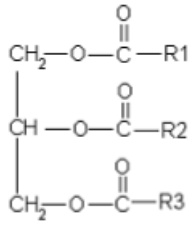
1 PRODUCT MEDICINE

Intralipid®10%, 20% and 30%, intravenous infusion for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Soya oil is a mixture of triglycerides, i.e. triacylglycerols. The triglycerides, triacylglycerols, are fatty acid triesters of glycerol (propane-1, 2, 3-triol). The main fatty acids are linoleic acid (C18:2), oleic acid (C18:1) and palmitic acid (C16:0). The number of double bonds in the different fatty acids can vary from zero (saturated) to three (unsaturated). As with most vegetable oils, the saturated acids are preferably esterified in sn-1 and sn-3 position. The molecular structure is well known from general literature on lipid chemistry.



Soya oil structural formula. General structure of a triglyceride, R1, R2 and R3 are long-chain alkyl groups.

Molecular weight: 871 g/mol (typical mean value, the molecular weight depends on the fatty acid pattern of the triglyceride). CAS number 8001-22-7.

Sterile fat emulsions for intravenous infusion containing:

Content per 1000 mL	Intralipid 10%	Intralipid 20%	Intralipid 30%
Active			
Soya oil	100 g	200 g	300 g
Osmolality (mOsmol/kg water)	300	350	310
Energy Content kcal (kJ)	1100 (4600)	2000 (8400)	3000 (12600)

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Intravenous infusion for Injection.
A milky white liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Part of the intravenous diet in all parenteral nutrition indications including:

1) Preoperative and postoperative nutritional disturbances where an improved nitrogen balance is required;
2) Nutritional disorders or disturbances of nitrogen balance due to inadequate or failing intestinal absorption caused by tumours in the gastrointestinal tract, acute or chronic intestinal diseases (peritonitis, ulcerative colitis, terminal ileitis);
3) Burns, to reduce the frequently excessive nitrogen losses;

4) Prolonged unconsciousness, eg following cranial trauma or poisoning in cases where enteral feeding is inappropriate or impossible;
5) Impaired renal function where a concentrated source of energy may be indicated to reduce protein breakdown;
6) Cachexia and
7) Patients with Essential Fatty Acid Deficiency who cannot maintain or restore a normal essential fatty acid pattern by oral intake.

4.2 Dose and method of administration

Intralipid 30% is particularly suitable for patients on fluid restriction due to its more concentrated form. This also provides an advantage in patients with a high energy requirement. A lower phospholipid/triglyceride ratio provides less phospholipids than the same amount of energy from Intralipid 100 mg/mL and Intralipid 200 mg/mL. About 60% of the fatty acids in Intralipid are essential fatty acids.

Adult dosage and infusion rate

Intralipid 10% and 20%

The quantity of Intralipid given intravenously should normally not exceed 2 g triglycerides/kg bodyweight/day. First day: no more than 1 g triglycerides/kg bodyweight/day. Second day: this dose can be doubled provided the patient's ability to eliminate administered fat has been established. (See under Dosage and Administration, Important).

In patients with raised caloric requirements, the supply of Intralipid can be further increased but should not, without special precautions, exceed 3 g triglycerides/kg bodyweight/day.

When starting, the rate of infusion of Intralipid should be about 1 mL/minute during the first 10 minutes. The infusion rate can then be gradually increased so that, after 30 minutes, it can be stabilised at the desired rate of 2 to 3 mL/minute for Intralipid 10% and 1 to 1.5 mL/minute for Intralipid 20%. At this rate, 500 mL can be infused in 3 to 5 and 5 to 8 hours respectively. The infusion times must not be shorter than 3 and 5 hours respectively.

Intralipid 30%

The ability to eliminate Intralipid 30% should govern the dosage and infusion rate. (See under Dosage and Administration, Important).

The daily supplementation of 330 mL Intralipid 30% (100 g fat) is regarded to be sufficient for a patient (weighing 70 kg) with basal energy requirement and on total parenteral nutrition. The recommended maximum dosage is 3 g triglycerides/kg bodyweight/day. Intralipid 30% can supply up to 70% of the energy requirements in patients with highly increased energy requirements. The infusion rate for Intralipid 30% is approximately 1 mL/minute and should not exceed 330 mL in 5 hours.

