

PRODUCT INFORMATION

NAME OF MEDICINE

SMOFLIPID® 20%

SMOFlipid is a white homogenous emulsion for infusion containing the following active ingredients: soya oil (CAS No.:8001-22-7), fish oil - rich in Omega-3 acids (CAS No.: 8016-13-5), medium chain triglycerides (CAS No.: 73398-61-5 and CAS No.: 65381-09-1) and olive oil (CAS No.: 8001-25-0).

DESCRIPTION

SMOFlipid emulsion for infusion is a white homogenous emulsion.

Each 1000 mL contains:

Soya oil	60 g
Medium chain triglycerides	60 g
Olive oil	50 g
Fish oil - rich in Omega-3 acids	30 g

Excipients includes:

Glycerol	25 g
Egg Lecithin	12 g
dl-alpha-Tocopherol	163 – 225 mg
Sodium Hydroxide	pH approx. 8
Sodium Oleate	300 mg
Water for injections	to 1000mL

Total energy:	8400 kJ (2000kcal)
pH:	approx. 8
Osmolality	380 mOsm/kg water

PHARMACOLOGY

The fat emulsion has a particle size and biological properties similar to those of endogenous chylomicrons. The constituents of SMOFlipid: Soya oil, Medium chain Triglycerides, Olive Oil and Fish Oil have their own pharmacodynamic properties in addition to their energy contents.

Soya Oil has a high content of essential fatty acids. The omega-6 (ω 6) fatty acid linoleic acid is the most abundant (approx. 55-60%). Alpha-linolenic acid, an omega-3 (ω 3) fatty acid, constitutes about 8%. This part of SMOFlipid provides essential fatty acids.

Medium-chain fatty acids are rapidly oxidised.

Olive Oil mainly provides energy in the form of mono-unsaturated fatty acids.

Fish Oil is characterised by a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA is an important structural component of cell membranes, whereas EPA is a precursor of eicosanoids as prostaglandins,

tromboxanes and leucotrienes.

Vitamin E protects unsaturated fatty acids against lipid peroxidation.

Pharmacokinetics

The individual triglycerides have different clearance rates.

Pharmacokinetic parameters of triglycerides following administration of SMOFlipid 20% at a dose of 0.125 g fat/kg/hour for 6 hours to 12 healthy adult volunteers are presented in the table below.

Parameter (unit)	SMOFlipid 20% Mean ± SD Median (range)
AUC _(0-t) (mg*h/dL)	3002 ± 1331 2598 (1288 – 6164)
C _{max} (mg/dL)	291 ± 144 260 (100 – 657)
t _{max} (h)	3.50 ± 0.80 3.00 (3.00 – 5.00)
t _{1/2} (h)	0.34 ± 0.11 0.35 (0.16 – 0.54)

SD=standard deviation

AUC_(0-t) = Area under the serum concentration-time curve from time zero until the last quantifiable concentration.

C_{max} = Maximum observed serum concentration.

t_{max} = Time to reach C_{max}

t_{1/2} = Apparent terminal disposition half-life

CLINICAL TRIALS

Nine studies examined the safety and tolerance of SMOFlipid with efficacy assessed in 4 studies. A total of 558 patients were assessed for safety and of these 282 received SMOFlipid (195 adults, and 87 paediatric patients including 72 preterm infants).

Adults

Two hundred and forty-nine post-surgical adult patients received either SMOFlipid (n=126) or an unregistered comparator containing 200g/L soya oil (n=123) for 5 days in a randomised, double-blind study. SMOFlipid 20% or the comparator were administered at a rate of 1.5g fat/kg bw/day starting on the morning of Day 1 (the day after surgery) and continuing for 5 days. Patients also received amino acids and glucose as additional parenteral nutrition. Electrolytes, trace elements and vitamins were administered as required.

