PRODUCT MONOGRAPH

Pr INTRALIPID®

Lipid Injectable Emulsion, Mfr. Std.

Soybean Oil 10%, 20%, 30% w/v

Lipid Emulsions for Intravenous Nutrition

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Date of Revision:
January 06, 2020

Submission Control No.: 233169

PRODUCT MONOGRAPH

Pr INTRALIPID®

Lipid Injectable Emulsion, Mfr. Std.

Soybean Oil 10%, 20%, 30% w/v

THERAPEUTIC CLASSIFICATION

Lipid Emulsions for Intravenous Nutrition

ACTION

Intralipid acts as an energy source in patients for whom the usual intravenous therapy would not be adequate and as a source of essential fatty acids to prevent essential fatty acid deficiency.

Providing sufficient amounts of calories to satisfy basal metabolic requirements plus the additional needs imposed by disease and/or surgical stress can be difficult and sometimes even impossible. If the intravenous route has to be used and only carbohydrates are given as an energy source large amounts of fluid or very hypertonic solutions must be employed. Fat has an energy value a little more than twice that of carbohydrates, and is therefore an excellent source of energy for use in parenteral nutrition. By including fat emulsion in the nutritional programme a balanced intravenous nutrition can be achieved.

Moreover, INTRALIPID is practically isotonic with blood which makes it possible to infuse large amounts of energy providing substrate in a small volume of fluid via peripheral veins. This property makes possible peripheral vein infusion of solutions that otherwise have to be administered by central veins, (see ADMINISTRATION).

Fat emulsions may be used to supply up to 40% of the non-protein energy requirements of the patient. Each mL of Intralipid 10% contains 4.6 kJ (1.1 kcal), each mL of Intralipid 20%

contains 8.4 kJ (2.0 kcal) and each mL of Intralipid 30% contains 12.6 kJ (3.0 kcal). Half a litre of Intralipid 10%, Intralipid 20% and Intralipid 30% thus contains 2.3 MJ (550 kcal), 4.2 MJ (1000 kcal) and 6.3 MJ (1 500 kcal), respectively. Particle size and biological properties are similar to those of natural chylomicrons.

The intravenously administered fat is utilized as an energy source by the organism in the same manner as orally ingested fat, as demonstrated in a number of investigations and by different methods e.g. growth experiments. Parenterally administered fat is utilized rapidly by the body for energy purposes.

The elimination of fat from the blood stream after intravenous administration has been studied in the dog, rabbit and in man by determination of the plasma triglyceride content.

Studies in the dog and man have demonstrated that after infusion of INTRALIPID, fat particles are cleared from the blood stream in a manner similar to that of chylomicrons. The rate of elimination of fat emulsion is dependent both on the capacity of the chylomicron receptor sites in the capillary walls of different organs and the rate of blood flow in these vessels.

Significant amounts of INTRALIPID are removed by skeletal muscle (47%), splanchnic viscera (25%), myocardium (14%) and subcutaneous tissue (13%), with no removal observed in the liver.
Even after the intravenous administration of large doses of fat no losses occur via the urine or feces.

INDICATIONS AND CLINICAL USES

INTRALIPID should be used as an energy source in patients for whom the usual intravenous fluid therapy would not be adequate and as a source of essential fatty acids to prevent essential fatty acid deficiency.

Pre-and post-operative nutritional disorders, in which an increased administration of energy is necessary.

Nutritive disorders resulting from decreased or inhibited intestinal absorption. Such disorders may be due to tumours of the digestive tract, or to acute or chronic intestinal diseases, such as ulcerative colitis or terminal ileitis.

In burn cases where the energy requirements can be excessive. In these cases every energy supplement is of the utmost importance. Even if the patients are able to take nourishment by mouth, difficulties are often encountered in supplying sufficient amounts of energy in the diet. The administration of intravenous fat is, therefore, indicated in such cases.

Prolonged states of unconsciousness e.g., following trauma, or intoxication, if tube feeding is inadvisable or impossible.

Cachexia due to serious diseases in organs other than the alimentary tract, e.g. metastasized tumours, systemic diseases.

Impaired renal function in which adequate energy supply is essential to reduce protein breakdown.

Essential fatty acid deficiency. To prevent clinical manifestations during parenteral nutrition.

CONTRAINDICATIONS

INTRALIPID is contraindicated in patients with acute shock and in patients with severe hyperlipidemia.

In conditions characterized by severely disordered fat metabolism such as in severe liver insufficiency, acute myocardial infarction, hemophagocytotic syndrome and shock, INTRALIPID *is* contraindicated. Hypersensitivity to egg, soya or peanut protein or to any of the active substances or excipients is also contra-indicated.

WARNINGS

Fat metabolism may be disturbed in patients with special diseases and conditions. In these cases, fat elimination must be checked daily. For instructions see **PRECAUTIONS**.

Use in Pregnancy and Lactation

The safety of INTRALIPID for use in pregnancy and lactation has not yet been established; therefore, it should not be used in pregnant women, unless, in the judgement of the physician, its use is deemed absolutely necessary to the welfare of the patient.

PRECAUTIONS

In patients with special diseases and conditions

INTRALIPID should be given with caution in conditions of impaired lipid metabolism as in renal insufficiency, uncompensated diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism (if hypertri-glyceridemic) and sepsis. If INTRALIPID is given to patients with these conditions, close monitoring of the serum triglyceride concentration is obligatory: fat elimination should be checked daily (see Fat elimination test) and the dosage adjusted to the patient's capacity for fat elimination. In cases of verified or suspected liver insufficiency, liver function must be closely followed.

INTRALIPID may interfere with certain laboratory measurements (bilirubin, lactate

dehydrogenase, oxygen saturation, Hb, etc.) if blood is sampled before fat has been adequately cleared from the blood stream. Fat is cleared after a fat free interval of 5-6 hours in most patients. If increased levels of transaminases, alkaline phosphatases or bilirubin appear, further infusion of INTRALIPID should be postponed, or the dosage decreased, until normalization is achieved.

This medicinal product contains soya-bean oil and egg phospholipids, which may rarely cause allergic reactions. Cross allergic reactions have been observed between soybean and peanut.

Soybean oil has a natural content of Vitamin K1. This is considered important only for patients treated with coumarin derivatives, which interfere with Vitamin K1.

Pediatric Patients

INTRALIPID should be given with caution to neonates and prematures with hyperbilirubinemia and cases with suspected pulmonary hypertension. In neonates, particularly prematures on long term parenteral nutrition, platelet count, liver test and serum triglyceride concentrations should be monitored.

Very low birth weight preterm infants and small for gestational age infants clear intravenous fat emulsion more slowly than term infants and are at a greater risk of developing hyperlipidemia. This has the potential risk for lowering oxygen tension. The rate of infusion of INTRALIPID should be as slow as possible, the daily dose preferably administered continuously over 24 hours by infusion pump. The infant's ability to eliminate infused fat from the circulation must be carefully monitored. The lipemia must clear prior to proceeding to the next daily infusion.