Paediatric dosage and infusion rate

Intralipid 10% and 20% only

The recommended dosage range in neonates and infants is 0.5 to 4g triglycerides/kg/day. The rate of infusion should not exceed 0.17g triglycerides/kg/hour (4g/kg in 24 hours). In premature and low birthweight neonates, Intralipid should preferably be infused continuously over 24 hours. The initial dosage of 0.5 to 1 g/kg/day may be increased by 0.5 to 1g/kg/day up to 2g/kg/day. Only with close monitoring of serum triglyceride concentration, liver function tests and oxygen saturation may the

dosage be increased to 4g/kg/day. No attempt should be made to exceed these rates in order to compensate for missed doses.

Intralipid 30%
Intralipid 30% is not recommended in infants and children because of lack of experience.

Method of administration
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 (see section 4.4 and 6.3).

Important
Following infusion of approximately 1 g Intralipid/kg bodyweight on the first day of parenteral nutrition, the patient's ability to eliminate the infused fat should be tested. Before the infusion begins on the second day, a sample of blood, preferably while the patient is in a fasting state, is taken in the morning. For infusions during a prolonged period, a sample of blood is taken once per week. The sample is taken as for ESR (citrate) and centrifuged at 1,200 to 1,500 RPM. If the plasma is then very opalescent or milky, the planned infusion should be postponed. In most cases, however, the plasma is quite clear 12 hours after the conclusion of an infusion of 2 g triglycerides/kg bodyweight. Hyperlipaemic serum will interfere with blood tests involving photometric determination. If the serum is milky, analysis should be postponed. Hence, the laboratory should always be advised when a patient is receiving Intralipid.

Route of administration
Intralipid, being isotonic, can be given by a peripheral or central vein, either alone or simultaneously with Vamin and/or glucose 10% to 30%, through a twin infusion set or separate sets connected to a single tap so that the mixture reaches the vein through the same cannula.

(i) Central vein
When given simultaneously with Vamin and/or glucose 10% to 30%, a combined infusion rate of between 2 and 4 mL/min is usually most suitable such that 1 L is infused during 4 to 8 hours in adults. Higher or lower infusion rates may be desirable for practical reasons and the individual's tolerance to the total fluid load.

When long-term total parenteral nutrition is considered for a patient, simultaneous infusion of the various nutrients after a period of time can lead to the accumulation of some sediment on the interior wall of the catheter. This complication can be avoided in long-term total parenteral nutrition by first administering the Intralipid. Then glucose solution followed by Vamin N or Vamin Glucose. In this way the catheter can be kept patent without any deposits at all for several months and probably even considerably longer.

(ii) Peripheral vein
Intralipid can be infused simultaneously with Vamin Glucose into a peripheral vein, thus providing a combined source of fat, glucose, L-amino acids and basal electrolyte requirements. By this method the risk of thrombophlebitis is reduced to an absolute minimum. This protection results from the dilution effect of the isotonic Intralipid and the transient coating of the blood vessel intima at the infusion site with lipid particles. Peripheral feeding is a means of supplying short-term total parenteral nutrition without the complication of a central venous catheter.

To reduce the risk of thrombophlebitis it is important that before beginning infusion, future infusion sites are marked and the infusion site is changed every 12 to 24 hours, dependent on the daily infusion period. It is also recommended that a few drops of Intralipid be administered alone at the beginning and end of the simultaneous infusion.

4.3 Contraindications

Intralipid is contraindicated in patients with:

- an impaired ability to metabolise fat, such as in severe liver damage and acute shock
- hypersensitivity to egg-, soya- or peanut protein or to any of the active substances or excipients.

4.4 Special warnings and precautions for use

Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes, pancreatitis, certain forms of liver insufficiency, metabolic disorders and sepsis. If intravenous fat is considered to be indicated in patients with the abovementioned disorders, the elimination of fat should be checked daily (see Dosage and Administration).

