PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

SMOFlipid® 20%

Lipid Injectable Emulsion

Emulsion, 20% (6% soybean oil, 6% medium chain triglycerides, 5% olive oil and 3% fish oil) for intravenous injection

Manufacturer's Standard

Lipid emulsion for intravenous nutrition

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RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SMOFlipid 20% (6% soybean oil / 6% medium chain triglycerides / 5% olive oil/ 3% fish oil) is indicated for:

- supply of energy and essential fatty acids and omega-3 fatty acids to adult patients, as part of a parenteral nutrition regimen, when oral or enteral nutrition is impossible, insufficient or contra-indicated.

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

SMOFlipid can be used in adult populations including geriatrics (See 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

Lipid injectable emulsion is contraindicated in patients with:

- Hypersensitivity to fish, egg, soybean or peanut protein or to any of the active ingredients or excipients.
- Severe hyperlipidemia.
- 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 edema, 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).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The patient's ability to eliminate the fat infused should determine the dosage and infusion rate.

4.2 Recommended Dose and Dosage Adjustment

The standard dose is 1 to 2 g lipid/kg body weight (b.w.)/day, corresponding to 5 to 10 mL/kg b.w./day.

The maximum infusion rate is 0.15 g lipid/kg b.w./hour, corresponding to 0.75 mL SMOFlipid/kg b.w./hour.

Table 1 Standard daily dose

	Per kg of body weight	For a 70 kg Adult
Usual lipid dose	1.0 to 2.0 g/kg/day	70 to 140 g/day
Infused volume of SMOFlipid 20%	5 to 10 mL/kg/day	350 to 700 mL/day

The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours, depending on the clinical situation. Treatment with parenteral nutrition may be continued for as long as is required by the patient's condition.

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

4.4 Administration

Intravenous infusion into a peripheral or central vein.

5 OVERDOSAGE

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

An impaired capacity to eliminate triglycerides may lead to "Fat overload syndrome" which may be caused by overdose. Monitoring for possible signs of metabolic overload is necessary. The cause may be genetic (individual differences in metabolism), or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridemia, 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 characterized by hyperlipidemia, fever, fat infiltration, hepatomegaly with or without jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorder, hemolysis and reticulocytosis, abnormal liver function tests and coma.

Should signs of a fat overload syndrome occur, the infusion of SMOFlipid should be interrupted. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued.

Overdosage may lead to side-effects (see 8 ADVERSE REACTIONS). In these cases, the lipid infusion should be stopped or, if necessary, continued at a reduced dosage.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/Composition	Non-medicinal Ingredients
Intravenous	Emulsion 20% (6% soybean oil / 6% medium chain triglycerides / 5% olive oil / 3% fish oil)	All-*rac*-α-tocopherol, Glycerol, Purified egg phospholipids, Sodium hydroxide, Sodium oleate, Water for Injection

SMOFlipid 20%, lipid injectable emulsion, is a white homogeneous emulsion.

Each 100 mL contains:

Soybean oil, refined	6.0 g
Triglycerides, medium-chain	6.0 g
Olive oil, refined	5.0 g
Fish oil, rich in omega-3 acids	3.0 g
Excipients include:	
Glycerol	2.5 g
Purified egg phospholipids	1.2 g
All-*rac*-α-tocopherol	16 – 23 mg
Sodium hydroxide to adjust pH	to pH approx. 8
Sodium oleate	30 mg
Water for injection	to 100 mL

Total energy:	840 kJ (200 kcal)
pH:	approximately 8
Osmolality	380 mOsm/kg water

Pack sizes:

100 mL in bag: Box of 10 units.

250 mL in bag: Box of 10 units.

500 mL in bag: Box of 12 units.

1000 mL in bag: Box of 6 units

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

- The primary plastic container is made from a multilayered film specifically designed for parenteral nutrition drug products. The film is polypropylene based comprising three co-extruded 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 overpouch consists of polyethylene terephthalate and polyolefin or polyethylene terephthalate, polyolefin and ethylene-vinyl alcohol copolymer (EVOH).
- 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.

7 WARNINGS AND PRECAUTIONS

General

Individual capacity to eliminate fat should be monitored according to standard practice, which generally includes checking triglyceride levels. Special caution should be taken in patients with a marked risk for hyperlipidemia (e.g., patients with high lipid dosage and severe sepsis).

Reduction of the dosage or cessation of the lipid emulsion should be considered if serum or plasma triglyceride concentrations during or after infusion exceed 3 mmol/L. An overdose may lead to fat overload syndrome (see 8 ADVERSE REACTIONS).

The addition of other medications or substances to SMOFlipid should generally be avoided unless compatibility is known.

