CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207648Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA: **207648**	Submission Date: 9/26/2014
Submission Type:	Original Submission
Brand/Code Name:	SMOFlipid 20%
Primary Reviewer:	Elizabeth Shang, Ph.D.
Secondary Reviewer	Sue-Chih Lee, Ph.D.
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Gastroenterology and Inborn Errors Products
Sponsor:	Fresenius Kabi
Formulation; Strength(s):	SMOFlipid 20%, Injection
Proposed Indications:	(b) (4)

Background

Smoflipid20% is a lipid emulsion intended for use as a source of calories in parenteral nutrition. This product is approved and used in Europe and other countries other than the US. Currently, the only FDA approved intravenous lipid emulsions are Intralipid® and Clinolipid. Intraplipid is a soy-based product available in 10% or 20% emulsions while Clinolipid is a mixture of (b) (4) olive oil and (b) (4) soybean oil in an approximate ratio of 4:1 (olive:soy). Smoflipid20% is a mixture of soy-based ((b) (4) (b) (4) lipids, medium chain triglycerides (b) (4), fish oil (b) (4) and olive oil-based (b) (4) lipids.

The results of two clinical pharmacology studies were submitted in support of this NDA; however, both studies were considered to be exploratory. The constituents of SMOFlipid20% used in these two studies were different from the current proposed product (Table 1). These studies were conducted with 10 to 12 healthy subjects each given single short term (4 to 6 hours) infusion and dated from 19 years ago. In addition, the bioanalytical methods were not described in detail and method validation results were not provided. As a consequence, the information is of limited value and will not be included in labeling. Because these studies are not necessary for the NDA approval, the weaknesses of these study reports are not considered a refuse-to-file issue.

Table 1. Active Substances in SMOFlipid20%, Current vs Earlier Formulations

Ingredients	Current	Earlier
Soybean oil	60 g/L	(b) (4)
Triglycerides, medium-chain	60 g/L	
Olive oil	50 g/L	
Fish oil	30 g/L	

Study FE-SM-01-BE (1996) was conducted in ten healthy males and compared plasma TGs (primary endpoint) following administration of a SMOFlipid or Lipovenos. Study FE-SM-02-BE (1996) was conducted in twelve healthy males and compared the pharmacokinetic parameters of plasma TGs following administration of a SMOFlipid or Lipovenos. As indicated above, there are several weaknesses in the study reports,

rendering them inappropriate for labeling.

Study Results
See individual study reports in Appendix 1 for a description of the study reports submitted in support of this application.

Recommendation
From the viewpoint of the Office of Clinical Pharmacology, the information generated from these studies has very limited value and will not be included in the labeling.

APPENDIX 1. INDIVIDUAL STUDY REPORTS

Study Number: FE-SM-01-BE
Date Study Completed: 1996

Study Objectives
To compare the intravascular metabolism of Smoflipid with that of Lipovenos.

Study Design
This was an open label, randomized, two-period crossover study of IV administration of two lipid formulations in healthy volunteers to measure infusion rate to maintain plasma TG at 3 mM, elimination rate of TG after stopping infusion, concentrations of lipids, apolipoproteins and fatty acid patterns, and safety. Lipid emulsions were infused over 4 hours. The starting dose was 1 g TG/kg/hour for six minutes, then reduced to 0.15 g TG/kg/hour and adjusted to maintain plasma TG at 3 mM.

Clin Pharm Related Inclusion Criteria
Male healthy Caucasians and Africans between 18 and 45 years of age

Clin Pharm Related Exclusion Criteria
- Abnormal plasma lipid panel ((fasting triglyceride level 3100 mgldL, total cholesterol level >200 mgldL, phospholipids >220 mg/d L)
- abnormal renal or hepatic functions (creatinine >1.5 mg/dL, abnormal values for total bilirubin, SGOT, SGPT, AlkPase, γ-GT)

Composition of the product:

SMOF 20% contains:

Components	g/l (b) (4)
Soybean oil	
MCT	
Olive oil	
Fish oil	
Glycerol	
Egg phospholipids	

Demographics
This study included ten healthy males with a mean age of 28 years, a mean weight of 72.4 kg, and a mean height of 180 cm. The numbers of Caucasians, Africans, and Latin American are 6, 3, and 1, respectively.

