CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020181

MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 13, 1997

FROM: Eric Colman, M.D., Medical Officer

SUBJECT: Safety Update for NDA 20-181

TO: File for NDA 20-181

The sponsor has submitted two safety studies to support the safety of the drug product:

(1) Protocol 92008 - Safety Clearance Study in 12 healthy males.
(2) Protocol 92010- Safety study of Liposyn III 30% by direct infusion to 8 adult TPN patients for seven days.

A current safety update (< 4 months) will not be required since the results of these limited studies provide assurance regarding safety of the product should a inadvertent direct infusion of the drug product occur.

/S/ 1/13/97

Eric Colman, M.D., Medical Officer
HFD-510

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ON ORIGINAL

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MEDICAL REVIEW

NDA #: 20-181

SPONSOR: Abbott

DRUG: Liposyn III 30% Pharmacy Bulk Package

DATE SUBMITTED: 9/24/96

DATE RECEIVED, M.O.: 9/29/96

DATE OF REVIEW: 11/4/96

Manufacturing controls
see chemistry review

Pharmacology
see pharmacology review

BACKGROUND

This submission is in response to the non-approval letter of November 29, 1991 issued from HFD-160. In the original medical review, conducted by Dr. John Kenealy, the NDA was considered not approvable because of the lack of data to demonstrate safety in the event of inadvertent direct infusion of a 30% lipid emulsion. Two potential options were offered to the Sponsor: 1) Use a container in which direct infusion is not possible and 2) Obtain data to demonstrate that direct infusion of a 30% lipid emulsion is safe. Dr. Kenealy did not feel that additional efficacy data were needed because, "the safety and efficacy of this product in the concentrations proposed, if used as it should be labeled, (ie as a 20% or lower concentration in a TPN admixture) has been adequately demonstrated."

The Sponsor, in response to the not approvable letter and the stated deficiencies, submitted 2 protocols that were reviewed by HFD-160 on 11/1/92. One protocol was a Phase 1 clearance study to be conducted in healthy subjects and the other study was a Phase 3 utility study to be conducted in adult TPN patients.

Regarding the Phase 3 study, in a letter dated 5/8/95, the Sponsor noted that data from 8 patients had been collected but investigators were having difficulty enrolling additional patients because of the protocol-specified need to remain NPO for a period of 7 days. According to the Sponsor's letter, Dr. Waymack (HFD-160) recommended that the study duration be shortened to 24 hours and an additional 20 patients be studied. The current submission contains data from 8 patients who received Liposyn III 30% for 7 days and data from 20 patients who received the lipid infusion for a 10-hour period x 1 day.

1.0 Indications

Liposyn III 30% pharmacy bulk package is indicated for use in a pharmacy admixture program for the preparation of 3-in-1 or total nutrient admixtures (TNAs). Liposyn III is indicated as a source of calories for patients requiring parenteral nutrition. Where such nutrition is required for extended periods of time (more than 5 days), Liposyn III is also indicated as a source of essential fatty acids to prevent or reverse biochemical changes in fatty acid composition of plasma lipids and the clinical manifestations of EFAD.

Clinical Studies

In response to the non-approvable letter the Sponsor conducted 2 studies reviewed below.

1.1 Liposyn III 30% Phase 1 Safety Clearance Study

Objective/Rationale: To determine the safety of administration and rate of clearance of triglyceride and/or cholesterol and free fatty acids from the blood of healthy volunteers administered 0.1 gm of fat per kg body weight as Liposyn III 30%.

Protocol Design: This was an uncontrolled study that enrolled 12 healthy males aged years who received 0.1 gm of fat/kg body weight administered undiluted via peripheral vein. The duration of infusion was minutes. The following observations were recorded prior, during and after drug administration:

- body weight
- vital signs
- urine analysis
- levels of triglyceride, total lipids, and free fatty acids (FFA)
- adverse events

Results: The mean age of the participants was 32 years (range . Ten of the 12 patients completed the study; 2 patients received an inappropriate dose of the medication. Triglyceride levels peaked at 10 minutes post infusion, total cholesterol levels remained relatively constant during the study period, and FFAs levels rose slightly up to 20 minutes post infusion, remained stable until 60 minutes post infusion and were back to baseline at 24-hours post infusion. Of note, one subject had a marked increase in the level of FFA that peaked at 20 minutes post infusion. The mean change from baseline to 60 minutes post infusion in triglyceride level was 37 mg/dl, for total cholesterol it was -3.0 mg/dl, for FFA it was 0.4 meq/l. The mean half-life for triglyceride was 26 minutes and time to clearance was 3 hours. There were no clinically meaningful changes in body weight or vital signs.

Conclusions: The calculated mean half-life of the 30% emulsion (25 minutes) was similar to the 10% and 20% liposyn III emulsions: 21 minutes, respectively. The results of this study suggest that

in the event that one dose of Liposyn III 30% emulsion is inadvertently administered directly into healthy male subjects significant adverse health consequences are unlikely.