Endocrine and Metabolism

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 eliminated by the simultaneous infusion of the long chain fatty acids included in SMOFlipid. Concomitant administration of carbohydrates will further eliminate this risk. Hence, simultaneous infusion of carbohydrate or a carbohydrate-containing amino acid solution is recommended.

Immune

This intravenous emulsion contains soybean oil, fish oil and egg phospholipids, which may rarely cause allergic reactions. Crossed allergic reaction has been observed between soybean and peanut.

If a hypersensitivity reaction occurs (anaphylactic reaction -such as fever, shivering, rash or dyspnoea) administration of the emulsion should be discontinued immediately and the appropriate treatment and supportive measures should be undertaken until symptoms have resolved (see 8 ADVERSE REACTIONS).

Monitoring and Laboratory Tests

Standard laboratory tests for monitoring parenteral nutrition should be performed regularly. These include blood glucose levels, liver function tests, triglycerides, acid base metabolism, fluid balance, full blood count and electrolytes.

High levels of lipids in plasma may interfere with some laboratory blood tests e.g., hemoglobin.

7.1 Special Populations

7.1.1 Pregnant Women

Parenteral nutrition may become necessary during pregnancy. SMOFlipid should only be given to pregnant women after careful consideration. There are no data available on exposure of SMOFlipid in pregnant women.

7.1.2 Breast-feeding

Parenteral nutrition may become necessary during lactation. SMOFlipid should only be given to breast-feeding women after careful consideration. It is unknown if SMOFlipid is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

The metabolism of SMOFlipid does not appear to be affected by advanced age.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 WARNINGS AND PRECAUTIONS.

Adverse reactions observed during the administration of lipid emulsions in general, including SMOFlipid, and reported spontaneously from post-marketing experience consisted of:

Table 3 Frequency of Adverse Drug Reactions*

System Organ Class	Adverse Drug Reaction	Frequency of Occurrence
Immune system disorders	Hypersensitivity-reactions (e.g., anaphylactic or anaphylactoid reactions, skin rash, urticaria, flush, headache)	Rare (>0.01% – ≤0.1%)
Vascular disorders	Hypotension, hypertension	Rare (>0.01% – ≤0.1%)
Respiratory, thoracic and mediastinal disorders	Dyspnea	Rare (>0.01% – ≤0.1%)
Gastrointestinal disorders	Lack of appetite, nausea, vomiting	Uncommon (≥0.1% – <1%)
Reproductive system and breast disorders	Priapism	Very rare (≤0.01%)
General disorders and administration site conditions	Slight increase in body temperature	Common (≥1% – <10%)
	Chills	Uncommon (≥0.1% – <1%)
	Heat or cold sensation, paleness, cyanosis, pain in the neck, back, bones, chest and loins	Rare (>0.01% – ≤0.1%)

* This applies to lipid emulsions in general.

Should these side-effects occur or should the triglyceride level during infusion rise above 3 mmol/L, the infusion of SMOFlipid should be stopped, or if necessary, continued at a reduced dosage.

SMOFlipid should always be a part of a parenteral nutritional treatment including amino acids, glucose and electrolytes. Nausea, vomiting and hyperglycemia are symptoms related to conditions requiring parenteral nutrition regimens and are sometimes believed to be caused by parenteral nutrition.

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

Fat overload syndrome: See Section 5 OVERDOSAGE.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The efficacy and safety of SMOFlipid have been studied in 7 clinical trials. Studies have been done in healthy volunteers and adult patients including one long-term study. One large study included 249 adult postoperative patients (ITT population) on total parenteral nutrition for 5 days and in another study in adults, the infusions were given up to two weeks. SMOFlipid is always a component of a regimen providing parenteral nutrition including at least the two other macronutrients (glucose and amino acid solution). Two studies have been performed with SMOFlipid as a part of a fixed regimen delivered in a 3-chamber bag. Altogether 675 subjects from 10 clinical studies have been studied for safety in the trials (338 on SMOFlipid and 337 on comparator products). Twenty-two of the subjects were healthy volunteers in the two Phase I studies with a cross-over design.