Light exposure of parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, INTRALIPID should be protected from ambient light until administration is completed.

Due to the lack of experience, INTRALIPID 30% is not recommended for use in infants and children.

Fat elimination test

Before the beginning of infusion in the morning a citrated blood sample is drawn, preferably when the patient is still in a fasting state. The blood sample is centrifuged at 20-25 Hz (or 1200-1500 rpm). If the plasma is then strongly opalescent or milky, the planned infusion is postponed. In the great majority of cases, plasma is completely clear 12 hours after the infusion of the daily dose. In patients with no suspected metabolic disturbances this test should be carried out once a week.

Laboratory tests - interference

Lipemic serum interferes with colorimetric laboratory analyses. To avoid this, blood samples should be drawn in the morning prior to infusion of INTRALIPID.

Interaction with other medicinal products and other forms of interaction

Some drugs, like insulin, may interfere with the body's lipase system. This kind of interaction seems, however, to be of only limited clinical importance.

Heparin in clinical doses causes a transient increase in lipolysis in plasma, resulting in a transient decrease in triglyceride clearance due to depletion of lipoprotein lipase.

Soybean oil has a natural content of vitamin K1. This is considered important only for patients treated with coumarin derivatives, which interfere with vitamin K1.

Effects on ability to drive and use machines

No effects on the ability to drive and operate machines are to be expected.

ADVERSE REACTIONS

INTRALIPID infusion may cause a rise in body temperature and, less frequently, shivering, chills, nausea, vomiting, headache, back or chest pain with dyspnea and cyanosis (incidence <1%).

Table 1 Frequency of Adverse Drug Reactions

SOC According to WHO	**Frequency**	**Symptom**
Body as a whole - general disorders	Uncommon (>1/1 000, <1/100 Very rare (<1/10 000)	Headache, Rise in body temperature, Shivering, Chills, Tiredness Anaphylactic reaction
Cardiovascular disorder	Very rare (<1/10 000)	Circulatory effects (hyper/hypotension)
Gastrointestinal disorders	Uncommon (>1/1 000 <1/100)	Abdominal pain, Nausea, Vomiting
Liver & biliary system disorder	Very rare (<1/10 000)	Transient increase in liver function test
Musculoskeletal, connective tissue and bone disorders	Very rare (<1/10 000)	Abnormal pain
Platelet, bleeding & clotting disorders	Very rare (<1/10 000)	Thrombocytopenia
Red blood cell disorders	Very rare (<1/10 000)	Haemolysis, Reticulocytosis
Reproductive disorders, male	Very rare (<1/10 000)	Priapism
Skin and appendages disorders	Very rare (<1/10 000)	Rash, Urticaria

Thrombocytopenia has been reported in association with prolonged treatment with INTRALIPID in infants. Transient increases in liver function tests after prolonged intravenous nutrition with or without INTRALIPID have also been noted. Increased cholesterol has been observed with infants after long term treatment with Intralipid 10%. The reasons are not clear at present.

Fat overload syndrome: An impaired capacity to eliminate INTRALIPID may lead to the fat overload syndrome as a result of overdosage. However, this syndrome may appear also at recommended rates of infusion in association with a sudden change in the patient's clinical condition, such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipemia, fever, fat infiltration and disorders in various organs and coma. All symptoms are usually reversible if the infusion of INTRALIPID is discontinued.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

See Adverse Reactions "Fat overload syndrome". Severe overdose of fat emulsions containing triglycerides can, especially if carbohydrates are not administered simultaneously, lead to acidosis.

When fat emulsion is given in amounts exceeding the capacity of fat elimination the following symptoms may occur: hyperlipemia, hepatosplenomegaly, jaundice, hemolytic anemia, prolonged clotting time and thrombocytopenia. All symptoms clear in days to weeks after cessation of fat infusion.

For further information on the management of suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Dosage:

Adults

Dosage should normally not exceed 2 g of fat per kg body weight/day (20 mL, 10 mL and 6.7 mL per kg of INTRALIPID 10%, 20% and 30%, respectively). In raised energy requirements, the supply of INTRALIPID can be increased but should not, without special precautions, exceed a quantity corresponding to 3 g fat (30 mL, 15 mL and 10 mL of Intralipid 10%, 20% and 30% respectively) per kg body weight/day.

For prevention of essential fatty acid deficiency: The recommended minimum requirement is approximately 4% of the caloric intake. In most patients, this can be supplied as 500 mL of INTRALIPID 10% administered intravenously twice weekly.
The drip rate is adjusted to about 2–3 mL per minute for INTRALIPID 10% and about 1-2 mL per minute of INTRALIPID 20% at which rates 500 mL can be infused in 3–5 hours and 5–9 hours, respectively. The infusion time for 500 mL must not be shorter than 3 and 5 hours, respectively. The infusion should be started at half the infusion rate during the first 30 minutes, under supervision.

A daily supplement of 333 mL of INTRALIPID 30% (100 g fat) is regarded as sufficient to meet the basal metabolic requirements of a 70 kg patient on total parenteral nutrition. The drip rate is adjusted to 0.6-1 mL per minute at which rate 333 mL can be infused over a period of 5-10 hours. The rate of infusion should not exceed 333 mL of INTRALIPID 30% over a 5 hour period. The infusion should be started at half the infusion rate during the first 30 minutes, under supervision.

Pediatrics

The infant's ability to eliminate fat should govern the dosage (see CONTRA-INDICATIONS and PRECAUTIONS). Recommended dosage per 24 hours is 0.5-4 g fat per kg body weight equivalent to 2.5-20 mL INTRALIPID 20% and 5-40 mL INTRALIPID 10% per kg body weight, respectively. The recommended initial dose in very low birth weight infants and small for gestational age infants is 0.5 g fat per kg bodyweight per 24 hours. The dose should be increased in relation to the infant's ability to eliminate fat, which should be checked daily (see Fat elimination test). The daily dose should preferably be administered continuously over 24 hours by infusion pump. Due to the lack of experience, INTRALIPID 30% is not recommended for use in infants.

Administration

Light exposure of parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, INTRALIPID (in bags and administration sets) should be protected from ambient light until administration is completed.

See ***SPECIAL HANDLING INSTRUCTIONS***.

STORAGE AND STABILITY

Shelf life of the *medicinal product as packaged for sale*: 24 months.
For use once the overwrap is removed.

Store up to 25°C. Do not freeze.
Do not use INTRALIPID after the expiry date printed on the container.

When used in neonates and children below 2 years, INTRALIPID (in bags and administration sets) should be protected from light exposure until administration is completed

Shelf life after first opening the container

The emulsion should be used directly due to the risk of microbiological contamination. From a microbiological point of view the emulsion should be used immediately after removing of the overwrap. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C. Any unused emulsion should be discarded.

Storage after mixing

When additions are made to infusion solution, the infusion should be completed within 24 hours, due to the risk of microbiological contamination. If admixtures are not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless additions have taken place in controlled and validated aseptic conditions.