Pharmacokinetic and Pharmacodynamic Endpoints Sampling Scheme

TG: Blood samples were collected at predose, 0, 6, 10, 30 min and then every 15 minutes until 4 hours post-dose.

Non-esterified fatty acids, glycerol, TG with and without glycerol, total cholesterol (TC), free cholesterol (FC), cholesteryl ester, total phosphate, inorganic phosphate, and phospholipids: Blood samples were collected at baseline (150 min prior to dosing), 0, 1, 2, 3, 4 hours post start of the infusion, and 10, 20, 30, 45, 60, 75, 90, and 120 min post end of infusion. Note not all the lipids were determined at each time point.

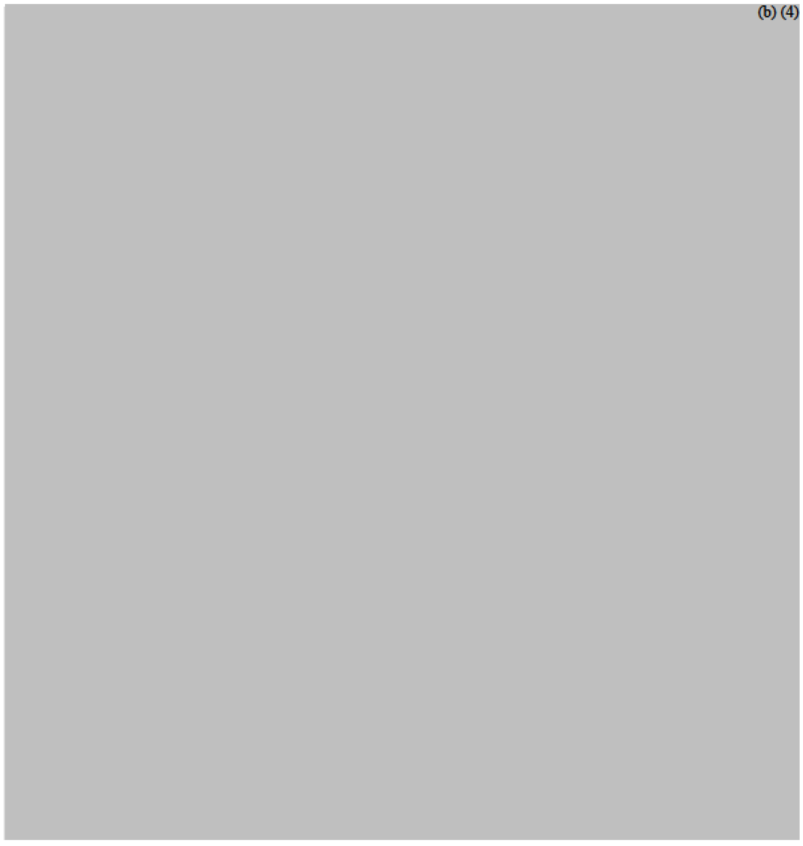
TG, TC, FC, and CE in lipoproteins (VLDL, LDL, HDL): 0, 4, 5 hours post dose.

Apolipoprotein (Apo A-I, A-II, B, C-I, C-II, C-III, E): 0, 4, and 5 hours

Fatty acid of plasma TG, non esterified fatty acids and cholesteryl esters: 0, 4, 5 hours.

Pharmacokinetic and Pharmacodynamic Results

Primary endpoints: Rate of lipid infusion and decay of plasma TGs



Reviewer's comments: As shown in the table, (b) (4) [redacted] *Comparison to Lipovenos was made by the sponsor. Lipovenos is not an FDA approved product. Therefore, the comparison is irrelevant to the approval for Smoflipid in US.*

Other endpoints:
Mean (SD) of concentrations of the following lipid parameters at each sampling time point were reported:

- lipids in plasma and lipoproteins
- apolipoproteins in plasma and VLDL
- fatty acids in plasma TGs and in plasma non esterified fatty acids as weight of total fatty acids at each sampling time point were also reported.

