

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204508Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA: **204508**

Submission Date: 3 JAN 2013

Submission Type:	Original Submission
Brand/Code Name:	ClinOleic 20%
Generic Name:	20% intravenous lipid emulsion
Primary Reviewer:	Kristina Estes, Pharm.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:	Baxter
Formulation; Strength(s):	ClinOleic 20% Injection
Proposed Indications:	For parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated

Background

ClinOleic20% is a lipid emulsion intended for use as a source of calories in parenteral nutrition. The only FDA approved intravenous lipid emulsion is Intralipid[®], which is a soy-based product available in 10% or 20% emulsions. ClinOleic 20% is a mixture of soy-based and olive oil based lipids that provide a higher percentage of linoleic acid and linolenic acid and a lower percentage of oleic acid relative to the soy-based product. A shortage of Intralipid[®] on the market has compelled the Agency to review this submission on a priority schedule.

The results of four clinical pharmacology studies were submitted in support of this NDA; however, all four studies are considered to be exploratory and, as a consequence, the information is of limited value and will not be included in labeling. These studies were conducted with 6-9 healthy male subjects each and date from 20-24 years ago. In addition, the bioanalytical methods were not described in detail and method validation results were not provided. Because these studies are not necessary for the NDA approval, the weaknesses of these study reports are not considered a refuse-to-file issue.

Study B9201E (1992) was conducted in six healthy males and compared plasma lipoproteins following *oral* administration of a 20% soybean oil emulsion or a mixture of 17% olive oil and 3% soybean oil. Study B9208E (1992) was very similar in design to 9201 but the oil emulsions were administered intravenously. Study C-88-CSW-6/3-04-F (1989) explored the plasma clearance of fatty acids and triglycerides as well as energy expenditure by indirect calorimetry following IV administration of either Intralipid or ClinOleic in six healthy males. Study C-91-CSW-6/3-12-F (1993) included nine healthy males and was conducted to assess biliary flow rate and plasma lipoproteins following IV administration of either Intralipid[®] or ClinOleic. 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.

Summary of Label Revisions

The proposed labeling under review includes the DRUG INTERACTIONS section as well as the CLINICAL PHARMACOLOGY section of the label. The sponsor's proposed text is in blue while Agency proposed insertions are in red and deletions are in strikethrough.

DRUG INTERACTIONS

The sponsor's proposed language in section 7 regarding coumarin derivatives is more specific than the language present in the approved Intralipid® label. There is no DRUG INTERACTIONS section in the approved Intralipid® label. The language in the WARNINGS section of the approved Intralipid® label related to coagulation states "Caution should be exercised in administering of Intralipid 20%® (a 20% intravenous fat emulsion) to patients with severe liver damage, pulmonary disease, anemia, or blood coagulation disorders, or when there is danger of fat embolism." There is an additional statement in the PRECAUTIONS section that advises "Frequent (some advise daily) platelet counts should be done in neonatal patients receiving parenteral nutrition with Intralipid® 20%."

The sponsor's proposed language for the DRUG INTERACTIONS section of the label. No additional information, apart from the Intralipid® label, was submitted to support the inclusion of the drug interaction.

7. DRUG INTERACTIONS

No drug interaction studies have been performed with ClinOleic 20%.

Olive and soybean oils have a natural content of Vitamin K1 that may counteract the anticoagulant activity of coumarin derivatives, including warfarin.

The Agency concurs with the sponsor's proposed inclusion of this interaction. The agency may also include monitoring recommendations; however, there are not any in the label at present.

CLINICAL PHARMACOLOGY

The sponsor has included a large amount of information from the exploratory studies which is not clinically meaningful or cannot be verified due to the lack of bioanalytical methodology reports.

12. CLINICAL PHARMACOLOGY

ClinOleic 20% administered intravenously provides biologically utilizable source of calories and essential fatty acids.

12.1 Mechanism of action. Fatty acids serve as an important substrate for energy production. The most common mechanism of action for energy production derived from fatty acid metabolism is beta oxidation. Fatty acids are important for membrane structure and function, precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

12.2 Pharmacodynamics. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4) infused essential fatty acids
(b) (4) higher derivative fatty acids.

Olive oil contains significant amounts of alpha-tocopherol that contributes to Vitamin E status.