SPECIAL HANDLING INSTRUCTIONS

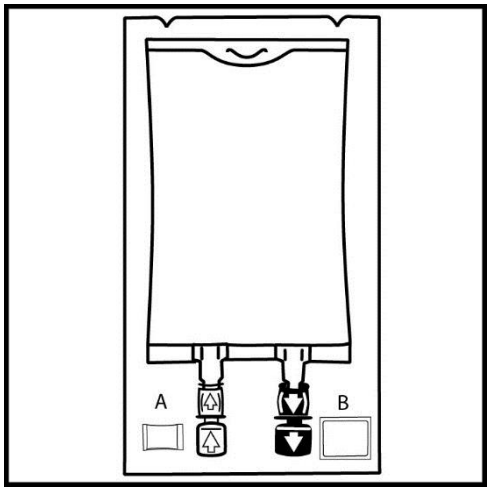
Instructions for use and handling

Before administering the product in plastic bags to patient, review these directions:

Intravenous emulsion

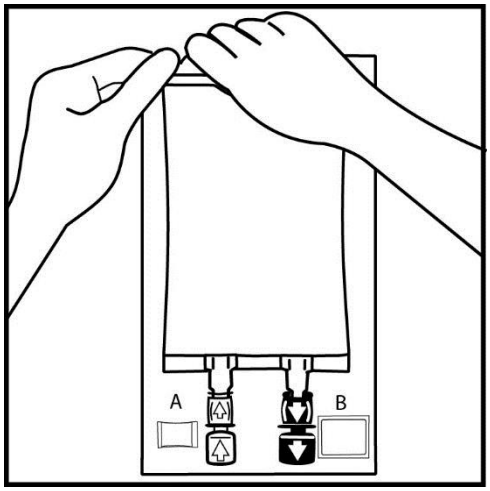
These instructions are only intended as guidelines for product use. Please refer to your own departmental guidelines.

1.



The integrity indicator (Oxalert™) A should be inspected before removing the overwrap. If the indicator is black the overwrap is damaged and the product should be discarded.

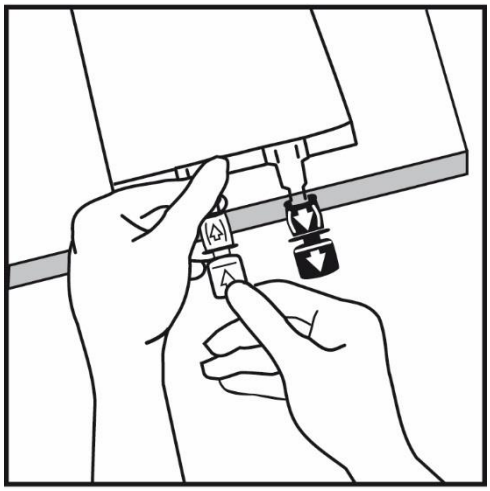
2.



Place the bag on the clean, flat surface. Remove the overwrap by tearing at the notch and pulling down along the container.

The Oxalert™ sachet A and the oxygen absorber B should be discarded.

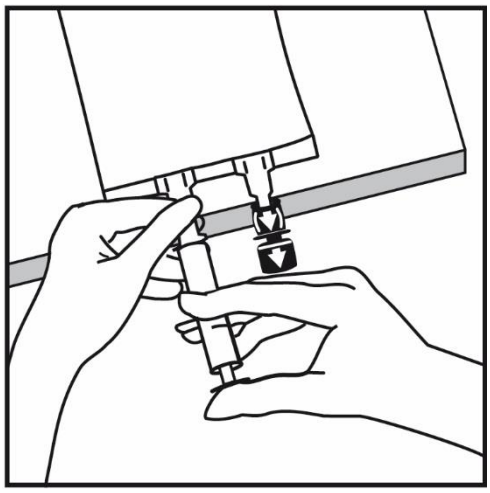
3.



Place the bag on the clean, flat surface. If additives are to be used break off the tamper-evident arrow flag from the white additive port.

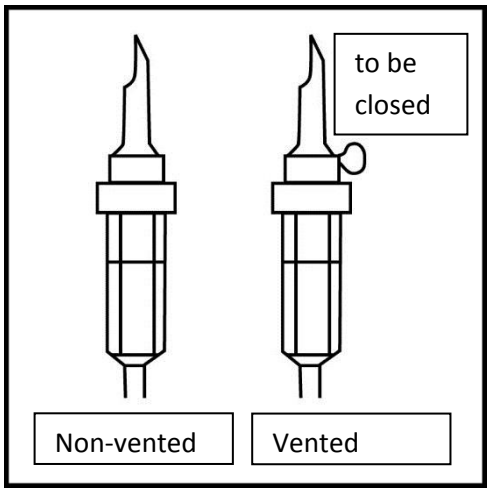
If no additives are to be used go to figure 5.

4.



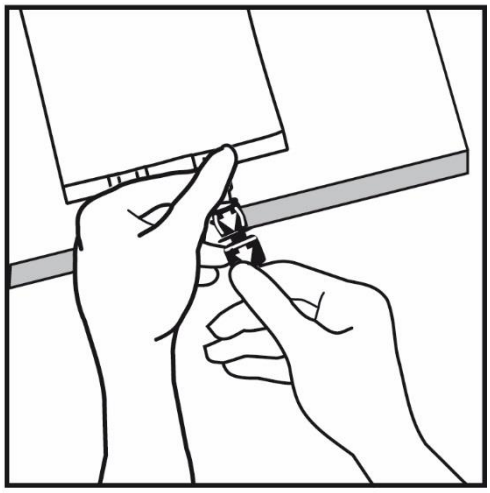
Place the bag on the clean, flat surface. Insert the needle horizontally through the centre of the septum of the additive port and inject the additives (with known compatibility). Use syringes with needles of 18-23 gauge and a length of max. 40 mm.

5.



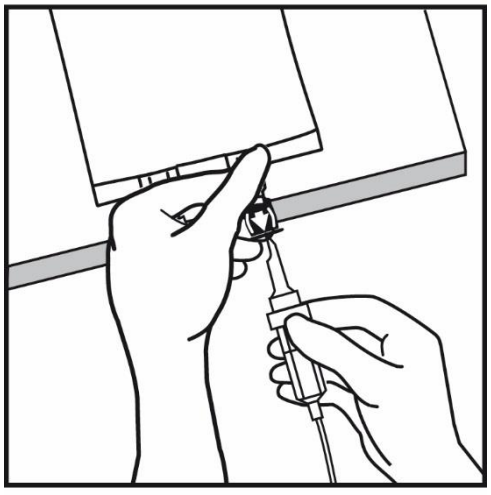
Use a non-vented infusion set or close the air vent on a vented set. Follow the instructions for use for the infusion set. Use a spike with diameter as specified in ISO 8536-4, 5.6 +/- 0.1 mm.

6.