Elimination of SMOFlipid 20% was at least as rapid as the elimination of the soya oil product over the 5 days of infusion. Mean serum total cholesterol and phospholipid were comparable in the treatment groups at all time points. Patients given SMOFlipid were hospitalised for a mean of 15.7 days compared with 17.8 days for patients given the comparator. Mean length of stay in ICU was 4.7 days for SMOFlipid vs. 5.2 days for the comparator. In a subgroup of 19 patients given SMOFlipid and 14 given the comparator who were examined for differences in fatty acid profiles there were higher mean concentrations of the ω3 fatty acids EPA and DHA and a lower mean concentrations of the ω6 fatty acids, linoleic acid in plasma free fatty acids and in plasma, leukocyte and platelet phospholipids. The ω3/ω6 ratio increased in the SMOFlipid group compared to the comparator group. The mean concentration of the EPA derived LTB5 increased to a greater extent following SMOFlipid administration

compared with the comparator. Mean concentrations of arachidonic acid-derived LTB₄ increased following administration of Lipovenos and decreased following administration of SMOFlipid.

Children

Twenty eight infants and children aged from 5 months to 2 years and from 2 to 11.5 years with stable disease requiring parenteral nutrition for at least 4 weeks received SMOFlipid or Intralipid 20% in a randomised, double-blind study. SMOFlipid or Intralipid were to be given as approx. 2g fat/kg/day over 12-14 hours for 4-5 days per week with a recommended infusion rate of 0.125g fat/kg/hour to a maximum of 0.15g fat/kg/hour. Oral/enteral intake was to be no more than 50% of caloric intake. Additional parenteral nutrition (amino acids and glucose) varied, dependent on patient total body weight.

Efficacy was a secondary objective in this study and was assessed by the fatty acid profile in plasma lipoproteins and RBC phospholipids and by body weight, height and body mass index. Changes from baseline in fatty acid concentrations in plasma lipoproteins or RBC phospholipids showed increased in EPA and DHA in patients given SMOFlipid compared with those given Intralipid. Small increases in weight, height and BMI were seen in both groups over the 4 week period.

Pre-term infants

Two randomised, controlled, double blind studies were conducted in pre-term infants aged 0 to 9 days with a gestation age of < 34 weeks. Intralipid 20% was the comparator in both studies. In one study, patient's birth weight was from 1000 to 2500g and in the other, birth weight was from 500 to 2000g. Patients required parenteral nutrition including fat for at least 7 days. Oral/enteral intake of ≤ 30% of energy intake on Days 1-3 and ≤ 50% on from Day 4 was permitted in both studies. In one study dosing commenced at 0.5g fat/kg/bw/day on Day 1 and increased in steps of 0.5g/fat/kg bw/day on Days 2, 3 and 4 and was given at 2.0g fat/kg bw/day from Days 4 to 14 with a maximum infusion rate of 0.125g fat/kg/hour. In the other study dosing commenced at 1.0g fat/kg birth weight /day on Days 1-3 then increased in 1.0g fat/kg/birth weight/day on Days 4 & 5 and was then given at a dose of 3.5g fat/kg birth weight/day from days 6 to 14 with a maximum infusion rate of 0.17g/fat/kg/hour. If actual body weight exceeded birth weight during treatment, dosing was to be adjusted according to actual body weight.

The primary efficacy measure in both studies was change in body weight during treatment. In one study 60 patients were enrolled with 30 receiving each treatment. Weight gain occurred in each group (mean of 5.01% for SMOFlipid vs. 5.1% for Intralipid 20%). There was considerable individual variation in weight gain in both groups. Higher ω₃ fatty acid content was seen in patients given SMOFlipid compared with Intralipid. Plasma α-tocopherol was higher in patients given SMOFlipid compared with those given Intralipid 20%. There were no major differences in clinical outcomes in the 2 treatment groups. In the other study 84 patients were enrolled but 37% of the ITT population received incorrectly calculated treatment doses. No major differences were seen in triglyceride levels in the 2 study groups.

INDICATIONS

Supply of energy and essential fatty acids to patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contraindicated.

CONTRAINDICATIONS

- Hypersensitivity to fish-, egg-, soya- or peanut protein or to any of the active ingredients or excipients.
- Severe hyperlipidaemia.
- Severe liver insufficiency.
- Severe blood coagulation disorders.
- Severe renal insufficiency without access to hemofiltration or dialysis.
- Acute shock.
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, decompensated cardiac insufficiency.
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis and severe sepsis and hypotonic dehydration).

PRECAUTIONS

The capacity to eliminate fat is individual and should therefore be monitored routinely by the clinician. This is in general done by checking the triglyceride levels. Special precaution should be taken in patients with a marked risk for hyperlipidaemia (e.g. patients with high lipid levels, severe sepsis and extremely low birth weight infants). The concentration of triglycerides in serum should in general not exceed 3mmol/L during infusion. Reduction of the dosage or cessation of the lipid emulsion should be considered if serum or plasma triglyceride concentrations during or after infusion exceed 3mmol/L. An overdose may lead to fat overload syndrome.