(b) (4)

12.3 Pharmacokinetics.

(b) (4)

Metabolism and excretion

The fatty acids, phospholipids, and glycerol found in lipid emulsions are metabolized by cells to carbon dioxide and water. The metabolism of these substances results in the generation of energy in the form of ATP. Some fatty acids are stored in the body in fat tissue, cell membranes, or as

intracellular triglycerides. There is constant turn-over of these tissues, with the result that the lipid components are eventually metabolized to carbon dioxide and water. Carbon dioxide is expired through the lungs. Water is excreted through the kidneys or lost through evaporation/expiration through the skin, lungs, and other tissue surfaces. Some lipids (i.e., phospholipids, cholesterol, and bile acids) are excreted through the biliary system.

(b) (4)

Individual Study Reports

Study Number: B9201E

Date Study Completed: 1992

Study Design

This was a randomized, crossover study of the oral administration of two lipid formulations in healthy male volunteers to determine serum chylomicron and non-chylomicron fragments. The dose of lipid administered to volunteers was 0.25 g triglyceride/m² following a 10-hour fast. Retinol palmitate (RP) (125,000 U per 250 mL emulsion) was added to the emulsion as a marker for chylomicron metabolism. Blood was collected hourly for eight hours and again at 24 hours post-dose for the assessment of triglycerides, retinol palmitate, cholesterol, and apo-AI and B.

Demographics

This study included six healthy young males with a mean age 24.2±2.3 (SD) years. The mean fasting plasma triglycerides (TGs) were 0.94±0.37 mmol/L and the mean total plasma cholesterol was 4.12±0.9 mmol/L. There was no other demographic information included in the report.

Inclusion and Exclusion Criteria

No specific inclusion or exclusion criteria was included in the study report.

Pharmacokinetic and Pharmacodynamic Monitoring

Blood was collected hourly for eight hours and again at 24 hours post-dose for the assessment of triglycerides, retinol palmitate, cholesterol, and apo-AI and B. The analytical methodology for the measurement of cholesterol and TG was not clearly described but appeared to be an enzymatic colorimetric assay. Apolipoproteins were measured by immunoturbidimetric assay. Retinyl palmitate was assayed by HPLC. Fasting insulin levels were determined by radioimmunoassay.

Pharmacokinetic and Pharmacodynamic Results

No RP was present at the start of the experiment but it could be detected in all fractions 1 hour after the ingestion of both fat emulsions. The RP C_{max} at approximately four hours post-dose and the peak mean chylomicron RP concentrations were higher after olive oil administration than after soybean oil. The mean plasma RP peak following administration of the soybean oil emulsion was 5.04 ± 0.49 (SD) mg/L and for the olive oil emulsion was 7.13 ± 2.06 mg/L. The mean chylomicron RP peak following administration of the soybean oil emulsion was 2.49 ± 0.80 mg/L and for the olive oil emulsion was 4.85 ± 1.24 mg/L. The mean peak RP concentration reached in the chylomicron fraction was higher for the olive oil emulsion (5.24 ± 2.16) compared to the soybean oil (3.82 ± 1.66).

Mean plasma TG levels increased 1 hour after both fat loads and peaked at 3 hours (range 2-4 hours). Mean chylomicron and non-chylomicron TGs increased from 1-3 hours post-dose. At seven hours post-dose, plasma TG levels were back to the starting values in both treatment groups. The maximal increase in plasma, chylomicron and non chylomicron TG concentrations was similar for the soybean oil and olive oil treated groups. Relative to baseline, the mean maximal TG increase in plasma was 274 ±

71.4% of the initial value for soybean oil treated subjects and 284 ± 68 % for the olive oil treated subjects.

Apo B concentrations in the chylomicron fractions were below the limit of detection at baseline and levels increased in the first three hours after both types of fat loads. Like the decline in TGs, apo B concentrations decreased to values below the starting levels by approximately 6 hours post-dose. Apo A-I concentrations appear not to decline following olive oil administration but decline slightly following soybean oil administration.

Sponsor's Conclusions

The sponsor concluded that the higher RP concentration in the chylomicron fraction following oral administration of the olive oil emulsion suggested that the absorption of olive oil is faster, or that the synthesis and secretion of chylomicron particles in the gut occurs at a faster rate.