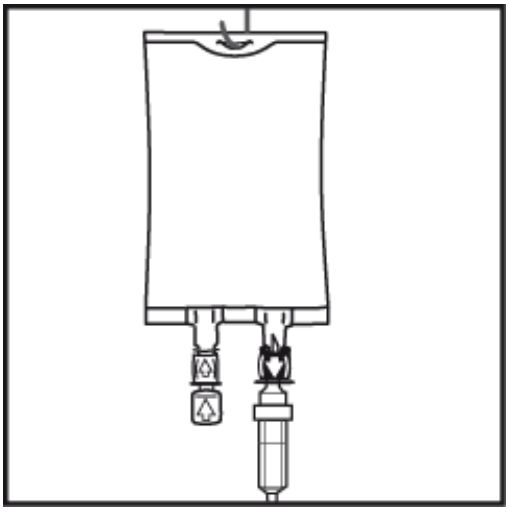
Place the bag on the clean, flat surface. Break off the tamper-evident arrow flag from the blue infusion port.

7.



Place the bag on the clean, flat surface. Hold the base of the infusion port. Insert the spike through the infusion port, by rotating your wrist slightly until the spike is inserted.

8.



Hang the bag in the hanger cut and start infusion.

Administration

The emulsion is intended for intravenous administration only using correct aseptic technique. Use only undamaged bags.

Gently invert the bag before use. Parenteral emulsions should be inspected visually for precipitate, discoloration, phase separation, and leakage prior to administration. Emulsions showing signs of discoloration, phase separation, and leakage should not be used.

Only administration sets and administration lines made from DEHP-free material should be used.

For single use only. Any unused emulsion should be discarded.

INTRALIPID must not be mixed with electrolyte or nutrient solutions, nor must drugs or vitamins be added to the emulsion in the infusion bag other than drugs or vitamins especially formulated for addition to fat emulsions.

When used in neonates and children below 2 years, INTRALIPID (in bags and administration

sets) should be protected from light exposure until administration is completed.
The simultaneous administration of INTRALIPID and amino acid solutions or carbohydrate can be achieved, using separate infusion sets where the two liquids are allowed to mix in a Y-tube just before the intravenous needle.
Use of an in-line filter (not less than 1.2 micro pore size) is recommended during administration of all parenteral nutrition admixtures.

If inappropriate spiking techniques are used during compounding, there is a potential for particles of the administration port to be dislodged into the bag (shedding of blue particles). To avoid damaging the spike port, use spike conforming to ISO 8536-4, diameter 5.6 mm $\pm$ 0.1 mm.
The remaining contents of a partly used bag must be discarded and should not be stored for later use.

PHARMACEUTICAL INFORMATION

Drug Substance:

Name: Purified soybean oil

Chemical Name: mixture of triglycerides of predominantly unsaturated fatty acids

Structural Formula:

$$\begin{array}{l} CH_2\text{-}OCO\text{-}R_1 \\ | \\ CH\text{-}OCO\text{-}R_2 \\ | \\ CH_2\text{-}OCO\text{-}R_3 \end{array}$$

where R_1, R_2 and R_3 represent the fatty acids specified in the identity test linked to the glycerol moiety of the triglyceride

Molecular Mass: approximately 870 g/mol

Physical Form: liquid

Solubility: Soluble in hexane, 2-propanol, trichlorethylene and chloroform
Partly soluble in ethanol and acetone
Not soluble in water

Melting Point/Freezing Point (range): -19ºC – +2 ºC / -10 ºC – -25 ºC

Composition:

Intralipid 10%

1 000 mL contain:

purified soybean oil	100 g
purified egg phospholipids	12 g
glycerol anhydrous	22.0 g
water for injection q.s.ad	1 000 mL
pH is adjusted with sodium hydroxide	to pH approx. 8
energy content /litre	4.6 MJ (1 100 kcal)
osmolality (approx)	300 mOsm/kg water
osmolarity (approx)	260 mOsm/L

Intralipid 20%

1000 mL contain:

purified soybean oil	200 g
purified egg phospholipids	12 g
glycerol anhydrous	22.0 g
water for injection q.s.ad	1 000 mL
pH is adjusted with sodium hydroxide	to pH approx. 8
energy content /litre	8.4 MJ (2000 kcal)

osmolality (approx)	350 mOsm/kg water
osmolarity (approx)	260 mOsm/L

Intralipid 30%

1000 mL contain:

purified soybean oil	300 g
purified egg phospholipids	12 g
glycerol anhydrous	16.7 g
water for injection q.s.ad	1 000 mL
pH is adjusted with sodium hydroxide	to pH approx.8
energy content /litre	12.6 MJ (3 000 kcal)
osmolality (approx)	310 mOsm/kg water
osmolarity (approx)	200 mOsm/L

Fatty Acid Pattern of Intralipid (%)

Considerable variation in the pattern can occur as a result of utilizing biological sources.

	%
Myristic acid	< 1 %
Palmitic acid	13 %

Stearic acid	4	%
Oleic acid	22	%
Linoleic acid	52	%
Linolenic acid	8	%
Others	1	%

Packaging (Biofine and Excel):

The packaging consists of an inner bag (primary package) with an oxygen barrier over-pouch. An oxygen absorber and an integrity indicator (Oxalert™) are placed between the inner bag and the over-pouch.

The primary plastic container is made from a multilayered film specifically designed for parenteral nutrition drug products. The film is polypropylene based comprising three coextruded layers. It contains no plasticizers and exhibits virtually no leachables. The container does not contain DEHP (di(2-ethylhexyl)phthalate), PVC or latex. The container is nontoxic and biologically inert.

The oxygen barrier over-pouch consists of polyethylene terephthalate with a barrier layer and polyolefin or polyethylene terephthalate with a barrier layer, polyolefin and ethylene-vinyl alcohol copolymer (EVOH).
The over-pouch, the oxygen absorber and the integrity indicator should be discarded after opening of the over-pouch. The integrity indicator (Oxalert™) will react with free oxygen and change colour from clear to black in case of damage in the over-pouch.

Each bag, is contained in a carton packaged as per *Availability of Dosage Forms*. (below)

Stability and Storage Recommendations:

Store at controlled temperature below 25˚C. Do not freeze.

AVAILABILITY OF DOSAGE FORMS

INTRALIPID 10% is supplied in Excel bags containing 100 mL and 500 mL or in Biofine bags containing 100mL, 250mL, and 500 mL

INTRALIPID 20% is supplied in Excel bags containing 100 mL, 250 mL, 500 mL and 1 000 mL or in Biofine bags containing 100 mL, 250mL, 500 mL, 1 000 mL

INTRALIPID 30% is supplied in Excel bags containing 250 mL, and 333 mL or in Biofine bags containing 250 mL and 500mL.

Package sizes:
100 mL bag: Box of 10 units.
250 mL bag: Box of 10 units.
500 mL bag: Box of 12 units.
1 000 mL bag: Box of 6 units

PHARMACOLOGY

INTRALIPID is a fat emulsion for parenteral nutrition and has no pharmacological action except the nutritive one. The shape and magnitude of the fat globules closely resemble those of naturally occurring chylomicrons circulating in the blood after an oral fatty meal.