This medicinal product contains Soya Oil, Fish Oil and Egg Lecithin, which may rarely cause allergic reactions. Cross allergic reaction has been observed between soya-bean and peanut.

SMOFlipid should be given with caution in conditions of impaired lipid metabolism, which may occur in patients with renal failure, diabetes mellitus, pancreatitis, impaired liver function, hypothyroidism and sepsis.

Clinical data in patients with diabetes mellitus or renal failure are limited.

Administration of medium-chain fatty acids alone can result in metabolic acidosis. This risk is to a great extent reduced by the simultaneous infusion of the long chain fatty acids included in SMOFlipid. Concomitant administration of carbohydrates will further reduce this risk. Hence, simultaneous infusion of carbohydrate or a carbohydrate-containing amino acid solution is recommended.

Any signs or symptoms of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion.

Effects on fertility

The potential effects of SMOFlipid on fertility and general reproductive performance have not been determined in animal studies.

Use in pregnancy (Category B3)

There are no adequate and well-controlled studies in pregnant women with SMOFlipid or its individual components; therefore the safety of SMOFlipid in pregnant women is not known.

No animal studies have been conducted with the combined lipid components of SMOFlipid to evaluate effects on reproduction. Embryotoxicity and increased incidences of fetal skeletal variations have been observed in rabbits that had received medium chain fatty acid-containing lipids similar to SMOFlipid during the period of organogenesis. SMOFlipid should not be used during pregnancy unless the expected therapeutic benefit clearly outweighs the potential risk to the fetus.

Use in lactation

It is not known whether SMOFlipid can enter maternal milk. Therefore, SMOFlipid should be used during lactation only if clearly needed.

Paediatric use

SMOFlipid should be given with caution to neonates and premature infants with hyperbilirubinaemia and cases with pulmonary hypertension. In neonates, particularly premature infants on long term parenteral nutrition, blood platelet counts, liver function tests and serum triglycerides should be monitored.

Genotoxicity

SMOFlipid was not mutagenic or clastogenic in a battery of genotoxicity studies, including the Ames bacterial mutagenicity assay, a mammalian mutagenicity assay, a chromosome aberration assay in human peripheral lymphocytes, and an *in vivo* rat micronucleus assay.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of SMOFlipid.

Interactions with other medicines

The addition of other medications or substances to SMOFlipid should generally be avoided unless compatibility is known (please also refer to section "Instructions on use and handling").

Heparin given in clinical doses causes a transient increase in lipoprotein lipase release into the circulation. This may initially result in increased plasma lipolysis, followed by a transient decrease in triglyceride clearance.

Soya Oil has a natural content of vitamin K1. The content is however so low in SMOFlipid that it is not expected to significantly influence the coagulation process in patients treated with coumarin derivatives.

Effects on laboratory tests

Laboratory tests generally associated with monitoring of intravenous nutrition should be checked regularly. These include blood glucose levels, liver functions tests, acid base metabolism, fluid balance, full blood count and electrolytes.

As with all lipid emulsions, SMOFlipid may interfere with certain laboratory measurements (bilirubin, haemoglobin, lactate dehydrogenase, oxysaturation), if blood is sampled before fat has adequately been cleared from the bloodstream. In most patients, fat is cleared after a fat free period or interval of 5 to 6 hours.

Fat Overload Syndrome

Impaired capacity to eliminate triglycerides can lead to “Fat Overload Syndrome” which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and 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 hyperlipaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leukopaenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued.

Should signs of a Fat Overload Syndrome occur, the infusion of SMOFlipid should be discontinued.

ADVERSE EFFECTS

Most common drug-related Treatment-Emergent Adverse Events (TEAEs) in SMOFlipid 20% and comparator pooled groups (i.e those occurring in more than 2 patients of any pooled group) observed in 7 clinical trials are presented in the table below.