1.2 Utility Study of Liposyn III 30% Given by Direct Intravenous Infusion to Adult TPN Patients (12/95-3/96)

Objective/Rationale: Evaluate the safety of direct administration of Liposyn III 30% for 7 days in adult patients receiving TPN.

Protocol Design: This was an uncontrolled, noncomparative study of 8 adult patients (originally designed to study 20 patients) who received either 1.0 or 1.5 gm/kg/day of Liposyn III 30% emulsion as a direct intravenous infusion. The infusion time was ~~10 hours~~. Amino acids and dextrose were also infused through a separate port. Body weight, vital signs, hematology and chemistry panels, triglyceride, cholesterol, and free fatty acid levels were determined pre, during, and post-drug infusion.

Results: Because of difficulty enrolling patients and product expiration in November 1994 the study was terminated and the results of 8 patients were reported. There were 6 male patients and 2 female patients. The age range was years. The patient's primary diagnoses are shown in the table below.

Patient	Diagnosis
101	acute pancreatitis
201	small bowel obstruction
202	complete SC1
203	gastric outlet obstruction
204	spinal fusion
205	thyroid cancer with lung mets
301	ovarian cancer
302	perforated appendix

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One patient died of septic shock during the study. The underlying pathologies that led to the requirement for TPN and the numerous concomitant medications the patients were receiving make it very difficult to draw firm conclusions regarding the independent effects of the Liposyn III infusions. With this caveat in mind, there were no overt abnormalities in hematology or chemistry parameters that could be attributed to the lipid infusion. In general, the levels of triglyceride and free

fatty acids tended to peak 4-hours post initiation of infusion and returned to normal by 24-hours post infusion. Cholesterol levels remained fairly constant throughout the period of lipid infusion and the remaining period of monitoring. There were no significant changes in the vital signs.

As noted above, this study was terminated because of inadequate enrollment. After discussion with HFD-160 it was decided to reduce the number of days of lipid infusion from 7 to 1 and to study an additional 20 patients. This study identified as Protocol 95017 is discussed below.

1.3 Utility Study of Liposyn III 30% Given by Direct Intravenous Infusion to Adult TPN Patients

Objective/Rationale: Evaluate the safety of direct infusion of Liposyn III 30% for 1 day in adult patients receiving TPN.

Protocol Design: This was an uncontrolled, non-comparative study of 20 adult patients who received 1 gm/kg/day of Liposyn III for a 10-hour period. Amino acids and dextrose were also infused through a separate port. Body weight, vital signs, hematology and chemistry panels, triglyceride, cholesterol, and free fatty acid levels were determined pre, during, and post-drug infusion.

Results: There were 9 males and 12 females enrolled in the study. The mean age was 66 years. The adverse events recorded during the study are listed in the table below.

Event	Number of Patients
Hypokalemia	3
Hypomagnesemia	3
Hypocalcemia	1
Decreased urine output	1
Atrial fibrillation	1
Anemia	1
Fever	1
Clotted mediport	1
Hypoxemia	1
Tachyarrhythmia	1
Low albumin	1

There were significant mean increases in the levels of glucose, BUN, and neutrophils. Again, due

to the varied underlying pathologies of the patients and the myriad of concomitant medications, it is difficult, if not impossible, to determine causality between the lipid infusion with the adverse events. The changes in the levels of cholesterol, triglyceride, and free fatty acids were not noteworthy.

Conclusions: It is difficult to make definitive statement regarding the safety of direct infusion of Liposyn III 30% in adult patients from the data presented in this submission primarily because of the small sample size. Nevertheless, the data do provide some reassurance that the inadvertent direct infusion of Liposyn III 30% will most likely not result in catastrophic consequence. In addition, although direct infusion of a 30% fat emulsion may occur in the clinical setting as a result of human error, this will most likely be a rare occurrence. The labeling should, as clearly as possible, convey the message that the 30% fat emulsion is to be diluted prior to use.

1.4 Labeling Review:

a) Description: adequate
b) Clinical Pharmacology: adequate
c) Indications and Usage: adequate
d) Contraindications: adequate
e) Warnings: recommend inserting and phosphates to the sentence that reads, ".....to the dosage levels of the divalent cations (Ca and Mg) and phosphates administered,.....
f) Precautions: adequate
g) Adverse Reactions: adequate
h) Overdose: adequate
I) Dosage and Administration: adequate
j) Mixing Instructions for Combined Administration: recommend inserting the following into the first sentence of the fifth paragraph: Because of the potential for life threatening events caution should be taken.....
k) Use Aseptic Technique: adequate
l) How Supplied: adequate

Recommendation: This Reviewer recommends approval of this NDA given that the following changes to the labeling are made:

1. **Warnings Section**: recommend inserting and phosphates to the sentence that reads, ".....to the dosage levels of the divalent cations (Ca and Mg) and phosphates administered,.....

2. **Mixing Instructions for Combined Administration**: recommend inserting the following into the first sentence of the fifth paragraph: Because of the potential for life threatening events caution should be taken.....

/S/ - 11/18/96

Eric Colman, M.D.

/S/ 11-22-96

cc: NDA file
McCort/Colman/Kcen/Troendle

/S/ 11/13/96

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