Reviewer's comments: The results are not presented in this review as these are exploratory data with an infusion rate adjusted for a constant plasma TGs and different from the proposed infusion mode (constant rate of infusion). These data are not included in the labeling.

Study Number: FE-SM-02-BE
Date Study Completed: 1996

Study Objectives
To evaluate the safety and tolerability of a 6-hour infusion of SMOFlipid 20% compared to a 6-hour infusion of Lipovenos 20% as well as to evaluate the elimination of triglycerides.

Study Design
This was a randomized, double-blinded, 2-way crossover study of IV administration of two lipid formulations (Smoflipid versus Lipovenos 20%) in healthy male volunteers to determine lipid parameters, clinical laboratory parameters, safety and injection site tolerability. The dose of lipid administered to volunteers was 0.125 g fat/kg/hour over six hours.

Composition of the product:

SMOF 20% contains:

Components	g/l (b) (4)
Soybean oil	[redacted]
MCT	
Olive oil	
Fish oil	
Glycerol	
Egg phospholipids	

Demographics

This study included 12 healthy young males with a mean age of 25.67±3.56 (SD) years,

a mean weight of 72.74 ±12.66 (SD) kg.

Clin Pharm related Inclusion Criteria
Caucasian healthy males aged from 18 to 45 years.

Clin Pharm related Exclusion Criteria
Triglycerides 2120 mg/dl, or cholesterol 2200 mg/dL, and phospholigids 2220 mg/dL.

Pharmacokinetic and Pharmacodynamic Endpoints and Sampling Scheme
Triglycerides (TG): predose, 10, 20, 40 min, 1, 2, 3, 4, 5, 6, 6h 10 min, 6 h 20 min,6 h 40 min, 7, 8, 9, 24 h after the beginning of infusion
Phospholipids, cholesterol, free fatty acids, free glycerol: predose, 1, 3, 6, 9 and 24 h after the beginning of infusion.

Pharmacokinetic and Pharmacodynamic Results
The PK parameters of TG, phospholipids, cholesterol, free fatty acids and free glycerol following 6 hours infusion of Smoflipid are listed in the tables below.

Triglycerides (TG)

Parameter	SMOF 20% mean ± SD median (range)
AUC(0-t) [mg*h/dl]	(b) (4)
C_{max} [mg/dl]	
t_{max} [h]	
λ_z [1/h]	
$t_{1/2}$ [h]	
C(4) [mg/dl]	
C(5) [mg/dl]	
C(6) [mg/dl]	

C(4), C(5) and C(6): Concentration data 4, 5, and 6 hours after start of infusion

Free fatty acids (FFA)

Parameter	SMOF 20% mean ± SD median (range)
AUC(0-t) [mMol*h/l]	(b) (4)
C_{max} [mMol/l]	
t_{max} [h]	

Free Glycerol

Parameter	SMOF 20% mean ± SD median (range)
AUC(0-t) [mg*h/dl]	(b) (4)
C_{max} [mg/dl]	
t_{max} [h]	

Total cholesterol

Parameter	SMOF 20% mean ± SD median (range)
AUC(0-t) [mg*h/dl]	(b) (4)
C_{max} [mg/dl]	
t_{max} [h]	

Phospholipids

Parameter	SMOF 20% mean ± SD median (range)
AUC(0-t) [mg*h/dl]	(b) (4)
C_{max} [mg/dl]	
t_{max} [h]	

Reviewer's Comments:

- *Comparison to Lipovenos was made by the sponsor on the PK parameters. Lipovenos is not an FDA approved product. In addition, the formulation of SMOFlipid used in the study is different from the proposed final product. Therefore, the comparison is irrelevant to the approval for Smoflipid in US.*

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/s/

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06/10/2015

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06/10/2015