In cases of verified or suspected liver insufficiency the condition, as well as function, of the liver must be closely followed.

Intralipid contains soya oil and egg lecithin which may rarely cause allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut.

Use in the elderly

No data available.

Paediatric use

Intralipid should be given with caution to neonates and premature infants with hyperbilirubinaemia and in cases with suspected pulmonary hypertension. In low birthweight infants, the risk of lipid infusions may outweigh potential benefits due to further diminution of defences against infection.

In infants, metabolism of lipids in peripheral tissues may be diminished by infection and heparin administration.

In neonates receiving long term parenteral nutrition, particularly premature neonates, platelet count, liver function tests and serum triglyceride concentration should be monitored.

Light exposure of solutions for intravenous 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 (see sections 4.2 and 6.3).

Effects on laboratory tests

Intralipid may interfere with certain laboratory measurements (bilirubin, lactate dehydrogenase, oxysaturation, haemoglobin), if blood is sampled before fat has been adequately cleared from the bloodstream. Fat is cleared after a fat free interval of 5 to 6 hours in most patients.

4.5 Interaction with other medicines and other forms of interactions

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.

Soya oil has a natural content of Vitamin K1. This is considered important only for patients treated with coumarin derivatives, which interfere with Vitamin K1. The dose of coumarin derivatives may need to be increased when soy bean oil containing fat emulsions are administered.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No studies have been performed.

Use in pregnancy

It is not known whether Intralipid can cause foetal harm when administered to pregnant women or can affect reproductive capacity. This matter should be taken into consideration when this therapy is indicated in pregnant women.

Use in lactation

It is not known whether Intralipid can enter maternal milk. This matter should be taken into consideration when this therapy is indicated in lactating women.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

Intralipid infusion may cause a rise in body temperature (incidence <3%) and, less frequently, shivering, chills and nausea/vomiting (incidence <1%). Reports of other adverse events in conjunction with Intralipid infusion are extremely rare, less than one report of certain events per one million infusions.

System Organ Class according to WHO	Frequency	Symptom
Body as a whole – general disorders	Uncommon (>1/1000, <1/100)	Headache Rise in body temperature, Shivering, chills, tiredness
	Very rare (<1/10 000)	Anaphylactic reaction
Cardiovascular disorders	Very rare (<1/10 000)	Circulatory effects (e.g. hyper/hypotension)
Gastrointestinal disorders	Uncommon (>1/1000, <1/100)	Abnormal pain Nausea, vomiting
Liver & biliary system disorders	Very rare (<1/10 000)	Transient increase in liver function test
Musculoskeletal, connective tissue and bone disorders	Very rare (<1/10 000)	Abdominal 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 Intralipid treatment in infants.

Transient increase 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 'fat overload syndrome' as a result of overdosage. It may also occur at recommended rates of infusion in association with a sudden change in the clinical condition such as renal function impairment or infection. Fat overload syndrome is characterised by bone marrow depression, anaemia, thrombocytopenia, hepatosplenomegaly, splenomegaly, hyperlipaemia, fever, fat infiltration, focal seizures and shock. All symptoms are usually reversible if the infusion of Intralipid is discontinued.

Pigmentation of tissues after prolonged therapy with lipid emulsion infusions has also been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Please refer to section 4.8 Adverse effects (undesirable effects), 'Fat Overload Syndrome'. Severe overdose of fat emulsions containing triglycerides can, especially if carbohydrates are not administered simultaneously, lead to acidosis.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Blood Substitutes and Perfusion Solutions, I.V. Solutions, Solutions for Parenteral Nutrition, Fat emulsions

ATC code: B05B A02

5.1 Pharmacodynamic properties

Mechanism of action

The particle size is less than 1 micron which gives a stable emulsion and excludes the risk of fat embolism. Intralipid enters the bloodstream in a similar manner to natural chylomicron-rich lymph in both size and form, and is eliminated from the circulation according to the same kinetic principles as dietary chylomicron-rich lymph. It is formulated as a concentrated source of energy to be used together with carbohydrates and amino acids in parenteral nutrition, is isotonic, and provides a

source of basal phosphate requirements (15 mmol/L) and a source of vitamin E. The vitamin E content in Intralipid 10%, 20% and 30% is 6.5, 13 and 19.5 microgram/mL, respectively.

