

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020181

PHARMACOLOGY REVIEW(S)

AUG 7 1997

NDA 20-181

Date of Review: August 8, 1997

Sponsor: Abbott Laboratories

Date Submitted: July 24, 1997

Date Received: July 25, 1997

PHARMACOLOGY TEAM LEADER MEMO TO FILE

DRUG: Liposyn III, 30%

The original pharmacology review submitted 4/14/92 and written by Dr. James E. Wilson offered three recommendations to be communicated to the sponso

Although the studies of carcinogenesis, mutagenesis, impairment of fertility and studies in nursing mothers have not been performed with Liposyn III, for consistency in labeling for these products, the fact that these studies have not been performed should be noted in the labeling.

These issues were communicated to the sponsor in an NA letter issued by the division on March 24, 1997. The sponsor has responded adequately to the pharmacology labeling requests outlined in the NA letter. The submission stamp dated July 25, 1997 supplies a complete response to pharmacology issues regarding this NDA.

From a pharmacology standpoint, no further action is necessary. Pharmacology recommends approval of NDA 20-181.

APPEARS THIS WAY
ON ORIGINAL

/S/

Ronald W. Steigerwalt, Ph.D.

8/7/97

cc: NDA Arch
HFD510
HFD510/Steigerwalt/McCort

APPEARS THIS WAY
ON ORIGINAL

DEC 18 1996

NDA 20-181

Date of Review: December 18, 1996

Sponsor: Abbott Laboratories

Date Submitted: September 24, 1996

Date Received: September 26, 1996

PHARMACOLOGY TEAM LEADER MEMO TO FILE

DRUG: Liposyn III, 30%

The original pharmacology review submitted 4/14/92 and written by Dr. James E. Wilson offered three recommendations to be communicated to the sponsor (see attached copy of review).

Although the studies of carcinogenesis, mutagenesis, impairment of fertility and studies in nursing mothers have not been performed with Liposyn III, for consistency in labeling for these products, the fact that these studies have not been performed should be noted in the labeling.

TO BE COMMUNICATED TO SPONSOR:

APPEARS THIS WAY
ON ORIGINAL

The following statements should be added to the labeling.

Carcinogenesis, mutagenesis, impairment of fertility

Long term studies in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility of Liposyn[®]III 30% have not been conducted

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Liposyn[®]III 30% is administered to a nursing mother.

APPEARS THIS WAY
ON ORIGINAL

/S/

12/18/96

Ronald W. Steigerwalt Ph.D.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/McCort

APPEARS THIS WAY
ON ORIGINAL

Wetzel

Attach to copy for HFD-502/J Weissinger

PHARMACOLOGY/TOXICOLOGY REVIEW

HFD-140

NDA# 20-181

DRUG NAME: LIPALON III 30%

IND# _____
INDICATIONS: Replenisher (fluid, natural)

OTHER NAMES: Intravenous fat emulsion

SPONSOR: Abbott Lab

STEREOISOMER? yes ___ no

DELIVERY SYSTEM? yes ___

no Toxicology Studies Included in this Review:

APR 15 1992

The source for soybean oil should be one that supplies a pesticide-free product.

Conclusions

1. IND: No objection Objection _____
NDA: No objection Objection _____

2. Tumorigen? yes ___ no ___ Neurotoxic? yes ___ no ___ Immunotoxic? yes ___ no ___

3. Put an asterisk by the studies that were conducted using the final formulation!

4. Inactive ingredient or metabolite concerns? _____

Reviewer James E. Wilson

Date 4/14/92

NDA 20-181

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division of Medical Imaging, Surgical, and Dental Drug Products
Original Summary

Letter Date: 4/10/91
CDER Date: 4/22/91

Reviewer: J.E. Wilson
Review Started: 3/06/92
Review Completed: 4/13/92

APPLICANT: Abbott Laboratories
Abbott Park, Illinois

DRUG: LIPOSYN® III 30% (an intravenous fat emulsion),
Pharmacy Bulk Package

CATEGORY: Replenisher (fluid, nutrient)

COMPOSITION:

Per Liter

Soybean Oil

Egg Phosphatide

Glycerin

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Sodium Hydroxide

Water for Injection

Osmolarity

pH

CONTAINER CHARACTERISTICS:

LIPOSYN III 30% will be packaged in Abbott's
500 and 1000 mL . The closure is

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ON ORIGINAL

DOSAGE: Adult Patients.—LIPOSYN III can provide up to 60% of daily calories at a dose not to exceed 3 g/kg of body weight per day. In most adult patients, this can be supplied as 153 mL of LIPOSYN III 30% administered three times weekly.

The initial infusion rate for the 3-in-1 admixture containing LIPOSYN III 30% should be slow for the first 15 minutes, approximately 1 mL/minute. If no adverse effects are observed during this initial infusion, the rate can be increased to allow 50 g of fat (167 mL of LIPOSYN III 30%) to be given over a period of not less than four to six hours.

