PRODUCT MONOGRAPH

LIPOSYN™ III 10%
LIPOSYN™ III 20%

(soybean oil and egg phosphatide emulsion for injection)

10/1.2% w/v
20/1.2% w/v

Intravenous Nutrient Supplement

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NAMES OF DRUG

LIPOSYN™ III 10%
LIPOSYN™ III 20%
(soybean oil and egg phosphatide emulsion for injection)
10/1.2% w/v
20/1.2% w/v

THERAPEUTIC CLASSIFICATION

Intravenous Nutrient Supplement

ACTION

LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) provides the patient requiring parenteral nutrition with a source of calories and the essential fatty acids normally obtained from a nutritionally complete oral diet. The supplemental polyunsaturated fat prevents biochemical changes of essential fatty acid deficiency (EFAD) and prevents and reverses EFAD clinical manifestations (scaliness of skin, growth retardation, poor wound healing, sparse hair growth). The infused fat particles are cleared from the bloodstream in a manner thought to be similar to the clearing of chylomicrons.

INDICATIONS AND CLINICAL USE

LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) are indicated as sources of calories for patients requiring parenteral nutrition. This includes pre- and post-operative nutritional disorders and nutritive disorders resulting from decreased or inhibited intestinal absorption, as with tumours of the digestive tract, or in ulcerative colitis and terminal ileitis.

LIPOSYN™ III 10% and 20% are also indicated in burn cases, where nitrogen loss can be excessive, in prolonged states of unconsciousness if tube feeding is inadvisable and in cachexia due to serious diseases other than of the alimentary tract.

Where such nutrition is required for extended periods of time (more than five days), LIPOSYN™ III 10% and 20% are also indicated as sources of essential fatty acids to prevent or reverse biochemical changes in fatty acid composition of plasma lipids (elevated triene/tetraene ratio) and the clinical manifestations of EFAD.

CONTRAINDICATIONS

Intravenous fat administration is contraindicated when normal fat metabolism is disturbed, such as in certain forms of liver disease, metabolic disturbance, or uncompensated diabetes. Since intravenously administered fat is removed from the bloodstream by the liver, patients with severe liver disease should not be given fat infusions until further experience has shown this to be without risk. Caution is required when LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) are administered to patients with moderately severe liver disease.

Infusion of fat emulsion is contraindicated in patients demonstrating disturbances in normal fat metabolism, such as pathologic hyperlipidemia, lipoid nephrosis, or acute pancreatitis if accompanied by hyperlipidemia. The use of fat emulsion with heparin is contraindicated in patients with coronary artery disease.

Because of the risk of acidosis, fat emulsion should not be used in diabetics who are not receiving insulin. The safety of fat infusions in diabetics treated with oral hypoglycemic agents is not known.

Lipid infusion should not be used in infants who are both jaundiced and premature (see **WARNINGS**).

This drug is contraindicated in patients with previous hypersensitivity to LIPOSYN™ III 10% and 20% or any of its excipients, including egg.

With the exception of heparin at 1 to 2 units/mL of fat emulsion, additives to the LIPOSYN™ III 10% and 20% bottles are contraindicated.

WARNINGS

LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) are supplied in single-dose containers. Partially used containers must be discarded and should not be stored or resterilized for later use. Do not administer the contents of any container in which the emulsion appears to be oiling out.

Deaths in preterm infants after infusion of intravenous fat emulsions have been reported in the medical literature (Levene, et al. 1980; Dahms, et al. 1980). Autopsy findings included intravascular fat accumulation in the lungs. Treatment of premature and low birth weight infants with intravenous fat emulsion must be based upon careful benefit-risk assessment. Strict adherence to the recommended total daily dose is mandatory; hourly infusion rate should be as slow as possible in each case and should not in any case exceed 1 g/kg in 4 hours. Lipid infusions should not be used in infants who are both jaundiced and premature.

Premature and small for gestational age infants have poor clearance of intravenous fat

emulsion and increased free fatty acid plasma levels following fat emulsion infusion; therefore, serious consideration must be given to administration of less than the maximum recommended doses in these patients in order to decrease the likelihood of intravenous fat overload. The infant's ability to eliminate infused fat from the circulation must be carefully monitored (such as triglyceride and/or plasma free fatty acid levels). The lipemia must clear between daily infusions.

