Public Assessment Report

Scientific discussion

Kombilipid 200mg/ml, emulsion for infusion

Fish oil, rich in omega-3-acids, Olive oil, refined, Soya-bean oil, refined and Triglycerides, medium-chain

SE/H/557/01

This module reflects the scientific discussion for the approval of Kombilipid 200 mg/ml emulsion for infusion. The procedure was finalised at February 14th, 2006. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Sweden has been acting as RMS in a MR-procedure of Kombilipid 200 mg/ml emulsion for infusion from the MAH Fresenius Kabi AB. The active substances in Kombilipid are the same as in SMOFlipid 200 mg/ml emulsion for infusion marketed by Fresenius KABI since 2004-02-06. The indications for the product are: Supply of energy and essential fatty acids and omega-3 fatty acids to adults, as part of a parenteral nutrition regimen when oral or enteral nutrition is impossible, insufficient or contraindicated.

Kombilipid was approved nationally in Sweden April 8th, 2005 as a duplicate to SMOFlipid approved nationally, February 6th, 2004.

II. QUALITY ASPECTS

II.1 Introduction

Kombilipid is presented in the form of an emulsion for infusion containing soya-bean oil refined 60 mg/ml, medium chain triglycerides 60 mg/ml, olive oil refined 50 mg/ml and fish oil rich in omega-3-acids 30 mg/ml (in total 200 mg/ml) as active ingredients. The excipients are egg lecithin, sodium oleate, glycerol, all-*rac*-*α*-tocopherol, sodium hydroxide and water for injections.

The emulsion is contained in colourless glass bottles with butyl rubber stoppers.

II.2 Drug Substance

The active ingredients soya-bean oil refined, medium chain triglycerides, olive oil refined and fish oil rich in omega-3-acids have monographs in the Ph. Eur.
All active substances are oils, which are mixtures of triglycerides. The triglycerides are liquids, practically insoluble in water, very soluble in acetone and in heptane and slightly soluble in ethanol.
The structure of each one of the oils has been adequately presented and its physico-chemical properties sufficiently described.
The manufacturing and refining processes used for the different oils have been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.
The ingredients specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Kombilipid 200 mg/ml is formulated using excipients described in the current Ph Eur, except for egg lecithin and sodium oleate which are controlled according to acceptable in house specifications..
All raw materials used in the product are of vegetable origin or of animal origin not susceptible to TSE. The product development has taken into consideration the physico-chemical characteristics and the stability of the active ingredients.

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 the presented data support the shelf life of 2 years, claimed in the SPC when stored below 25°C, protected from freezing.

III. NON-CLINICAL ASPECTS

III.1 Introduction

All components of Kombilipid are well known and present in other fat-emulsions for parenteral use that are already approved in Europe. However, the MAH has submitted a number of toxicity studies in rat (acute) and dog (4- and 13-weeks), mutagenicity studies and local tolerance studies in rabbits.

III.2 Pharmacology

Not applicable.

III.3 Pharmacokinetics

Not applicable.

III.4 Toxicology

In the dog studies, the infusion rate was 10-fold higher and the dose was up to 4.5 times higher than the maximal clinical dose. There were generally slight changes in haematological and biochemical parameters. Those were partly related to the administration of fat to dogs with a normal nutritional status, but also considered to be due to a hypervolaemic effect caused by the relatively rapid infusion of a large volume. Histological changes were attributed to accumulation of lipids and confirmed the changes in biochemical/haematological parameters. The changes were mainly seen at a dose ≥ 3-fold the maximum clinical dose of 10 ml/kg/day and were in essence reversible.

A standard mutagenicity package was performed with Kombilipid. As expected, there was no evidence of a mutagenic potential. No studies on toxicity to reproduction or the oncogenic/carcinogenic potential have been performed. This is adequate considering the nature of the active substances. Nevertheless, the MAH has submitted a number of publications regarding effects on reproduction of phytosterols (especially β-sitosterol), which are present in Kombilipid, but also normal constituents in certain foods.