Rossner (1974) has shown that there is a rapid elimination of the INTRALIPID globules from the blood stream. He found the K_2-values for male patients to be 6.09 $\pm$ 0.4%/min and for the females 7.15 $\pm$ 0.33, which give half-lives ($T^1/_2$) of 8.8 $\pm$ 0.59 and 10.3 $\pm$ 0.48 minutes, respectively.

The influence of INTRALIPID on the reticuloendothelial system (RES) has been investigated by Lemperle et al. (1970) and they found no accumulation in Kupffer cells or any significant reduction in the formation of antibodies in the guinea pig.
Rapid infusion of INTRALIPID showed no reduction of the pulmonary function and no interference with the oxygen supply to the tissues were found (Steinberethner and Wagner, 1967). On the other hand, measurement of steady state pulmonary diffusion capacity and membrane-diffusing capacity showed a transient decrease in these functions. These changes returned to normal values within 24 hours (Greene et al, 1976).

Pharmacodynamics properties

INTRALIPID provides essential and non-essential long-chain fatty acids for energy metabolism and apposition in cell membranes.

INTRALIPID in the recommended dosage does not cause any hemodynamic changes. No clinically significant changes in pulmonary function have been described when INTRALIPID is used properly. The transient increase in liver enzymes seen in some patients on TPN including INTRALIPID is reversible and disappears when TPN is interrupted. Similar changes are seen also in parenteral nutrition without fat emulsions.

Pharmacokinetic properties

INTRALIPID has biological properties similar to those of endogenous chylomicrons. Unlike chylomicrons, INTRALIPID does not contain cholesterol esters or apolipoproteins, while its phospholipid content is significantly higher.

INTRALIPID is eliminated from the circulation via the same pathway as endogenous chylomicrons, at least early on in the catabolism. The exogenous fat particle is hydrolysed in the circulation and taken up by LDL receptors peripherally and by the liver. The elimination rate is

determined by the composition of the fat particles, the nutritional status, the disease and the rate of infusion. In healthy volunteers the maximum clearance rate of INTRALIPID after fasting overnight is equivalent to 3.8 $\pm$ 1.5 g of triglycerides/kg body weight/24 hours.

Both the elimination and the oxidation rates are dependent on the patient's clinical condition; elimination is faster, and utilization is increased in postoperative patients and in trauma, while patients with renal failure and hypertriglyceridemia show lower utilization of exogenous fat emulsions.

Preclinical Safety Data

Preclinical safety studies with INTRALIPID 10%, 20% and 30% demonstrated good tolerance.

TOXICOLOGY

Acute toxicity

When Intralipid is administered in a single dose intravenously in mice, the infusion rate is of importance. An estimation of the median lethal dose (LD_{50}) must therefore be carried out at a constant infusion rate, which means that the total volume injected should be administered in several minutes.

Despite these precautions, a meaningful LD_{50} value is not obtained. The animals tolerate a single dose of more than 100 mL of INTRALIPID 10% per kg bodyweight and currently there is no rationale for testing intravenous volumes exceeding 10% of the body weight. This means that the LD_{50} is more than 10 g fat per kilogram bodyweight.

Long-term tolerance

In rats, using a central venous catheter, INTRALIPID has been infused continuously for 20 hours per day for 28 consecutive days. Even if the dose level is as high as 180 mL of INTRALIPID 10%/kg/day and 60 mL of INTRALIPID 30%/kg/day, the animals tolerated the preparation well

and the following postmortem examination did not show any abnormalities.

Also in the dog, using peripheral veins, INTRALIPID has been given for 28 consecutive days at a dose level of 9 g fat per kilogram bodyweight per day. This almost corresponds to the dog's total need for energy and has been tolerated without any clinical sign of toxicity. The investigated parameters, concerning a battery of tests for hematology, liver status, enzymology and so on were without any remarkable deviations from normal values.

No significant histopathological lesions were observed in visceral tissues. There was a slight to moderate centrolobular lipid deposit in the liver, which is known to be transient and supposed to be a result of the high fat dose used.

BIBLIOGRAPHY

Allardyce, D.B.: The postmortem interval as a factor in fat embolism. Arch. Path. 92, 248-253, (1971).

Amris, C.J., Brockner, J., Larsen, V.: Changes in the coagulability of blood during the infusion of Intralipid. Acta Chir. Scan. Suppl 325, 70-74 (1964).

Andersen, G.E., Hertel, J., Tygstrup, I.: Pulmonary fat accumulation in preterm infants. Lancet I, 441, (1981).

Andrew, G., Chan, G., and Schiff, D.: Lipid metabolism in the neonate. J. Pediatr. 92, 995-997 (1978).

Ayers, P., Boullata, J., Gervasio, J., et al.: A.S.P.E.N. Parental Nutrition Safety Consensus Recommendations. Journal of Parenteral and Enteral Nutrition. 38, 296-333 (2014).

Bark, S., Holm, I., Hakansson, I., and Wretlind, A.: Nitrogen-sparing effect of fat emulsion compared with glucose in the post-operative period. Acta Chir. Scand. 142, 423-427 (1976).

Barson, A.J. Safety of Intralipid (letter to the editor). Lancet II, 1020-1021 (1980).
Blumenthal, I.: Parenteral nutrition in the newborn (letter to the editor). Lancet II, 1021-1022 (1980).

Bradfield, J.W.B.: Intralipid and reticuloendothelial blockade. Lancet II, 1138 (1980).

Bryan, H., Shennan, A., Griffin, E., and Angel, A.: Intralipid - Its rational use in parenteral nutrition of the newborn. Pediatrics 58, 787-790 (1976).

Borresen, H.C., Coran, A., and Knutrud, O.: Metabolic results of parenteral feeding in neonatal

surgery. Ann. Surg. 172, 291-301 (1970).

Carlsson, L.A., and Liljedahl, S.O.: Lipid metabolism and trauma. Acta Chir. Scand. 137, 123-129 (1971).

Cashore, W.J., Sedaghatian, M.R. and Usher, R.H.: Nutritional supplements with intravenously administered lipid, protein hydrolysate, and glucose in small premature infants. Pediatrics 56, 8-16 (1975).

Cohen, I.T., Dahms, B., and Hays, D.M.: Peripheral total parenteral nutrition employing a lipid emulsion (Intralipid): Complications encountered in pediatric patients. J. Pediatr. Surg. 12, 837-845 (1977).

Collins, F.D., Sinclair, A.J., Royle, J.P., Coats, D.A., Maynard, A.T., and Leonard, R.F.: Plasma lipids in human linoleic acid deficiency. Nutr. Metab. 13, 150-167 (1971).

Coran, A.: The intravenous use of fat for the total parenteral nutrition of the infant. Lipids 7, 455-458 (1972).

Craig, R.P., et al. Intravenous glucose, amino acids and fat in the post-operative period. A controlled evaluation of each substrate. Lancet II, 8-11 (1977).