Reviewer's Comments:

- There are a number of limitations regarding the utility of the results for the purposes of labeling that were presented in this study report. Most importantly, the study drugs were administered orally, which is not the proposed method of administration and may not be clinically meaningful. The report did not include a description of either inclusion or exclusion criteria for this study. The demographics of the volunteers in this study were very narrow; this included the participation of only six healthy young males. The analytical methods were not described clearly and bioanalytical reports were not included as part of the study report. Lastly, the analytical methodology may have been appropriate for the time period in which the study was conducted but the relevance to methods that might be used today is not clear.*

Study Number: B9208E

Date Study Completed: 1992

Study Design

This was a randomized, crossover study of the parenteral administration of two lipid formulations in healthy male volunteers to determine serum chylomicron and non-chylomicron fragments. The dose of lipid was administered following a 10-hour fast as a single bolus injection of 0.1 g triglyceride (TG) per kg of body weight followed by an infusion of 0.25 g TG/kg for 60 minutes. Retinol palmitate was added to the emulsion as a marker for chylomicron metabolism. Blood was collected hourly for eight hours and again at 24 hours post-dose for the assessment of triglycerides, retinol palmitate, cholesterol, and apo-AI and B. There was a three-week washout period between treatments.

Demographics

This study included six healthy young Dutch males with a mean age 24.2 ± 2.3 (SD) years and a weight range of 68 – 89 kg. The mean fasting plasma TGs were 0.97 ± 0.33 mmol/L with a range of 0.48-1.35 and the mean total plasma cholesterol was 3.59 ± 0.69

mmol/L. Volunteers also had fasting plasma insulin concentration and plasma glucose valued within the normal range at baseline.

Inclusion and Exclusion Criteria

Specific inclusion and exclusion criteria were not provided in the study report.

Pharmacokinetic and Pharmacodynamic Monitoring

Blood was collected hourly for eight hours and again at 24 hours post-dose for the assessment of triglycerides, retinol palmitate, cholesterol, and apo-AI and B. The Light Scattering Index was used to measure triglyceride rich particles in blood samples. Commercially available enzymatic colorimetric assays were used to measure TG, cholesterol, and phospholipids. Apolipoproteins AI and CII were measured by immunoturbidimetry.

Pharmacokinetic and Pharmacodynamic Results

The maximum plasma TG concentration reached at the end of the one-hour infusion was significantly higher with olive oil emulsions (TG 5.31 ± 1.28 mmol/L) than with soybean oil emulsions (3.74 ± 0.81 mmol/L; $p=0.005$). The phospholipids (PL) levels in plasma increased by approximately 12% to 2.73 ± 0.25 mmol/L after the infusion of the soybean oil emulsion, and by approximately 20% to 2.90 ± 0.49 mmol/L with the olive oil emulsion.

Infusion of TG-rich particles saturated the removal system of lipoproteins in each subject, since plasma TG concentrations exhibited an increase during the continuous infusion for 60 min. In 5 of the 6 subjects, the maximal removal capacity was higher with the soybean oil emulsion. The fractional catabolic rates, which were calculated from the disappearance curves, were higher with the soybean oil emulsion, indicating faster elimination. After withdrawal of the soybean oil infusion, individual disappearance curves exhibited exponential decay with a single exponent in all subjects. Following withdrawal of the olive oil infusion, individual disappearance curves represented straight lines in five of the six subjects indicating zero order kinetics; a single exponential decay curve was observed in one case only.

Mean plasma apo CII concentrations declined to the same extent following administration of both lipid emulsions. Mean apo CII concentrations in chylomicrons increased during the infusion but the increase was similar in both treatment groups. The HDL associated apo AI concentration did not change in either treatment group. Apo AI plasma concentration in plasma did increase in both groups to the same extent.

Sponsor's Conclusions

The elimination of the olive oil emulsion, as measured by plasma lipoproteins and TGs, was slower relative to the soybean based emulsion. This difference could not be explained by a difference in the binding of apo CII, the cofactor for lipoprotein lipase. The linear disappearance observed with the olive oil emulsion indicating zero order kinetics is consistent with elimination by hepatic lipase. The exponential elimination curve of the soybean oil emulsion remnants suggests an additional pathway such as the reticuloendothelial system.