In very low-birth weight infants, the adverse effects of fat emulsion infusion on pulmonary function and bacterial defences may outweigh the benefits (Fisher, et al. 1980; Levene, et al. 1980). See special precautions for use in premature and small-for-gestational age infants under **DOSAGE AND ADMINISTRATION** -Premature and Small-for-Gestational-Age Infants.

Caution should be exercised in administering Intravenous Fat Emulsion to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders or when there is danger of fat embolism. The too rapid administration of LIPOSYN™ III 10% and 20% can cause fluid and/or fat overloading resulting in dilution of serum electrolyte concentrations, over-hydration, congested states, pulmonary edema, impaired pulmonary diffusion capacity, or metabolic acidosis.

The consequences of long-term infusion of fat emulsion with a high linoleic acid content are not known.

Caution should be exercised when admixing LIPOSYN™ III 10% and 20%. See **DOSAGE AND ADMINISTRATION** -Admixture and Admixture Mixing Instructions.

It is absolutely essential that the admixture be prepared using strict aseptic technique as this nutrient mixture is a good growth media for microorganisms.

PRECAUTIONS

General:
Because free fatty acids displace bilirubin bound to albumin, the use of lipid infusions in jaundiced or premature infants should be undertaken with caution (see **WARNINGS**).

During fat emulsion therapy, the patient's hemogram, blood coagulation, liver function, platelet count and plasma lipid profile must be closely monitored. Lipemia (as determined from observation of a centrifuged sample of plasma) must clear between daily infusions. LIPOSYN™ III 10 % and 20% (soybean oil and egg phosphatide emulsion for injection) should be discontinued should a significant abnormality in any one of these parameters be attributed to therapy.

Use in Pregnancy:
The safety of fat emulsion for intravenous use during pregnancy or lactation has not yet been established; therefore, it should not be given to pregnant women or to women of

childbearing potential unless its use is deemed essential to the welfare of the patient.

Use in Patients with Liver Disease:
Extreme care should be used in administering fat infusions to patients with liver disease (see **CONTRAINDICATIONS**). Liver function should be monitored frequently if fat emulsion is given to patients with moderately severe liver disease. In long-term administration, liver function tests should also be performed.

Use in Patients with Renal Disease/Blood Disorders:
Lipid infusion should be used with caution in patients with acute renal disorders and in those with coagulation disturbances or blood dyscrasias.

The serum of such patients should be examined regularly for the presence of lipids.

Use in Patients with Diabetes:
Extreme care should be used in administering fat infusions to diabetics controlled with insulin (see **CONTRAINDICATIONS**).

Influence on Laboratory Values:
Automatic counting devices can fail to distinguish fat particles and leukocytes. A false leukocyte count can occur during fat infusion.

Infused fat emulsions can interfere with serum bilirubin determinations, showing test values which are artificially high. To minimize interference, blood specimens should be collected only after completion of the fat clearance, i.e. approximately 4 to 8 hours after completion of the daily fat infusion.

All photometric laboratory tests can be affected by lipemic plasma.

An increase in the triglyceride, cholesterol, FFA and glycerin levels can be expected during fat infusion.

ADVERSE REACTIONS

Sepsis due to contamination of administration equipment and thrombophlebitis due to vein irritation from concurrently administered hypertonic solutions have been encountered. These are attributable to IV therapy in general or to the type of infusion administered.

Adverse reactions directly related to fat emulsions are of two types: (1) immediate (acute) and (2) long term (chronic). In studies of lipid products in general, the following immediate reactions have been noted: fever, chills, allergic reactions, anemia, fatty thrombus, hyperlipidemia, flushing, dizziness, headache, sleepiness, nausea, vomiting, hyperthermia, sweating, "colloid reaction" (chest and back pain with dyspnea and

cyanosis), thrombocytopenia (rarely in neonates), hypercoagulability and transient increases in liver enzymes.