Cronberg, S., and Nilsson, I.M.: Coagulation studies after administration of a fat emulsion, Intralipid. Thromb. Diath. Haemorrh. 18, 664-669 (1967).

Dainow, I.I.: Safety of Intralipid (letter to the editor). Lancet II, 1020 (1980).

Deitel, M., and Kaminsky, V.: Total nutrition by peripheral vein - the lipid system. C.M.A.J. 111, 152-154 (1974).

Deitel, M., Kaminsky, V.M.: Growth of common bacteria and Candida albicans in 10% soybean oil emulsion. Can. J. Surg. 18, 531-535 (1975).
Editorial. Parenteral nutrition in the newborn - a time for caution. Lancet II, 838-839 (1980).

Elwyn, D.H.: Nutritional requirements of adult surgical patients. Crit. Care Med. 8, 9-20 (1980).
Filler, R.M., Takada, Y., Carreras, T., and Heim, T.: Serum Intralipid levels in neonates during parenteral nutrition: The relation to gestational age. J. Pediatr. Surg. 15, 405-410 (1980).

Fischer, G.W. et al.: Diminished bacterial defences with Intralipid. Lancet II (8199): 819-820 (1980).

Fischer, G.W., Hunter, K.W., Wilson, S.R.: Intralipid and reticuloendothelial clearance. Lancet II, 1300 (1980).

Friedman, Z.: Essential fatty acids revisited. Am. J. Dis. Child. 134, 397-408 (1980).

Friedman, Z., and Frolich, J.C.: Essential fatty acids, and the major urinary metabolites of the E prostaglandins in thriving neonates and in infants receiving parenteral fat emulsions. Pediatr Res 13 (8), 932-936 (1979).

Fujita, T.: Intravenous feeding in gastroenterological surgery, particularly in disorder of liver function. Proceedings of the International Congress of Parenteral Nutrition, Université de Montpellier, pp. 487-500 (1974).

Gordon, D.: Parenteral nutrition in the newborn (letter to the editor). Lancet II, 1021-1022 (1980).

Greene, H.L.: Effect of Intralipid on pulmonary function. In: Fat Emulsion in Parenteral

Nutrition. Eds: Meng & Wilmore, AMA 1976, pp. 95-98.

Grotte, G., Esscher, T., Hambraeus, L., and Meurling, S.: Nutrition parentérale compl□te dans la chirurgie infantile. Ann. Anesth. Franc. Spécial 11, 65-73 (1975).

Grotte, G., Jacobson, S., and Wretlind, A.: Possibilities and limits of intravenous fat emulsions. Symposium in Rome, May 30-June 2, 1975, pp. 47-73 (1975).

Gunn, T., Reaman, G., Outerbridge, E.W., and Colle, E.: Peripheral total parenteral nutrition for premature infants with the respiratory distress syndrome: A controlled study. J. Pediatr 92, 608-613, (1978).

Gustafson, A., Kjellmer, I., Olegard, R., and Victorin, L.: Nutrition in low birth weight infants. I. Intravenous injection of fat emulsion. Acta Paediatr. Scan. 61, 149-158, (1972).

Gustafson, A., Kjellmer, I., Olegard, R., and Victorin, L.: Nutrition in low birth weight infants. II. Repeated intravenous injections of fat emulsions. Acta Paediatr. Scan. 63, 177-182 (1974).

Hallberg, D.: Therapy with fat emulsion. Acta Anaesth. Scand. Suppl. 55, 131-136 (1974).

Hallberg, D., Holm, I., Obel, A.L., Schuberth, O., and Wretlind, A.: Fat emulsions for complete intravenous nutrition. Postgrad. Med. J. 43, 307-316 (1967).

Hanc, I., Kleczkowska, H., and Rodkiewicz, B.: On intravenous infusions of fat emulsions in pediatric surgery. Pediatria Polska XLIII, 1355-1364 (1968).

Holm, I.: Parenteral nutrition in surgical and medical gastroenterology. Acta Chir. Scand. 143, 297-305 (1977).

Jacobson, S.: Complete parenteral nutrition in man for seven months. In Advances in Parenteral Nutrition, pp. 6-19 (Georg Thieme Verlag, Stuttgart 1970).

Jeejeebhoy, K.N., Anderson, G.H., Sanderson, I. and Bryan, M.D.: Total parenteral nutrition: nutrient needs and technical tips. Part 1 and 2. Mod. Med. 29, No. 9 & 10 (1974).

Jeejeebhoy, K.N., Zorhab, W.J., Langer, B., Phillips, M.J., Kuksis, A., and Anderson, G.H.: Total parenteral nutrition at home for 23 months, without complication and with good rehabilitation. Gastroenterol. 65, 811-820 (1973).

Johnston, I.D.A.: The role of parenteral nutrition in surgical care. Ann. Roy. Coll. Surg. Engl. 50, 196-206 (1972).

Kamath, K.R., Berry, A., Cummins, G.: Acute hypersensitivity reaction to Intralipid. N. Engl. J. Med. 304, 360 (1981).

Kapp, J.P., Duckert, F., and Hartmann, G.: Platelet adhesiveness and serum lipids during and after Intralipid infusions. Nutr. Metab. 13, 92-99 (1971).

Kaijser, L., Rossner, S.: Removal of exogenous triglycerides in human forearm muscle and subcutaneous tissue. Acta Med. Scand. 197, 289-294 (1975).

Kjekshus, J.K., Ellekjaer, E., and Rinde, P.: The effect of free fatty acids on oxygen consumption in man: the free fatty acid hypothesis. Scand. J. Clin. Lab. Invest. 40, 63-70 (1980).

Lemperle G., Reichelt, M., Denk, S.: The evaluation of phagocytic activity in men by means of a lipid-clearance-test. Abstract. 6th International Meeting of the Reticuloendothelial Society. Freiburg, Germany. July 28-Aug 1, 1980.

Levene, M.I., et al.: Pulmonary fat accumulation after Intralipid infusion in the preterm infant. Lancet II (8199), 815-818 (1980).

Levene, M.I., Wigglesworth, J.S., Desai, R.: Safety of Intralipid (letter to the editor). Lancet II, 1020-1021 (1980).

Liljedahl, S.O., and Birke, G.: The nutrition of patients with extensive burns. Nutr. Metab. 14, Suppl., 110-113 (1972).

Melly, M.A., Meng, H.C., Schaffner, W.: Microbial growth in lipid emulsions used in parenteral nutrition. Arch. Surg. 110, 1479-1481 (1975).

Michel, H., Raynaud, A., Nalet, B., and Bertrand, L.: Tolerance des cirrhotiques aux lipides intraveineux. Proceedings of the International Congress of Parenteral Nutrition. Université de Montpellier, pp. 131-1137 (1974).

Nordenström, J. et al: Decreased chemotactic and random migration of leukocytes during Intralipid infusion. Am. J. Clin. Nutr. 32, 2416-2422 (1979).