Pediatric Patients.—LIPOSYN III can provide up to 60% of daily calories at a dose not to exceed 4 g/kg of body weight per day. The daily dosage of LIPOSYN III ranges from 2.5 mL to 5 mL per kilogram for the 30% emulsion, depending upon the size and maturity of the patient.

The initial infusion rate for the 3-in-1 admixture containing LIPOSYN III 30% should be slow for the first 15 minutes, approximately 0.1 mL/minute. If no adverse effects are observed during this initial infusion, the rate can be increased to deliver not more than 10 g fat/hour (equivalent to 33 mL of LIPOSYN III 30%/hour). NOTE: For preterm infants, the maximum rate of fat administration is lower and should not exceed 1 g fat/kg body weight over four hours.

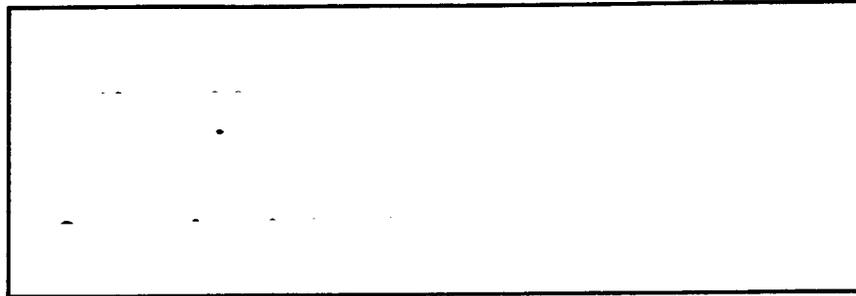
Administration.—LIPOSYN III can be infused into the same central or peripheral vein as the carbohydrate/amino acid solution by means of a short Y-connector near the infusion site.

EVALUATION:

The subject drug is identical in qualitative composition to that in Abbott's currently approved LIPOSYN® III 10% and LIPOSYN® 20% (intravenous fat emulsions). It differs in fat concentration and it is intended for use only as a Pharmacy Bulk Package. LIPOSYN® III 30% (an intravenous fat emulsion), Pharmacy Bulk Package, is packaged in different size Abbovac glass containers than the 10% and 20% concentrations (addition of the 1000 mL pharmacy bulk package and the elimination of smaller 100 and 200 mL single-dose containers).

One of the concerns earlier reviewers have had about soybean oil emulsions is the presence of pesticides. The specifica-

tions for this ingredient in the current NDA do not include pesticides. One of the alternate suppliers, submitted a response to related LIPOSYN III 20%. Their testing laboratory, indicated that no pesticides were detected at the following detection limits:



Apparently these values represent the detection limits of the assays and hence are in accordance with the recommendation of Dr. Inscoe (the Supervisory Pharmacologist at that time) that a limit be the acceptable level. He stated that before acceptance of any other level, the applicant should submit appropriate toxicity data along with a risk assessment. This opinion has been conveyed to Abbott in connection with other submissions for fat emulsions.

The other alternate supplier of soybean oil, has not provided an analysis for pesticides. The current reviewer (J.E. Wilson) feels that the bulk of the pesticides may be removed in the , and that only residual amounts could remain. The oil is subjected to a and then separated by the into a is then . The combination of should the . Finally, the oil is then to a which plus formed by the and

by an undisclosed procedure . The were tested subacutely in mice with daily infusions of 20 mL/kg/

Members of the review team have expressed a concern over the misinjection of undiluted LIPOSYN III 30% (an intravenous fat emulsion), Pharmacy Bulk Package, directly into a peripheral vein instead of the diluted 3-in-1 admixture. LIPOSYN III 30% is isotonic and no increased erythrocyte fragility is expected when the undiluted solution is misinjected into a vein. Labeling for the adult patient stipulates that 50 g of fat (167 mL of LIPOSYN III 30%) may be given over a period of not less than four to six hours (0.17-0.25 g fat/kg/hr for a 50-kg individual). For preterm infants, the maximum rate of fat administration should not exceed 1 g fat/kg body weight over four hours (0.25 g fat/kg/hour). Nonclinical studies were conducted in which rats and dogs were administered 3 g fat/kg intravenously daily for 13 weeks. Rates of administration were 1.5 g fat/kg/hr and 0.75 g fat/kg/hr respectively for the rat and dog and both rates exceed the maximum 0.25 g fat/kg/hr recommended for human patients. The inadvertent administration of undiluted LIPOSYN III 30% at the proper dosage should not, in the reviewer's opinion, present a safety hazard.

CONCLUSION:

Application is approvable from the standpoint of pharmacology with recommendations to the applicant.

CC:
Orig. NDA 20-181
HFD-160/Division files
HFD-160/JEWilson
HFD-160/MO/JKenealy
HFD-160/Micro/PCooney
HFD-160/CSO/AMWeikel
HFD-160/Chem/SKoch
HFD-502/JWeissinger
R/D Init. by LMDewitt 4/08/92
F/T by JEWilson 4/14/92
A:\N020181.ORG

APPEARS THIS WAY
ON ORIGINAL

/S/ 4/15/92
James E. Wilson. Ph.D.

/S/

PGW 4/15/92

APPEARS THIS WAY
ON ORIGINAL