Reviewer's Comment:

- *There are a number of limitations regarding the utility of the results for the purposes of labeling that were presented in this study report. The report did not include a description of either inclusion or exclusion criteria for this study. The demographics of the volunteers in this study were very narrow; this included the participation of only six healthy young Dutch males. It's not clear in the volunteers used in this study were the same volunteers from the previous study. The analytical methods were not described clearly and bioanalytical reports were not included as part of the study report. Lastly, the methodology may have been appropriate for the time period in which the study was conducted but the relevance to methods that might be used today is not clear.*

Study Number: C-88-CSW-6/3-04-F

Date Study Completed: 1989

Study Design

This was a randomized, crossover study of the parenteral administration of two lipid formulations in healthy male volunteers to measure indirect calorimetry and determine differences in plasma or serum fatty acids and triglycerides. Following a 12-hour fast, volunteers were administered an infusion of glucose and amino acid for eight hours. After three hours of this infusion, subjects received an additional infusion of lipid emulsion for the remaining five hours at a rate of 0.1 g TG/kg/h. There will be a one-week washout period between treatments.

Demographics

This study included six healthy young males with a mean age of 25 years, a mean weight of 70 kg, and a mean height of 178 cm. No other demographic data was provided in the study report.

Inclusion and Exclusion Criteria

To be included in the study, subjects must be male between the ages of 18 and 40 years old and be "free of any known visceral disorders". Subjects were excluded if they had a history of any of the following: insulin-dependent or non-insulin-dependent diabetes, acute or chronic renal disease, acute or chronic hepatobiliary disease, pulmonary disease, dyslipoproteinemia, or had a Body Mass Index > 27.

Indirect Calorimetry

Indirect calorimetry was performed using the Deltatrac Metabolic Monitor. The methodology was not described and the results were not clearly presented. The sponsor concluded that there was "no significant difference between the two treatments in terms of indirect calorimetry". The results presented below do not differentiate between the lipid emulsions.

The oxygen consumption varied in much the same way for both types of lipid infusions, progressing from 260 (254) ml/min to 271 (263) under the effect of the glucose and amino acids and finally to 280 (281) ml/min under combined infusion including lipids.

The CO₂ production progressed from 212 (207) ml/min to 231 (227) under the effect of the glucose and amino acids and finally to 224 (227) ml/min after lipids were added.

The respiratory quotient progressed from 0.81 (0.82) to 0.85 (0.86) under the effect of the glucose and amino acids, subsequently falling to 0.80 for both lipid emulsions.

The energy expenditure at rest (REE) progressed from 1785 (1741) kcal/24 h to 1880 (1823) under the effect of the glucose and amino acids and then to 1915 (1932) kcal/24 h after the lipid emulsions were added.

The oxidation of carbohydrates, calculated on the assumption of a urinary nitrogen loss of 13 g/24 h, progressed from 133 (131) g/24 h to 202 (212) under the effect of the glucose and amino acids, subsequently dropping to 125 (129) g/24 h after the lipid emulsions were added.

The oxidation of lipids decreased from 92 (88) g/24 h to 72 (61) under the effect of the glucose and amino acids, subsequently increasing to 109 (105) g/24 h after lipids were added.

Pharmacokinetic and Pharmacodynamic Monitoring and Results

Blood samples were collected at baseline and at 2.5, 2.75, 3, 4, 5, 6, 7, 7.5, and 8 hours post-dose. No explanation was provided for these sampling time points. The parameters to be evaluated were blood glucose, TG, phospholipids, total and free cholesterol, glycerol, free fatty acids, beta-hydroxybutyrate, erythrocyte membrane phospholipid and cholesterol levels, fatty acid composition of TGs and the fatty acid composition of free fatty acids.

The reduction in the plasma triglyceride concentration resulting from the administration of glucose and amino acids uniformly affected all fatty acids with the exception of arachidonic acid, whose concentration was unchanged. After the olive-oil emulsion was added, a rapid increase in the oleic acid (C18:1) fraction of the triglycerides was observed. The relative concentration of the other fatty acids was reduced with the exception of linolenic acid (C18:3). Administration of Intralipid caused an increase in the relative concentration of linoleic acid (C18:2) and linolenic acid (C18:3) to the detriment of the proportion of other fatty acids. Linolenic acid (C18:3) was detected only during the Intralipid infusions and arachidonic acid (C20:4) was detected only during olive-oil emulsion infusion.

The cholesterol and phospholipid concentrations in the erythrocytes were unchanged following administration of both lipid emulsions. The mean glucose concentration increased from 93 to 98 mg/dl during the glucose and amino acid infusion, then to 109 mg/dl after the lipid emulsions were added. The mean triglyceride concentration decreased from 0.58 mmol/L at baseline to 0.46 during the glucose and amino acid infusion, subsequently rising to 1.88 mmol/L after the lipid emulsions were added.