The adverse events "Hypoesthesia and/or Paraesthesia" on subjects' hands and/or forearms were observed in 4 healthy volunteers participating in pharmacokinetics studies (FE-SM-02- DE and FE-SM-01-BE) and coded as possibly related by the investigator. These events were transient, non-serious and mild, and resolved spontaneously without added medication or any other action. See Table 4 Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Patients

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Gastrointestinal disorders	**23 (7.3)**	**18 (5.7)**
Nausea	13 (4.1)	13 (4.1)
Vomiting	13 (4.1)	6 (1.9)
Flatulence	4 (1.3)	1 (0.3)
Abdominal Pain	1 (0.3)	1 (0.3)
Investigations	**10 (3.2)**	**10 (3.2)**
Blood triglycerides increased	6 (1.9)	4 (1.3)
Liver function test abnormal	2 (0.6)	3 (1.0)
Gamma-glutamyltransferase increased	1 (0.3)	3 (1.0)
Blood alkaline phosphatase increased	1 (0.3)	2 (0.6)

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Blood pressure increased	1 (0.3)	0
Heart rate increased	1 (0.3)	0
Hepatic enzyme increased	0	1 (0.3)
Glucosuria	1 (0.3)	0
Metabolism and nutrition disorders	**8 (2.5)**	**6 (1.9)**
Hyperglycemia	5 (1.6)	3 (1.0)
Hypertriglyceridemia	3 (0.9)	3 (1.0)
Hyperchloremia	1 (0.3)	0
Hypernatremia	1 (0.3)	0
Metabolic acidosis	0	1 (0.3)
Hepatobiliary disorders	**6 (1.9)**	**8 (2.5)**
Hyperbilirubinaemia	4 (1.3)	5 (1.6)
Cholestatis	2 (0.6)	2 (0.6)
Cytolytic hepatitis	2 (0.6)	2 (0.6)
Nervous system disorders	**3 (0.9)**	**2 (0.6)**
Dysgeusia	2 (0.6)	0
Headache	1 (0.3)	1 (0.3)
Tremor	0	1 (0.3)
General disorders and administration site conditions	**2 (0.6)**	**3 (1.0)**
Edema	1 (0.3)	0
Pyrexia	1 (0.3)	0
Infusion site erythema	0	1 (0.3)
Infusion site swelling	0	1 (0.3)
Chest discomfort	0	1 (0.3)
Pain	0	1 (0.3)
Vascular disorders	**2 (0.6)**	**1 (0.3)**
Thrombophlebitis	1 (0.3)	1 (0.3)
Hypertension	1 (0.3)	0
Injury, poisoning and procedural complications	**0**	**2 (0.6)**
Accidental overdose	0	1 (0.3)
Post gastric surgery syndrome	0	1 (0.3)
Infections and infestations	**0**	**1 (0.3)**
Enterobacter sepsis	0	1 (0.3)
Blood and lymphatic system disorders	**0**	**1 (0.3)**
Anaemia	0	1 (0.3)

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.3)**
Muscle spasms	0	1 (0.3)

Note that the numbers in each column cannot be added because a subject may have had more than one adverse event.

*Total number of the patients treated

Table 5.

Only one patient in the comparator group was reported to have a drug related TESAE: one adult male patient had an accidental overdose.

Clinical trials reported pneumonia and respiratory failure as adverse events that were classified as not related to the product. Pneumonia occurred in 3 (1.3%) and 4 (1.7%) patients in the SMOFlipid 20% group and the comparator group while 2 (0.9%) and 3 (1.3%) patients experienced respiratory failure in the SMOFlipid 20% group and the comparator group.

The treatment emergent adverse events classified as "at least possibly related" are presented in Table 4. All adverse events classified under Gastrointestinal disorders came mainly from postoperative patients after abdominal surgery.

Table 4 Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Patients

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Gastrointestinal disorders	**23 (7.3)**	**18 (5.7)**
Nausea	13 (4.1)	13 (4.1)
Vomiting	13 (4.1)	6 (1.9)
Flatulence	4 (1.3)	1 (0.3)
Abdominal Pain	1 (0.3)	1 (0.3)
Investigations	**10 (3.2)**	**10 (3.2)**
Blood triglycerides increased	6 (1.9)	4 (1.3)
Liver function test abnormal	2 (0.6)	3 (1.0)
Gamma-glutamyltransferase increased	1 (0.3)	3 (1.0)
Blood alkaline phosphatase increased	1 (0.3)	2 (0.6)
Blood pressure increased	1 (0.3)	0
Heart rate increased	1 (0.3)	0
Hepatic enzyme increased	0	1 (0.3)
Glucosuria	1 (0.3)	0
Metabolism and nutrition disorders	**8 (2.5)**	**6 (1.9)**
Hyperglycemia	5 (1.6)	3 (1.0)