Intralipid prevents Essential Fatty Acid Deficiency (EFAD) and corrects the clinical manifestations of EFAD. However, for patients requiring complete parenteral nutrition, complementary vitamin supplements are required.

Clinical trials
No data available.

5.2 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 a pathway similar to that of 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+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 utilisation is increased in postoperative patients and in trauma, while patients with renal failure and hypertriglyceridaemia show lower utilisation of exogenous fat emulsions.

There is no information available on the elimination half-life.

5.3 Preclinical safety data
Intralipid has been in clinical use for many years. Safety evaluation is based on clinical experience and documentation.

Genotoxicity
No studies have been performed.

Carcinogenicity
No studies have been performed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients

	Quantity per 1000 mL		
	Intralipid 10%	Intralipid 20%	Intralipid 30%
Excipients			
Egg lecithin	12 g	12 g	12 g
Glycerol	22.0 g	22.0 g	16.7 g
Sodium hydroxide	to pH 6.0-9.0	to pH 6.0-9.0	to pH 6.0-9.0
Water for injections	to 1000 mL	to 1000 mL	to 1000 mL

6.2 Incompatibilities

Additions may only be made to Intralipid where compatibility is documented. Additions made for which compatibility has not been documented may cause the mixture to crack.

The following additions have been shown to be compatible with Intralipid:

1. Vitalipid N Adult or Vitalipid N Infant
2. Soluvit N (see Soluvit N Product Information for details on reconstitution)

Additions should be made aseptically.
Intralipid can also be delivered from a phthalate-free plastic bag (ethylene vinyl acetate (EVA), for example) as one part of an All-in-One admixture containing also carbohydrates, amino acids, electrolytes, vitamins and trace elements. (See Section 6.3 Shelf life, Intralipid All-in-One Admixtures)

Admixtures prepared with these amino acids must be used within 24 hours of admixing. (See Section 6.3 Shelf life, Intralipid All-in-One Admixtures)

Apart from the components of approved admixtures, nutrient solutions, electrolytes, water soluble vitamins (other than Soluvit N) or other drugs should not be added to Intralipid. However, nutrient solutions such as Vamin with electrolytes and glucose can be infused simultaneously using a short Y-connector or 3-way tap, where the common segment in which the solutions are in contact should be no longer than 10 to 15 cm. Fat soluble vitamins may be added directly to Intralipid.

<u>All-in-One mixing guidelines and limitations</u>
Using aseptic techniques, Intralipid 10%, 20% or 30% may be combined with other nutrients by adding the emulsion to a mixture of amino acids and glucose in the proportions listed in Table 1. Do not add electrolytes or trace elements directly to Intralipid. Total quantities of electrolytes, trace minerals and vitamins in the admixture must not exceed those listed below. Amino acids with a low pH such as Aminosyn® and Tropamine® <u>must not be used for All-in-One admixing</u>.

TABLE 1
Fresenius Kabi range of recommended All-in-One admixtures for Intralipid 10%, 20% and 30% (Amounts in mL)

Intralipid	Intralipid 10%		Intralipid 20%	Intralipid 30%				
	500* - 1000	1000	500* -1000	200* - 500	200-500	250	250-500	350-500
Glucose: Add either 10%	1000	1000	1000	1000	1000	1000	1000	1000
20%	1000	1000	1000	1000	-	-	1000	1000
30%	1000	1000	1000	-	-	-	-	-
Vitalipid N Adult	10	10	10	10	10	10	10	10
Soluvit N	1 vial	1 vial	1 vial	1 vial	1 vial	1 vial	1 vial	1 vial
Vamin: Add either Vamin with Glucose	1000-1500	-	1000-1500	-	1000-1500	-	-	-
Vamin 9	1000-1500	-	1000-1500	1000-1500	-	-	-	-

Vamin 14	-	1000	1000	1000	-	-	-	-
Vamin 14EF	1000	-	1000	1000	-	-	-	-
Vamin 18EF	-	500-1000	500-1000	-	-	500	1000	500

Electrolyte limits (mmol/L) per total admixture volume.