Drug-related TEAEs n(%) of patients	SMOFlipid 20% pooled (n=282)	Comparator pooled (n=276)
Number of patients with at least 1 drug-related TEAE	45 (16.0)	43 (15.6)
Nausea	12 (4.3)	13 (4.7)
Vomiting	12 (4.3)	6 (2.2)
Blood triglycerides increased	6 (2.1)	3 (1.1)
Hyperglycaemia	5 (1.8)	3 (1.1)
Hyperbilirubinaemia	4 (1.4)	5 (1.8)
Flatulence	4 (1.4)	1 (0.4)
Liver function test abnormal	2 (0.7)	3 (1.1)
Hypertriglyceridaemia	2 (0.7)	3 (1.1)
Gamma-glutamyltransferase increased	1 (0.4)	3 (1.1)

Since SMOFlipid has been marketed, there was only 1 spontaneous report of an adverse drug reaction (a case of non-serious erythema) in a 75 year old female patient.

Should triglyceride levels during infusion of SMOFlipid rise above 3mmol/L, the infusion should be stopped or, if necessary, continued at a reduced dosage.

SMOFlipid should always be a part of a complete parenteral nutritional treatment including amino acids and glucose. Nausea, vomiting and hyperglycaemia may sometimes be associated with parenteral nutrition.

Monitoring of triglycerides and blood glucose levels are recommended to avoid elevated levels, which may be harmful.

DOSAGE AND ADMINISTRATION

The patient's ability to eliminate the fat infused should govern the dosage and infusion rate, (please also refer to section "PRECAUTIONS").

Adults

The standard dose is 1.0 – 2.0 g fat/kg body weight (b.w) / day, corresponding to 5 – 10 mL / kg b.w / day.

The recommended infusion rate is 0.125 g fat / kg b.w / hour, corresponding to 0.63 mL SMOFlipid / kg b.w / hour, and should not exceed 0.15 g fat / kg b.w / hour, corresponding to 0.75 mL SMOFlipid / kg b.w / hour.

Neonates and infants

The initial dose should be 0.5 – 1.0 g fat / kg b.w / day followed by a successive increase by 0.5 – 1.0 g fat / kg b.w / day up to 3.0 g fat / kg b.w / day.

It is recommended not to exceed a daily dose of 3g fat / kg b.w / day, corresponding to 15 mL SMOFlipid / kg b.w / day.

The rate of infusion should not exceed 0.125 g fat / kg b.w / hour.

In premature and low birth weight neonates, SMOFlipid should be infused continuously over around 24 hours.

Children

It is recommended not to exceed a daily dose of 2g fat / kg b.w / day, corresponding to 10 mL SMOFlipid / kg b.w / day. With increased requirements in the youngest children a dose up to a maximum of 3g fat / kg b.w / day can be considered.

The daily dose should be increased gradually during the first week of administration.

The infusion rate should not exceed 0.15 g fat / kg b.w / hour.

Administration

Intravenous infusion into a peripheral or central vein.

Instructions for use

Use only if the emulsion is homogeneous.

For inner bag: The integrity indicator (Oxalert) should be inspected before removing the overpouch. If the indicator is black, oxygen has penetrated the overpouch and the product should be discarded, (please also refer to section "SPECIAL HANDLING INSTRUCTIONS").

Inspect the emulsion visually for phase separation prior to administration. Ensure that the final emulsion for infusion does not show any evidence of phase separation. For single use only. Any unused emulsion should be discarded.

Additives

SMOFlipid may be aseptically admixed with amino acid, glucose, and electrolyte solutions to produce "All-In-One" Total Parenteral Nutrition (TPN) admixtures.

Additions should be made aseptically. Any mixture remaining after infusion must be discarded.

Shelf life after first opening the container

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view the emulsion should be used immediately. 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 2-8°C.

OVERDOSAGE

Overdose leading to Fat Overload Syndrome may occur as a result of a too rapid infusion rate, or chronically at recommended rates of infusion in association with a change in the patients clinical conditions e.g. renal function impairment or infection.

Over dosage may lead to side-effects (please also refer to section "ADVERSE EFFECTS"). In these cases the lipid infusion should be stopped or, if necessary, continued at a reduced dosage.

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C. Do not freeze.

Storage after mixing

If additions are made to SMOFlipid, the admixtures should be used immediately from a microbiological point of view. 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 2-8°C.

Pack sizes

SMOFlipid 20% is available in pack sizes of:

10 x 100mL, 20 x 100mL	AUST R 262963
10 x 250mL	AUST R 262964
12 x 500mL	AUST R 158359

Not all pack sizes may be marketed.