The following reactions have been noted with long-term therapy with lipid infusions in general: hepatomegaly, jaundice due to central lobular cholestasis, splenomegaly, thrombocytopenia, leukopenia, transient increases in liver function tests, overloading syndrome (fever, headache and/or hyperirritability, often in the presence of hyperlipidemia), and the deposition of brown pigment ("fat pigment") in the reticuloendothelial tissue of the liver. The significance of this last occurrence and its cause are unknown.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of fat overload during therapy, the infusion should be stopped immediately. Re-evaluate the patient and institute appropriate corrective measures. When symptoms have abated, the plasma is clear and other blood lipid measurements have returned to normal, LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) may be restarted, cautiously.

For management of suspected drug overdose, consult the regional poison control centre.

DOSAGE AND ADMINISTRATION

LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) should be administered as part of an intravenous total nutrition program via peripheral vein or central venous catheter.

LIPOSYN™ III 10% has a caloric value of 1.1 kcal/mL. Of this total, 0.5 kcal/mL is supplied by linoleic acid. LIPOSYN™ III 20% has a caloric value of 2.0 kcal/mL. Of this total 1.0 kcal/mL are supplied by linoleic acid.

Adult Patients:
LIPOSYN™ III 10% and 20% can provide up to 60% of daily calories at a dose not to exceed 3 g/kg of body weight per day. The other 40% should be provided by carbohydrate and amino acids.

For the prevention of essential fatty acid deficiency, the recommended daily requirement is approximately 4% of the caloric intake as linoleate. In most adult patients, this can be supplied as 500 mL of LIPOSYN™ III 10% or 250 mL of LIPOSYN™ III 20% administered twice weekly.

The initial infusion rate for the first 15 minutes should be 1.0 mL/minute for the first 15 minutes for LIPOSYN™ III 10% and 0.5 mL/minute for LIPOSYN™ III 20%. If no

adverse effects are observed during this initial infusion, the rate can be increased to allow no more than 500 mL of LIPOSYN™ III 10%, or 250 mL of LIPOSYN™ III 20% to be given over a period of four to six hours.

Pediatric Patients:
LIPOSYN™ III 10 % and 20% can provide up to 60% of daily calories at a dose not to exceed 4 g/kg of body weight per day. The other 40% should be provided by carbohydrate and amino acids.

For the prevention of essential fatty acid deficiency, the recommended daily requirement is approximately 4% of the caloric intake as linoleate. The daily dosage ranges from 5 mL to 10 mL per kg for LIPOSYN™ III 10% and 2.5 mL to 5 mL per kg for LIPOSYN™ III 20%, depending on the size and maturity of the patient.

The infusion should be started at a rate of 0.1 mL/minute for the first 15 minutes. If no adverse effects are observed during this initial infusion, the rate can be increased to allow no more than 100 mL per hour of LIPOSYN™ III 10% or 50 mL per hour of LIPOSYN™ III 20%.

For infants who require small volumes of LIPOSYN™ III 10% and 20% at slow, controlled administration rates, consider using a Syringe Pump Unit (see **AVAILABILITY**).

Premature and Small-for-Gestational-Age Infants:
Sick infants, premature and small-for-gestational-age infants are at greater risk of developing hyperlipidemia. Lipidemia has the potential for lowering oxygen tension, especially in infants with pulmonary insufficiency. Small babies tolerate fat infusion better if it is given by continuous infusion at a rate of 0.2 g/kg body weight per hour over a 20 to 24 hour period.

For infants who require small volumes of LIPOSYN™ III 10% and 20% at slow, controlled administration rates, consider using a Syringe Pump Unit (see **AVAILABILITY**).

Administration
LIPOSYN™ III 10% and 20% can be infused into the same central or peripheral vein as the carbohydrate/amino acid solutions by means of a short, Y-connector near the infusion site. (Note: Hypertonic solutions must be given by central vein infusion only). This allows for mixing of the solutions immediately before entering the vein or for alternation of each solution. Flow rates of each solution should be controlled separately by infusion pumps if these are used. Fat emulsion may also be infused through a separate peripheral site.

With the exception of heparin at 1 to 2 units/mL of fat emulsion, additives to the LIPOSYN™ III 10% and 20% bottles are contraindicated.

Filters should not be used for administration of the emulsion.