Sodium	20 to 80	Phosphate **	2.5 to 15
Potassium	20 to 60	Chloride	0 to 130
Calcium	2.0 to 5.0	Acetate	0 to 100
Magnesium	0.6 to 3.5	Zn	0 to 0.07

***** To avoid the risk of instability, an admixture with Vamin with glucose should be restricted to Glucose 10% & 20%.

****** Includes the amount from Intralipid (15 mmol/L).

6.3 Shelf life

Approved Shelf Life before mixing

2 years

Shelf life after first opening the container

The emulsion should be used directly due to the risk of microbiological contamination.
Any unused emulsion should be discarded.

Shelf life after addition or mixing according to directions

Although physical and chemical stability of the nominated admixtures of Intralipid has been demonstrated for 6 days when packed in EVA bags stored at 2-8°C followed by one day at 25°C, it is recommended that in order to reduce microbiological contamination hazards, infusion should be commenced as soon as practicable after preparation of the mixture. The resulting solution should be used within 24 hours and any residue discarded.

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 (see section 4.2 and 4.4).

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

Emulsions which have been frozen should be discarded.
Any remaining emulsion from an opened bottle must be discarded.
Do not use if emulsion is discoloured.
When stored correctly, Intralipid can be used until the expiry date printed on the labels.

Intralipid 10%, 20% and 30% contain no preservatives.

Gravity Dispersion

Separation of the product (gravity dispersion) occurs after a period of time hence inverting or gently shaking the solution before usage is needed. Do not use if inversion or gentle shaking does not result in an even mixture.

6.5 Nature and contents of container

Glass Bottles

Type II clear glass bottle with rubber stopper and aluminium cap.

Infusion Bags

The container consists of an inner bag and an overpouch. An oxygen absorber and integrity indicator are placed between the inner bag and the overpouch. The inner bag is the primary container for Intralipid. The overpouch provides protection during storage by contributing with barrier properties towards water and oxygen to the Intralipid container system. The oxygen absorber will absorb and bind oxygen remaining between the inner bag and the overpouch. The integrity indicator will react with free oxygen and change from clear to black in case of a damaged overpouch.

- The inner bag is made of a multilayer polymer film called Biofine. The Biofine inner bag film consists of poly(propylene-co-ethylene), synthetic rubber poly[styrene-block-(butylene-co-ethylene)] (SEBS) and synthetic rubber poly(styrene-block-isoprene) (SIS). The infusion and additive ports are made of polypropylene and synthetic rubber SEBS equipped with synthetic polyisoprene (latex-free) stoppers. The blind port, which is only used during manufacturing, is made of polypropylene equipped with a synthetic polyisoprene (latex-free) stopper.
- The oxygen barrier overpouch consists of polyolefin and polyethylene terephtalate or polyolefin, polyethylene terephtalate and poly(ethyl vinyl) alcohol (EVOH).
- The oxygen absorber consists of iron powder in a polymer sachet.
- The integrity indicator (Oxalert™) consists of an oxygen sensitive solution in a polymer sachet.

All packaging components for the bottle and the bag are latex- and PVC-free.

Pack sizes

Glass bottles:

Intralipid 10%: 100ml, 250ml, 500 mL
Intralipid 20%: 100 mL, 250ml, 500 mL, 1000 mL
Intralipid 30%: 250 mL, 333 mL, 500 mL, 1000 mL

Biofine Bags:

Intralipid 10%: 500 mL
Intralipid 20%: 100 mL, 500 mL
Intralipid 30%: 250 mL

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

Fresenius Kabi New Zealand Limited
60 Pavilion Drive
Mangere, Auckland 2022
New Zealand
Freecall: 0800 144 892

9 DATE OF FIRST APPROVAL

08 Mar 1994 (Bottles)
11 Dec 2001 (Biofine Bags)

10 DATE OF REVISION OF THE TEXT

03 February 2020

Summary table of changes

Section Changed	Summary of new information
4.2, 4.4 & 6.3	Added PN solution light protection for neonates/children during administration