The container consists of an inner bag (primary package) with an overpouch. An oxygen absorber and an integrity indicator (Oxalert™) are placed between the inner bag and the overpouch. The Biofine inner bag is made of a multilayer polymer film.

- The Biofine inner bag consists of a poly(propylene-co-ethylene) copolymer and thermoplastic elastomers (SEBS and SIS).
- The oxygen barrier overpouch consists of polyethylene terephthalate and polyolefin or polyethylene terephthalate, polyolefin and ethylene-vinyl alcohol copolymer (EVOH).
- The oxygen absorber consists of iron powder in a polymer sachet.
- The integrity indicator consists of oxygen sensitive solution in a polymer sachet.

The overpouch, the oxygen absorber and the integrity indicator should be discarded after opening of the overpouch. The integrity indicator (Oxalert™) will react with free oxygen and change colour from clear to black in case of damage in the overpouch.

NAME AND ADDRESS OF SPONSOR

Fresenius Kabi Australia Pty Limited
Level 2, 2 Woodland Way
Mount Kuring-gai NSW 2080
Australia
Telephone: (02) 9391 5555

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

POISON SCHEDULE

Australia: Not Scheduled
New Zealand: General Sale Medicine

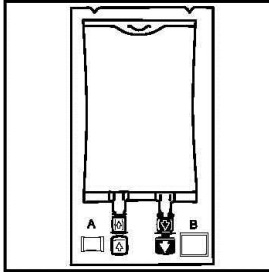
DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS: 24 March 2010

DATE OF MOST RECENT AMENDMENT: 07 December 2018

SPECIAL HANDLING INSTRUCTIONS

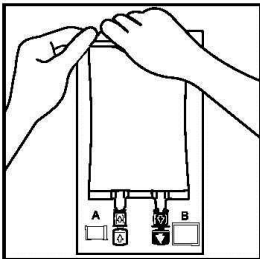
Infusion bag with Biofine 1 chamber primary bag

1.



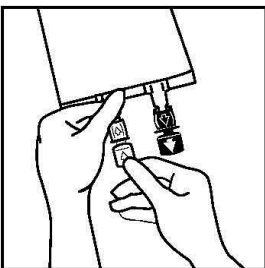
The integrity indicator (Oxalert™) **A** should be inspected before removing the overwrap. If the indicator is black the overwrap is damaged and the product should be discarded.

2.



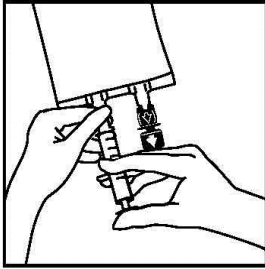
Remove the overwrap by tearing at the notch and pulling down along the container. The Oxalert™ sachet **A** and the oxygen absorber **B** should be disposed.

3.



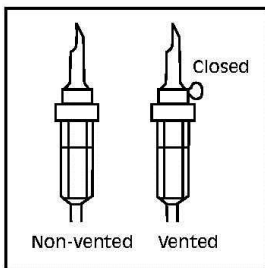
If additions are to be used, break off the tamper-evident arrow flag from the white additive port. If no additives are to be used, go to figure 5.

4.



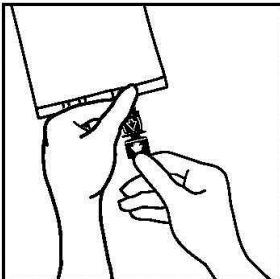
Insert the needle horizontally through the centre of the septum of the additive port and inject the additives (with known compatibility). Mix thoroughly by inverting container several times.

5.



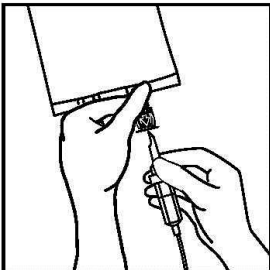
Use a non-vented infusion set or close the air vent on a vented set. Follow the instructions for use for the infusion set.

6.



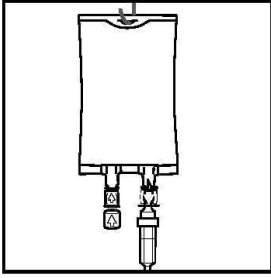
Break off the tamper-evident arrow flag from the blue infusion port.

7.



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.



To hang the bag, invert and place hanger through the container notch.