The mean phospholipid concentration was 192 mg/dl at baseline and 182 mg/dl after the glucose and amino acid administration, subsequently rising to 215 mg/dl after 5 h of lipid infusion. The cholesterol concentration remained constant throughout the duration of infusion. The free cholesterol concentration was unchanged by glucose and amino acid infusion, slightly increasing to 44 mg/dl after lipids were added.

The mean glycerol concentration decreased from 33 to 20 $\mu\text{mol/L}$ during the glucose and amino acid infusion, subsequently rising to 113 (92) $\mu\text{mol/L}$ after lipids were added. The mean free fatty acid concentration decreased from 0.24 to 0.11 mmol/L during the glucose and amino acid infusion, increasing to 0.26 mmol/L after both lipid emulsions were added. The mean beta-hydroxybutyrate concentration decreased from 21 to 12 $\mu\text{mol/L}$ during the glucose and amino acid infusion, increasing to 36 $\mu\text{mol/L}$ after lipids were added.

Reviewer's Comments:

- The methodology for the indirect calorimetry was not described and the results were not clearly displayed. The sponsor indicates that there is no difference between the two treatment groups. Given the composition of the two products is 20% lipid, it seems reasonable to accept an equivalent contribution of calories between the two lipid emulsions for the purposes of parenteral nutrition in lieu of a description of the study results. For other bioassays, there are no details of the methodology and the validation reports are lacking.*

Study Number: C-91-CSW-6/3-12-F

Date Completed: 1993

Study Design

This was a randomized, double-blind, crossover study in nine healthy subjects to assess the effects of two intravenously administered lipid emulsions on biliary secretion. Physiological saline infusion and use of a non-absorbable marker were used to quantify the output and absorption of the constituents of bile and approximate the biliary flow rate. A triple-catheter probe was inserted through the nose into the small intestine; the tip of the proximal catheter was positioned at the hepatopancreatic ampulla and the tips of the other two catheters were positioned at specified distances downstream. Each subject underwent the procedure three times with a washout of period of 7-45 days in between. The three test period included the use of olive oil emulsion, soybean oil emulsion, or a saline solution. Test drugs were administered intravenously at a constant rate of 100 ml/h for four hours. Prior to administering the test drugs, saline was infused for three hours.

Demographics

The study included nine healthy males between the ages of 22 and 30 years. The only demographic data available in the report are the gender, age, weight, height, and BMI of the participants. The subjects' BMI ranged from 21.2 to 25.5 indicating the absence of any obese participants.

Inclusion and Exclusion Criteria

To be included in the study, subjects must have been males between the ages of 18 and 50 years with normal baseline laboratory values (WBC, serum TGs, cholesterol, hepatic enzymes, prothrombin, electrolytes, and creatinine) and negative for HBV and HIV. Subjects were excluded if they had a history of gastrointestinal disease, were currently participating in another study, or were obese as defined by a BMI > 30 kg/m².

Pharmacokinetic and Pharmacodynamic Monitoring

Blood samples were collected every 30 minutes during the lipid (or saline) infusion for the determination of serum bile acids, TGs, and cholesterol. Samples of intestinal fluid were collected from the two distal catheters every 15 minutes starting 90 minutes after the initiation of the saline infusion and continuing during the lipid (or saline) infusions. The methodologies for determining serum bile acids and intestinal bile acids were not clearly described.