Olegard, R.: Stores of essential fatty acids and tolerance of intravenous fat emulsion in newborn infants. Proceedings of the International Congress of Parenteral Nutrition. Université de Montpelier, pp. 747-756 (1974).

Olegard, R., Gustafson, A., Kjellmer, I., and Victorin, L.: Nutrition in low birth weight infants. III. Lipolysis and free fatty acid elimination after intravenous administration of fat emulsion. Acta Paediatr. Scand. 64, 745-751 (1975).

Palmblad, J., Brostrom, O., Udéen, A-M., Venizelos, N., Lahnborg, G.: (letter to the editor). Lancet II, 1138-1139 (1980).

Pereira, G.R., et al: Decreased oxygenation and hyperlipemia during intravenous fat infusions in premature infants. Pediatrics 66, 26-30 (1980).

Reimer, S.L., Michener, W.M., Steiger, E.: Nutritional support of the critically ill child. Pediatr. Clin. North Am. 27, 647-660 (1980).

Rossner, S.: Studies on an intravenous Fat Tolerance Test. Acta Med. Scand. Suppl. 564, (1974).

Shenkin, A., and Wretlind, A.: Parenteral nutrition. Wld. Rev. Nutr. Diet. 28, 1-111 (1978).

Simonsen, S. and Kjekshus, J.K.: The effect of free fatty acids on myocardial oxygen consumption during atrial pacing and catecholamine infusion in man. Circulation 58, 484-491 (1978).

Steinbereithner, K., and Wagner, O.: Das verhalten des arteriellen sauerstoffdrucks nach intravenoser fett - und laevulosebelastung bei schweren schadelverletzten. Agressologie 8, 389-393 (1967).

Sternberg, A., Gruenevald, T., Deutsch, A.A., Reiss, R.: Intralipid-induced transient sinus bradycardia. N. Engl. J. Med. 304, 422-423 (1981).

Swolin, K.: Experimentelle studien zur prophylaxe von intraabdominalen verwachsungen. Acta Obst. et Gynec. Scandinav. 45, 473-498 (1966).

Wolfe et al: Substrate interaction in intravenous feeding. Ann. Surg. 186, 518-540 (1977).

Wretlind, A.: Modern principles of the use of fat emulsions in parenteral nutrition. Zeitschrift

fur Ernahrungswissenschaft, Suppl. 13, 27-37 (1972).

Zorhab, W.J., McHattie, J.D., and Jeejeebhoy, K.N.: Total parenteral alimentation with lipid. Gastroenterol. 64, 583-592 (1973).

Yu, V.Y.H., James, B., Hendry, P., and MacMahon, R.A.: Total parenteral nutrition in very low birth weight infants: a controlled trial. Arch. Dis. Child. 54, 653-661 (1979).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr INTRALIPID®

Lipid Injectable Emulsion, Mfr. Std.

Soybean Oil 10%, 20%, 30% w/v

Lipid Emulsion for Intravenous Nutrition

Read this carefully before you start taking **INTRALIPID** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **INTRALIPID.**

What is INTRALIPID used for:

INTRALIPID infusion delivers energy (fats):

- directly into the blood,
- when normal eating is not possible,
- in the form of fatty acids,
- and helps prevent fatty acid deficiency.

How does INTRALIPID work?

INTRALIPID contains fatty acids added directly to the blood. The body uses fatty acids to make energy.

What are the ingredients in INTRALIPID?

Purified soybean oil, purified egg phospholipids, glycerol anhydrous, sodium hydroxide and water for injection.

INTRALIPID comes in the following dosage forms:

INTRALIPID 10% comes in bags containing 100 mL, 250 mL, and 500 mL.

INTRALIPID 20% comes in bags containing 100 mL, 250 mL, 500 mL and 1000 mL.

INTRALIPID 30% comes in bags containing 250 mL and 500 mL.

Do not use INTRALIPID if:

- You are in acute shock,

- You have very high amounts of fats in your blood (severe hyperlipidemia),
- Your body's ability to break down fat is severely damaged in following cases:
    - Your liver is severely damaged and does not work properly,
    - You are suffering from a severe heart attack,
    - You have a disease affecting your blood and immune system, called hemophagocytotic syndrome,
    - You are in shock and have such a drop-in blood pressure that you could die,
- You are allergic (hypersensitive) to egg, soya or peanuts or to any of the ingredients of INTRALIPID. (See **What are the ingredients in INTRALIPID),**

IMPORTANT: When INTRALIPID is mixed, especially with other vitamins and / or minerals, and is exposed to light, it may produce peroxides. If you are giving INTRALIPID (in a bag or an administration set) to a newborn or a child below 2 years of age, you should protect it from light until administration is complete.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take INTRALIPID. Talk about any health conditions or problems you may have, including if:

- You are pregnant or planning to become pregnant,
- You are breast feeding or planning to breastfeed,
- You have:
    - Kidney or liver problems
    - High levels of sugar in the blood, or diabetes
    - An inflamed pancreas (pancreatitis)
    - Low amounts of thyroid hormones (hypothyroidism)
    - Full body infection (sepsis), which can lead to death

  These conditions may interfere with your body's handling of fats (lipids). Your doctor may order tests to check the fat levels in your blood.
- You want to do a laboratory test,
- You are allergic to soybean oil and egg. Patients who are allergic to peanuts may also have reactions to soybean oil,
- You are using medications that help preventing blood clots that contain coumarin,

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with INTRALIPID:

- Insulin,
- Heparin,
- Cumarin derivatives which interfere with Vitamin K (e.g. anticoagulants that help preventing blood clots),

Drug-Laboratory Interactions

This medicine may interfere with certain laboratory tests. It is important to tell any doctor doing tests that you are using INTRALIPID.

How to take INTRALIPID:

Your healthcare professional may add INTRALIPID to other substances that can be matched with INTRALIPID.

INTRALIPID can be given at:

- A hospital,
- A managed care facility,
- A home
    - under the supervision of a doctor or other healthcare professionals,
    - by yourself if you receive required training and get agreement of your healthcare team.

Use INTRALIPID only if:

- It looks like milk,
- The bag is not damaged,
- It is used under clean and germ-free conditions,
- The expiry date printed on the bag has not been passed.

The bag should only be used one time. Throw away any remaining product. Do not use the bag if it was used before.

Usual dose:

Your medicine will go directly into the blood.

Your doctor checks your medical condition and your body needs and decides how much and how fast INTRALIPID should be given to you (please also see section **"Do not use INTRALIPID if"**).

Overdose:

If you receive too much fat, there may be a case of overdose. This is called "fat overload syndrome". In these cases, the fat infusion should be stopped or, if necessary, continued at a reduced dosage. See section **"Serious side effects and**

what to do about them" for more information.

If you have any further questions on the use of this product, ask your doctor or nurse.

