiring postoperative parenteral nutrition. Lipoplus or Intralipid (LCT) were given in daily doses of 0.7 g/kg on the 1st and 2nd postoperative days and then 1.4 g/kg/day on the 3rd to 5th day (n=13 in both groups). Postoperatively the mean values for fat oxidation were 70.7/24 h in the Lipoplus group and 71.8/24 h in the LCT group. No differences could be seen in carbohydrate oxidation and RQ between the two treatment groups.
The studies are small but support the conclusion that Lipoplus is essentially equivalent to conventional lipid emulsions as regards energy supplementation.
IV.5 Clinical safety
One multicenter, prospective, randomised double blind study, which is the pivotal safety study in this application, compared five days postoperative nutritional treatment with Lipoplus and a LCT lipid emulsion (Intralipid). The most frequently AE’s were metabolic and nutritional disorders (16.4 vs. 10.4%, respectively), liver and biliary system disorders (11.1 vs. 8.2%) and GI disorders (10.4 vs. 14.9%). Before day 8, 6.1% of the Lipoplus treated patients experienced serious AE:s compared to 4.5% of the LCT treated patients (ns), most of which were considered not related to treatment. No serious laboratory AE’s were recorded that was considered as possibly related to treatment. No differences were seen in allergic reactions or in bleeding time, which was measured in a subgroup of patients. The incidences and pattern of adverse events do not seem to differ between patients that received Lipoplus or a conventional LCT emulsion or from what could be clinically expected.

IV.6 Discussion on the clinical aspects
The basis for Lipoplus is the well-established lipid emulsion Lipofundin MCT/LCT/ Vasolipid from which 10% of the total fat content has been replaced by OAT. It is recognised that the inclusion of OAT in the composition is in line with what is recommended in several current general nutrition recommendations. Theoretically, the addition of OAT may have advantages over conventional lipid emulsions with regard to effects on the immune system and on platelets.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC in the procedure SE/H/422/II/03. The results showed that the package leaflet met the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Based on provided clinical data, the efficacy and safety profile of Lipoplus is judged to be similar to the lipid emulsions available on the market.

The risk/benefit ratio is considered positive and Lipoplus, emulsion for infusion, 200 mg/ml, is recommended for approval.

VI. APPROVAL
The Mutual Recognition procedure for Lipoplus, emulsion for infusion, 200 mg/ml was successfully finalised on 2004-10-05. The repeat-use procedure was successfully finalised on 2014-06-25.
## Public Assessment Report – Update

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