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Hypertriglyceridemia	3 (0.9)	3 (1.0)
Hyperchloremia	1 (0.3)	0
Hypernatremia	1 (0.3)	0
Metabolic acidosis	0	1 (0.3)
Hepatobiliary disorders	**6 (1.9)**	**8 (2.5)**
Hyperbilirubinaemia	4 (1.3)	5 (1.6)
Cholestatis	2 (0.6)	2 (0.6)
Cytolytic hepatitis	2 (0.6)	2 (0.6)
Nervous system disorders	**3 (0.9)**	**2 (0.6)**
Dysgeusia	2 (0.6)	0
Headache	1 (0.3)	1 (0.3)
Tremor	0	1 (0.3)
General disorders and administration site conditions	**2 (0.6)**	**3 (1.0)**
Edema	1 (0.3)	0
Pyrexia	1 (0.3)	0
Infusion site erythema	0	1 (0.3)
Infusion site swelling	0	1 (0.3)
Chest discomfort	0	1 (0.3)
Pain	0	1 (0.3)
Vascular disorders	**2 (0.6)**	**1 (0.3)**
Thrombophlebitis	1 (0.3)	1 (0.3)
Hypertension	1 (0.3)	0
Injury, poisoning and procedural complications	**0**	**2 (0.6)**
Accidental overdose	0	1 (0.3)
Post gastric surgery syndrome	0	1 (0.3)
Infections and infestations	**0**	**1 (0.3)**
Enterobacter sepsis	0	1 (0.3)
Blood and lymphatic system disorders	**0**	**1 (0.3)**
Anaemia	0	1 (0.3)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.3)**
Muscle spasms	0	1 (0.3)

Note that the numbers in each column cannot be added because a subject may have had more than one adverse event.

*Total number of the patients treated

Table 5 Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Healthy Volunteers

System organ class Adverse event (preferred term)	SMOFlipid 20% n= 22* (%)	Comparator product n= 22* (%)
Nervous system disorders	**5 (22.7)**	**0**
Headache	2 (9.1)	0
Hypoaesthesia	1 (4.5)	0
Paraesthesia (slight sensation of stinging and itchiness in one patient)	3 (13.6)	0
Vascular disorders	**1 (4.5)**	**0**
Thrombophlebitis	1 (4.5)	0

Note that the numbers in each column cannot be added because a subject may have had more than one adverse event.

*Total number of the healthy volunteers treated

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

See Table 4 and Table 4 Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Patients

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Gastrointestinal disorders	**23 (7.3)**	**18 (5.7)**
Nausea	13 (4.1)	13 (4.1)
Vomiting	13 (4.1)	6 (1.9)
Flatulence	4 (1.3)	1 (0.3)
Abdominal Pain	1 (0.3)	1 (0.3)
Investigations	**10 (3.2)**	**10 (3.2)**
Blood triglycerides increased	6 (1.9)	4 (1.3)
Liver function test abnormal	2 (0.6)	3 (1.0)
Gamma-glutamyltransferase increased	1 (0.3)	3 (1.0)
Blood alkaline phosphatase increased	1 (0.3)	2 (0.6)
Blood pressure increased	1 (0.3)	0
Heart rate increased	1 (0.3)	0
Hepatic enzyme increased	0	1 (0.3)
Glucosuria	1 (0.3)	0
Metabolism and nutrition disorders	**8 (2.5)**	**6 (1.9)**
Hyperglycemia	5 (1.6)	3 (1.0)
Hypertriglyceridemia	3 (0.9)	3 (1.0)
Hyperchloremia	1 (0.3)	0
Hypernatremia	1 (0.3)	0
Metabolic acidosis	0	1 (0.3)

System organ class Adverse event (preferred term)	SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)	Comparator product n= 315* (%)
Hepatobiliary disorders	**6 (1.9)**	**8 (2.5)**
Hyperbilirubinaemia	4 (1.3)	5 (1.6)
Cholestatis	2 (0.6)	2 (0.6)
Cytolytic hepatitis	2 (0.6)	2 (0.6)
Nervous system disorders	**3 (0.9)**	**2 (0.6)**
Dysgeusia	2 (0.6)	0
Headache	1 (0.3)	1 (0.3)
Tremor	0	1 (0.3)
General disorders and administration site conditions	**2 (0.6)**	**3 (1.0)**
Edema	1 (0.3)	0
Pyrexia	1 (0.3)	0
Infusion site erythema	0	1 (0.3)
Infusion site swelling	0	1 (0.3)
Chest discomfort	0	1 (0.3)
Pain	0	1 (0.3)
Vascular disorders	**2 (0.6)**	**1 (0.3)**
Thrombophlebitis	1 (0.3)	1 (0.3)
Hypertension	1 (0.3)	0
Injury, poisoning and procedural complications	**0**	**2 (0.6)**
Accidental overdose	0	1 (0.3)
Post gastric surgery syndrome	0	1 (0.3)
Infections and infestations	**0**	**1 (0.3)**
Enterobacter sepsis	0	1 (0.3)
Blood and lymphatic system disorders	**0**	**1 (0.3)**
Anaemia	0	1 (0.3)
Musculoskeletal and connective tissue disorders	**0**	**1 (0.3)**
Muscle spasms	0	1 (0.3)

Note that the numbers in each column cannot be added because a subject may have had more than one adverse event.