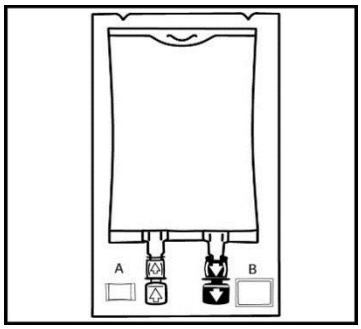
If you think you have received too much INTRALIPID, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Instructions for use and handling

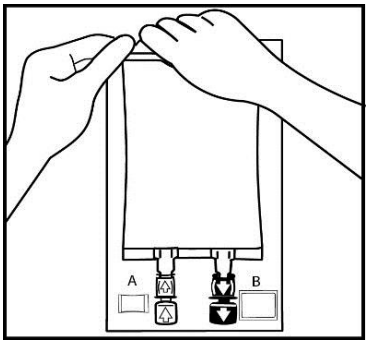
Before administering the product in plastic bags to the patient, review these directions:

Intravenous emulsion

These instructions are only intended as guidelines for product use. Please refer to your own departmental guidelines.

1. 

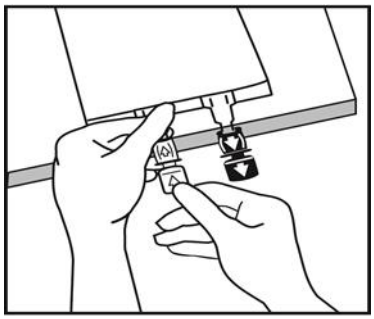
The integrity indicator (Oxalert™) A should be inspected before removing the overwrap. If the indicator is black the overwrap is damaged, and the product should be discarded.

2. 

Place the bag on the clean, flat surface. Remove the overwrap by tearing at the notch and pulling down along the container.

The Oxalert™ sachet A and the oxygen absorber B should be discarded.

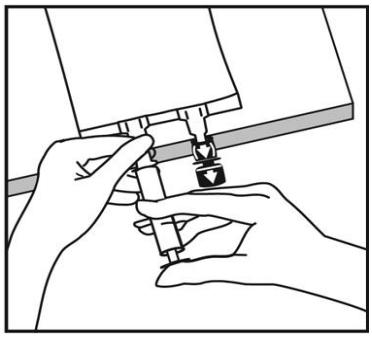
3.



Place the bag on the clean, flat surface. If additives are to be used, break off the tamper-evident arrow flag from the white additive port.

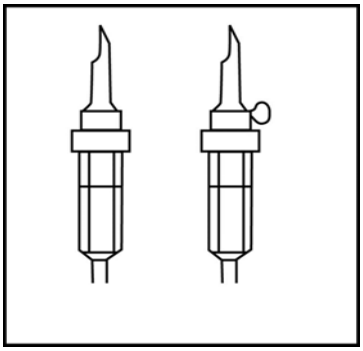
If no additives are to be used go to figure 5.

4.



Place the bag on the clean, flat surface. Insert the needle horizontally through the center of the septum of the additive port and inject the additives (with known compatibility). Use syringes with needles of 18-23 gauge and a length of max. 40 mm.

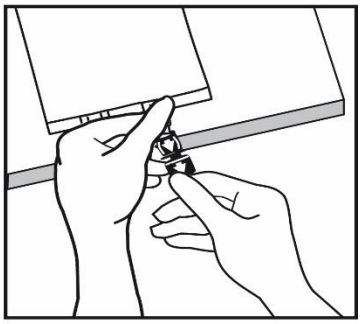
5.



Use a non-vented infusion set or close the air vent on a vented set. Follow the instructions for use for the **i**nfusion set.

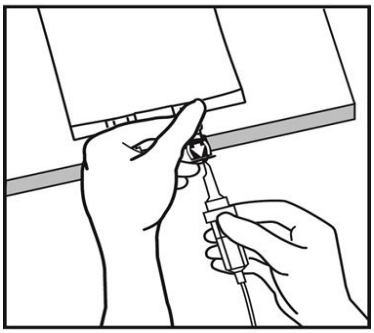
Use a spike with diameter as specified in ISO 8536-4, 5.6 +/- 0.1 mm.

6.



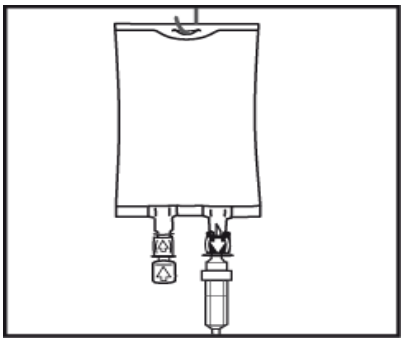
Place the bag on the clean, flat surface. Break off the tamper-evident arrow flag from the blue infusion port.

7.



Place the bag on the clean, flat surface. Hold the base of the infusion port. Insert the spike through the infusion port, by rotating your wrist slightly until the spike is inserted.

8.



Hang the bag in the hanger cut and start infusion.

When used in neonates and children below 2 years, INTRALIPID (in bags and administration sets) should be protected

from light exposure until administration is completed

What are possible side effects from using INTRALIPID?

These are not all the possible side effects you may feel after receiving INTRALIPID. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warning and Precautions.

INTRALIPID may cause a rise in body temperature and, not so often, shivering, chills, nausea, vomiting, headache, back or chest pain with shortness of breath and bluish skin (number of people getting sick <1%). If any of these signs or symptoms of an allergic reaction develop, stop the infusion immediately and contact your doctor

Fat overload syndrome:
If you are given too much INTRALIPID you may have too much fat in your blood. Stop INTRALIPID and contact your doctor if you have symptoms such as:

• yellowing of the skin and eyes (jaundice), abdominal pain,
• headaches, fever, fatigue, weakness,
• increased bleeding (e.g. nosebleeds) or bruising due to low blood platelets.

Serious side effects observed during administration of lipid emulsions are listed in the table:

Serious side effects and what to do about them				
Symptom / effect		Talk with your doctor or nurse		Stop taking drug and call your doctor or nurse
		Only if severe	In all cases	
Very Rare	• **allergic reactions** with symptoms such as: • skin rash, redness, hives • swelling of mouth, throat, lips and limbs • difficulty breathing • **decrease in blood cells** (platelets) that stop bleeding (thrombocytopenia) with symptoms such as: • increased bleeding (nose, gums) • increased bruising, red/purple spots on the skin • **low blood pressure** with symptoms such as: • dizziness, fainting, nausea • weakness, fatigue, blurred vision • **high blood pressure** with symptoms such as: • vision changes, slurred speech • shortness of breath, fatigue • chest pain, muscle pain, numbness, heaviness in the legs			√

If you have a troublesome symptom or feeling that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children. Store up to 25 °C. Do not freeze.
When used in neonates and children below 2 years, the solution (in bags and administration sets) should be protected from light exposure until administration is completed

If you want more information about INTRALIPID:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/); the manufacturer's website (http://www.fresenius-kabi.ca), or by calling 1-877-821-7724 (toll-free-telephone).

This information is current up to the time of the last revision date shown below, but more current information may be available from Fresenius Kabi.

Last revised: January 06, 2020

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON, M9W 0C8
Questions or concerns? 1-877-821-7724