Pharmacokinetic and Pharmacodynamic Results

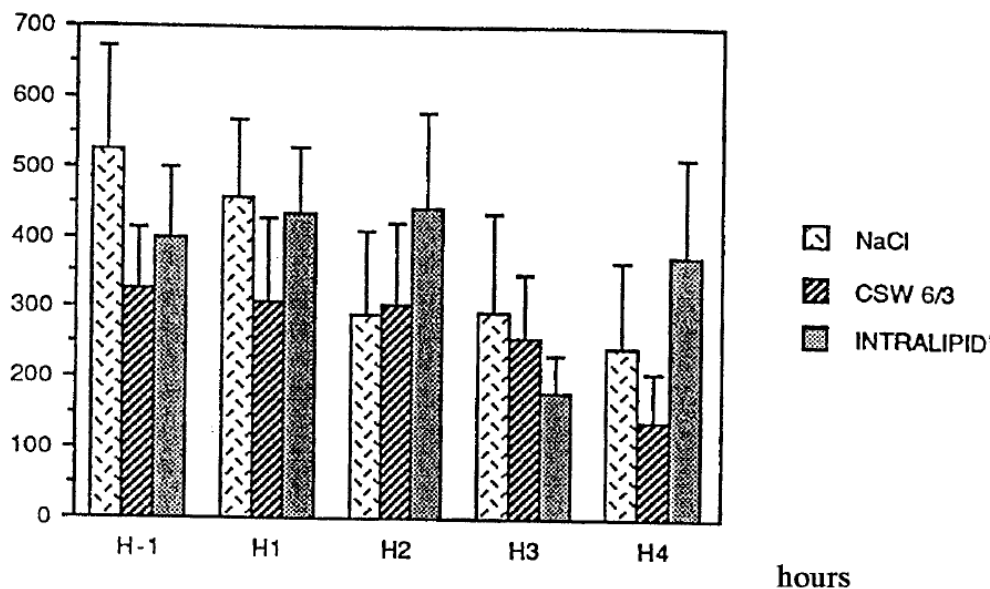
Serum samples

There was no difference in serum total cholesterol following administration of the lipid formulations, which were both higher than the saline-treated subjects. Serum triglycerides were higher in subjects who received the olive-oil emulsion relative to subjects who received the soybean oil emulsion.

Intestinal samples

During the baseline infusion, in which saline was infused prior to the infusion of test drug, the biliary flow rate at the middle catheter tip increased significantly from the first to the third test independent of the treatments that were administered subsequently. During study drug infusion, the flow rate of bile acids at the middle (Figure 1 below) and distal catheter tips (data not shown) appeared to decline from hour one to hour four for subjects receiving the olive oil emulsion or the saline infusion; however, the rates for Intralipid® treated subjects appeared to be more variable throughout the four hour time period.

Figure 1. Hourly flow of bile acids (μmol/h) at the middle catheter tip during infusion of NaCl, CSW 6/3 (olive oil emulsion), and Intralipid.



The figure above shows an apparent decline in hourly bile acid flow for subjects treated with saline and the olive oil emulsion over the time period of the study. The rate for Intralipid declines at the 3-hour timepoint but does not show a consistent decline over the 4-hour time period. The total flow of substrates for each hour was obtained by adding the flow rates calculated for each 15 minute interval.

Sponsor's Conclusions

The finding that saline resulted in a change in biliary flow rate, as measured by the intestinal movement of bile acids between catheter tips, was unexpected. The sponsor concluded that there was no difference in biliary secretion between the three infusions tested; however, the mechanism of stimulation may be different for the saline relative to the lipid infusions.

Reviewer's Comments:

- *The results of this study are difficult to interpret and, with regard to biliary flow rate, do not appear to be clinically meaningful or useful for practitioners. For example, the author repeatedly describes an increase in flow rate of bile acids whereas the data appears to show a decrease in these flow rates.*
- *The dose of lipid used in this study was a fixed dose of 100 ml/hr for four hours, which is approximately twice the maximum recommended rate of lipid infusion for a 70 kg patient receiving total parenteral nutrition.*
- *The inclusion of these results in labeling does not appear to be supported.*
- *The reliability of the study procedure involving a triple-catheter probe cannot be verified.*

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/s/

KRISTINA E ESTES
07/26/2013

SUE CHIH H LEE
07/26/2013

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	204508	Brand Name	
OCP Division (I, II, III, IV, V)	III	Generic Name	ClinOleic 20%
Medical Division	DGIEP	Drug Class	Parenteral lipid emulsion
OCP Reviewer	Kris Estes	Indication(s)	parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or CI
OCP Team Leader	Sue-Chih Lee	Dosage Form	IV emulsion
Pharmacometrics Reviewer		Dosing Regimen	QD
Date of Submission	January 3, 2013	Route of Administration	IV
Estimated Due Date of OCP Review		Sponsor	Baxter
Medical Division Due Date		Priority Classification	Priority
PDUFA Due Date	July 3, 2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling				
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		4		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	Standard clinical lab tests
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X
Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			
General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Kristina Estes

29 JAN 2013

Reviewing Clinical Pharmacologist

Date

Se-Chih Lee

Team Leader/Supervisor

Date

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/s/

KRISTINA E ESTES
03/04/2013

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03/04/2013