LIPOSYN™ III 10% and 20% are supplied in single-dose containers. Partially used containers must be discarded and should not be stored or re-sterilized for later use. Do not administer the contents of any container in which the emulsion appears to be oiling out.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The prime destabilizer of emulsions are excessive acidity (low pH) and inappropriate electrolyte content. Careful consideration should be given to the dosage levels of the divalent cations (Ca^{++} and Mg^{++}) administered, as these have been shown to cause emulsion instability. Amino acid solutions exert a buffering effect, protecting the emulsion.

Fat-containing fluids such as LIPOSYN™ III 10% and 20% have a propensity to extract phthalates from phthalate-plasticized polyvinyl chloride (PVC). Although the amount is very small and no adverse clinical effects have been reported from administration of such amounts of phthalate, it may be advisable to consider administration of LIPOSYN™ III 10% and 20% or LIPOSYN™ III admixtures (in one container) through a non-phthalate infusion set.

Admixture

Caution should be exercised when admixing LIPOSYN™ III 10% and 20%. IT IS ABSOLUTELY ESSENTIAL THAT THE ADMIXTURE BE PREPARED USING STRICT ASEPTIC TECHNIQUES AS THIS NUTRIENT MIXTURE IS A GOOD GROWTH MEDIA FOR MICROORGANISMS.

Hypertonic admixtures must be given by central vein infusion only. Reference should be made to the individual product monographs for detailed information on each component.

Compounded admixtures may be stored under refrigeration (2-8 ^{o}C) for up to 24 hours. Administration of admixtures should be completed within 24 hours after removal from refrigeration. Reference should be made to the individual product monographs for detailed information on each component.

Studies have documented the stability of LIPOSYN™ III 10% and 20% with necessary Hospira electrolytes, Hospira trace metals, and Hospira 10% through 70% Dextrose Injection, USP in a TPN admixture container with the following Hospira amino acid solutions:

Concentrations	Aminosyn™ II	Aminosyn™ II with Electrolytes
7%	X	X
8.5%	X	X
10%	X	X

Admixture Mixing Instructions

Solutions should be prepared in the hospital pharmacy under a laminar-flow hood using careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients.

The following proper mixing sequence must be followed to minimize pH-related problems by ensuring that typically acidic dextrose injections are not mixed with lipid emulsion alone:

1 LIPOSYN™ III 10% and 20% is transferred to the empty container by inserting the transfer spikes of the pooling bags into the fat emulsion bottle and allowing the emulsion to fill by gravity.
2 AMINOSYN™ II is added to the fat emulsion followed by dextrose injection.
3 The bag is squeezed occasionally during transfer to facilitate mixing.
4 Electrolytes and trace metals are added after LVP transfer via the additive port.
5 The container is then inverted at least ten times to ensure uniformity of mixing.
6 Compounded admixtures may be stored under refrigeration (2-8°C) for up to 24 hours.
7 Multivitamins are added at the conclusion of the refrigeration storage.
8 Administration of admixtures should be completed within 24 hours after removal from refrigeration.

AVAILABILITY

LIPOSYN™ III 10% (soybean oil and egg phosphatide emulsion for injection) is supplied in 500 mL single-dose containers.

LIPOSYN™ III 20% is supplied in 500 mL single-dose containers.

STORAGE CONDITIONS

Store at 20 to 25 °C (see USP controlled room temperature). Do not freeze.

CHEMISTRY

Description

LIPOSYN™ III 10% and 20% (soybean oil and egg phosphatide emulsion for injection) are sterile, non-pyrogenic fat emulsions prepared for intravenous administration.

LIPOSYN™ III 10% contains 10% soybean oil, 1.2% egg phosphatides and 2.5% glycerin in water for injection. Sodium hydroxide has been added to adjust the pH to

approximately 8.3. LIPOSYN™ III 10% has an osmolarity of approximately 284 mOsm/litre.

The total caloric value of LIPOSYN™ IIII 10% including fat, phospholipid and glycerol is 1.1 kcal/mL. Of this total 0.5 kcal/mL is supplied by linoleic acid.