Phytosterols have oestrogenic activity that impairs fertility in rodents, rabbits and other species. The relevance on this activity is difficult to apply to humans, but it is clear that rodents and dogs regulate their normal reproduction cycles and pregnancy on lower levels of 17β-oestradiol than humans do. In the 13-week dog study, no effects on the gonads in either sex were observed. In this study, the β-sitosterol levels were calculated to 1.9 mg/kg/day, which was marginally above the clinical maximal dose at the suggested limits. However, phytosterols are normal constituents of certain foods. The estimated daily intake of total phytosterols in Sweden is estimated to 0.3 g and the highest recommended daily intake is 1-3 g (National Food Administration, 2003). After the maximal dose of Kombilipid, the total daily intake of phytosterols would be approximately 0.4 g calculated to a 70 kg person. Taking the route of administration into account, at least the C_{max} levels of phytosterols are most likely somewhat higher after intravenous administration with Kombilipid, than after oral ingestion as food. Still, the levels are not considered high enough to pose a risk to humans. Nevertheless, the administration of Kombilipid during pregnancy and lactation should be carefully considered.

Kombilipid was well tolerated after intravenous infusion, while after applications made in error (intraarterial, paravenous, subcutaneous) slight but transient inflammatory reactions were observed in a few animals. After intramuscular administration, a moderate, but reversible inflammation and a mild to marked tissue necrosis was seen in a few treated animals. This information is adequately reflected in the SPC.

No haemolytic effect is expected during infusion with Kombilipid since the osmolarity is adequate compared to serum, and the infusion rate is low (< 1 ml/min).

Fish oil was sensitising in guinea pigs, but no anaphylactoid reactions were induced. Further, Kombilipid contains egg lecithin and may contain trace amounts of soy protein. Appropriate warnings are included in the SPC.

There are no impurities of toxicological concern. The emulsion is supplied in a glass bottle, and consequently there are no concerns regarding possible migration products from a plastic container.

III.5 Ecotoxicity/environmental risk assessment

No environmental risk assessment has been submitted. Considering the nature of the ingredients, no such assessment has been considered necessary.

III.6 Discussion on the non-clinical aspects

The non-clinical data support the use of Kombilipid in humans.

IV. CLINICAL ASPECTS

IV.1 Introduction

The content of MCT in lipid emulsions can nowadays be considered as well established and such products have a reassuring safety record. The amount of MCT in Kombilipid is lower than in the already commercially available physical mixtures of MCT/LCT.

The bibliographic support for the addition of fish oil to intravenous lipid emulsions derives in part from the clinical documentation included in the application file for Omegaven which was approved in 1998 (DE/H/139/01) and is marketed by the MAH in several Member States.

There are four MAH initiated clinical trials in support for the application for Kombilipid, two primarily pharmacokinetic phase I studies in healthy volunteers and two phase III studies, all performed according to current standards of GCP. All studies were performed against control treatment with Lipovenös; a conventional 20% fat emulsion based on soybean oil.

Summary of clinical studies

Study	Design	Primary variable measured/Primary efficacy end-point	Secondary variable measured/Secondary efficacy end-points	Primary safety end-point
Carpentier et al Phase I, 1997 Data on MAH file	Rand. open, parallel groups, cross-over study, clamp to maintain TG levels at 3 mmol/L, 10 healthy volunteers	Infusion rate required Decay of plasma triglycerides following end of lipid infusion.	Conc of lipids Fatty acid pattern	Vital signs, haematology, clinical chemistry, adverse events
Seiberling et al Phase I, 1997 Data on MAH file	Rand., double-blind, cross-over, 12 healthy volunteers Infusion rate 0.125 g fat/kg/h for 6 hours	Rate of elimination of TG	PK data for phospholipids, cholesterol, free fatty acids, glycerol	Vital signs, haematology, clinical chemistry, adverse events
Wulkow et al Phase III 1999 Data on MAH file	Rand., double blind, parallel groups, multicentre, n=249 undergoing major surgery	Serum concentrations of triglycerides	Fatty acid profile, eicosanoid synthesis, vitamin E, other lipid metabolism parameters. Clinical outcome	Vital signs, haematology, clinical chemistry, adverse events
Pichard et al	Rand., double-blind,	Serum		Vital signs,

Phase III 1999 Data on MAH file	parallel groups, n=32 with need for parenteral nutrition for ≥10 days	concentrations of triglycerides		haematology, clinical chemistry, adverse events. Indirect calorimetry, bioelectrical impedance