LIPOSYN™ III 20% contains 20% soybean oil, 1.2% egg phosphatides, and 2.5% glycerin in water for injection. Sodium hydroxide has been added to adjust the pH to approximately 8.3. LIPOSYN™ III 20% has an osmolarity of approximately 292 mOsm/litre. The total caloric value of LIPOSYN® II 20% including fat, phospholipid and glycerol is 2.0 kcal/mL. Of this total, approximately 1.0 kcal/mL are supplied by linoleic acid.

LIPOSYN™ III 10% and 20% contain emulsified fat particles of approximately 0.4 micron in diameter, similar to naturally-occurring chylomicrons.

The soybean oil is a mixture of neutral triglycerides of predominantly unsaturated fatty acids. The fatty acids forming the major component of soybean oil is described below:

	Fatty Acid Content (%)				
Substance	Linoleic	Oleic	Palmitic	Stearic	Linolenic
Soybean Oil	54.5	22.4	10.5	4.2	8.3

TOXICOLOGY

Acute Toxicity Studies:
The following studies have been conducted on LIPOSYN™ 10% and 20%, and not on LIPOSYN™ III 10% and 20%.

Mice given LIPOSYN™ 10% and 20% Injection in single doses up to 10 g fat/kg showed no signs of toxicity. Rats given LIPOSYN™ 20% Injection at a single dose of 4 g fat/kg also exhibited no signs of toxicity. Dogs given 5.0 g fat/kg of LIPOSYN™ 10% or 20% Injection at a rate of 4 mL/minute showed no deaths or signs of toxicity, but greatly elevated serum total lipids and triglycerides and slightly elevated serum cholesterol were observed for several hours.

Subacute Toxicity Studies:
The following studies have been conducted on LIPOSYN™ 10% and 20%, and not on LIPOSYN™ III 10% and 20%.

Rats given LIPOSYN™ 10% Injection at 10 or 20 mL/kg/day (1.0 to 2.0 g/kg) for 6 weeks showed no treatment-related deaths. Mild anemia occurred at 20 mL/kg (2.0 g/kg).

Rats given LIPOSYN™ 10% Injection at doses of 2.0 or 3.0 g/kg (20 to 30 mL/kg) developed overt hemoglobinuria and anemia within 5 days.

Dogs given LIPOSYN™ 10% Injection at 6 mL/kg (0.6 g fat/kg) daily for 6 weeks showed no signs of toxicity or changes in body chemistry.

Rats given LIPOSYN™ 20% Injection and a commercially available soybean oil emulsion 20% at doses of 10 or 20 mL/kg/day (2 or 4 g fat/kg/day) for 4 weeks developed overt hemoglobinuria, decreases in hemoglobin and hematocrit values, deposition of "lipid pigments" in reticuloendothelial tissues and the formation of hepatic microgranulomata.

Dogs were given LIPOSYN™ 20% Injection and a commercially available soybean oil emulsion 20% at a dose of 45 mL/kg (9 g fat/kg) daily for 4 weeks. Several treatment-related adverse effects were observed in dogs treated with either product. Increase in serum lipid parameters, elevation of alkaline phosphatase and cholesterol values, decrease in total serum proteins and red blood cell parameters were reported. One mortality in the LIPOSYN® 20% treated group was recorded. It was attributed to acute necrotic pancreatitis and serofibrinous peritonitis possibly due to a high fat-low protein intake. Histologically, the most significant finding was the deposition of "lipid pigment" in reticuloendothelial cells and disseminated microgranulomata in the liver parenchyma and Kupffer cells hyperplasia.

Chronic Toxicity:

The following studies have been conducted on LIPOSYN™ 10% and 20%, and not on LIPOSYN™ III.

Rats were given LIPOSYN™ 10% and 20% Injection at doses of up to 3.0 g fat/kg daily for thirteen weeks. Normal growth was observed. There were no treatment-related deaths and no signs of toxicity. Some dose-related hemoglobinuria was seen. Deposition of "lipid pigment" in the reticuloendothelial system was reported.

Dogs were given LIPOSYN™ 10% and 20% Injection 30 or 15 mL/kg/day respectively (3.0 g fat/kg/day) for 4 hours daily for 13 weeks. The most significant finding was the deposition of "lipid pigment" in the reticuloendothelial system and Kupffer cell hyperplasia and disseminated hepatic microgranulomas in the liver. Liver function remained unchanged.

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