IV.2 Pharmacokinetics

The study by **Carpentier et al.** was designed as a cross-over study with a wash-out period of at least 28 days. Ten healthy male volunteers were given an initial infusion of either Kombilipid, or Lipovenös containing 1 g TG/kg BW/h for 6 minutes and thereafter a dose which created a clamp at a steady state triglyceride level at 3 mmol/l for four hours. A numerically but statistically insignificant lower infusion rate of Lipovenös was needed to maintain a clamp as compared with Kombilipid.
Similar changes in plasma lipoprotein composition and in plasma levels of apoliporoteins were observed after infusions of the two emulsions. The fatty acid pattern of the plasma triglycerides at the end of the infusion grossly reproduced the composition of the TG in the emulsion particles.
In the study by **Seiberling et al.** the serum triglyceride levels rose from baseline levels following infusions and reached essentially similar levels in the two treatment groups. The mean TG half-life was significantly shorter for Kombilipid, (34 min) than for Lipovenös (59 min).

IV.3 Clinical efficacy

The study by **Wulkow et al.** included 249 patients and was conducted in patients in need of parenteral nutrition after major abdominal, thoracic or urological surgery. The patients received a complete regimen including also glucose, amino acids, electrolytes, trace elements and vitamins as required. The fat dosage was 1.5 g fat/kg BW/day from the day after surgery until 5 days postoperatively. The observation period was 8 days including the day before surgery and day 6 after surgery.
The primary end point was serum triglycerides and the statistical method used was to measure the area under the curve (AUC) of the difference between the pre-infusion value before starting the treatment the day after surgery and the value at each measurement point, up to day 6. There was no difference in achieved serum triglycerides between Kombiliopid (mean daily AUC 0.7340 mmol/l) or Lipovenös infusion (0.7197 mmol/l).
In a sub-group study including 33 patients the fatty acid profile, cell membrane and plasma phospholipids, eicosanoids (leucotriens and thromboxanes) were analysed and the expected differences were found reflecting the different compositions of the two lipid emulsions.

The small study by **Picard et al.** was performed mainly in patients with underlying malignancy and is mainly a safety trial but also provides some additional support for the efficacy of Kombilipid.

IV.4 Clinical safety

The safety profile in the **two phase I studies** shows mainly the same results after exposure of the study drug or the control emulsion. No clinically relevant changes could be observed during the study regarding the vital signs, ECG evaluations, and other laboratory parameters (haematology, clinical chemical or urine analysis).
In the trial by **Seiberling et al.** with 6 hours infusion 3 volunteers experienced mild and transient peripheral par- and hyperesthetic sensations during Kombilipid infusion compared to none during Lipovenös infusion. These symptoms appeared to be related to the intravenous administration procedure rather than to the study drugs as such.

The study by **Wulkow et al.** can be considered as the pivotal study demonstrating the safety profile of Kombilpipid. The assessment of adverse events (AE) in this study showed an equal number in each group. A total of 102 (41.0%) patients experienced at least one AE during the study, 51 (40.5%) of the

126 patients in the Kombilpipd group and 51 (41.5%) of the 123 patients in the Lipovenös group. The most frequently reported AEs by body system were disorders of the gastrointestinal tract (14.3% in Kombilipid and 13.8% in controls). Nausea, hyperglycemia and vomiting were the three most common AEs. Treatment related AEs (defined as being the opinion of the investigator) were registered in 17 patients (6.8%) with 8 in the Kombilipid group and 9 in the Lipovenös group.
The majority of the AEs were mild or moderate.

The pattern of adverse reactions in the smaller study by **Pichard et al** was similar to the Wulkow study and there were no clinically relevant differences between the treatment groups.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The composition of lipids in the Kombilipid 200 mg/ml emulsion may theoretically have some advantages over conventional LCT or MCT/LCT emulsions. Submitted data has, however, not demonstrated any obvious clinical advantages from the use of Kombilipid as compared to Lipovenös (a LCT fat emulsion based on soy bean oil). The efficacy and safety of Kombilipid as part of parenteral nutrition is therefore judged to be similar to the lipid emulsions available on the market and risk/benefit ratio of this product is considered favourable.