*Total number of the patients treated

Table 5.

8.5 Post-Market Adverse Reactions

Hypersensitivity Reactions

There are three cases of Adverse Drug Reactions reported spontaneously since first registration worldwide. One case was assessed as serious. All three patients showed labelled anaphylactic reactions including rash, flushing, chills and erythema.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

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.

Table 6 Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Heparin	T	A possible transient decrease in triglyceride clearance	These findings are based on basic research and not reported as adverse events in clinical practice
Coumarin derivatives	T	May decrease anticoagulant effect	Soybean oil has a natural content of vitamin K_1. 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

T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

High levels of lipids in plasma may interfere with some laboratory blood tests e.g., hemoglobin.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The fat emulsion has a particle size and biological properties similar to those of endogenous chylomicrons. The constituents of SMOFlipid; soybean oil 6%, medium chain triglycerides 6%, olive oil 5% and fish oil 3%, have except for their energy contents, their own pharmacodynamic properties.

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

Medium-chain fatty acids are rapidly oxidized and provide the body with a form of immediately available energy.

Olive oil mainly provides energy in the form of mono-unsaturated fatty acids, which are much less prone to peroxidation than the corresponding amount of poly-unsaturated fatty acids.

Fish oil is characterized 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 prostaglandines, thromboxanes and leukotrienes.

Vitamin E protects unsaturated fatty acids against lipid peroxidation.

10.2 Pharmacodynamics

The pharmacodynamic functions of SMOFlipid 20% are the provision of energy, essential fatty acids and omega-3 fatty acids. SMOFlipid 20% comprising of 4 different lipid components, soybean oil, MCT, olive oil, and fish oil is a source of energy with high caloric density, essential fatty acids and omega-3 fatty acids.

The pharmacodynamic properties of SMOFlipid 20% have not been systematically examined in clinical trials because the individual lipid components have been examined in great depth in many years of previous research. The pharmacodynamic effect of SMOFlipid 20% is expected to be a result of the combined effects of the individual components.

Soybean oil

Soybean oil is the main source of essential fatty acids in SMOFlipid 20%. Both linoleic and α-linolenic acid are long-chain fatty acids (LCFA; >12 carbon atoms) as well as polyunsaturated fatty acids (PUFAs). PUFAs are important constituents of all cell membrane phospholipids and serve as precursors for the synthesis of lipid mediators called eicosanoids (e.g., prostaglandins and leukotrienes). An excess of either ω-6 or ω-3 PUFA in parenteral lipid emulsions may be immunosuppressive. The more balanced the ω-6 to ω-3 ratio, the less immunosuppressive effects of the lipid emulsion in a rat heart allotransplantation model were observed. According to clinical and experimental data, it has been suggested that the most favorable ω-6:ω-3 ratio is in the range of 2:1 to 4:. The ratio of ω-6:ω-3 fatty acids in SMOFlipid 20% is approximately 2.5:1.

Medium-chain triglycerides (MCT)

MCT are more rapidly cleared from the blood stream than long-chain triglycerides (LCT), and MCFA are more rapidly oxidized compared to LCFA, thus providing the body with a form of immediately available energy. MCFA are not stored in fat tissue and do not accumulate in the liver. Intravenous MCT administration has not been associated with fatty infiltration of the liver or hepatic dysfunction. Hepatic metabolism of MCFA results in stimulation of synthesis of ketone bodies, which can be used as an energy source, but eventually result in acidosis. Therefore, it is of importance not to include an excessive quantity of MCT in a lipid emulsion. An emulsion containing as much as 75% MCT (and 25% LCT) has been tested in critically ill patients without observing any harmful effects. The amount of MCT (30%) in SMOFlipid 20% is considered safe in that it is lower than in the physical mixtures of MCT/LCT already commercially available in Europe. Replacing a part of LCT by MCT in SMOFlipid 20% reduces the total amount of PUFA, and thus reduces the risk of lipid peroxidation and the associated requirements for antioxidants.

Olive oil

SMOFlipid 20% contains 50 g/L olive oil, which includes LCT rich in monounsaturated fatty acid (MUFA). Olive oil is rich in the monounsaturated fatty acid oleic acid (C18:1ω9) and mainly provides energy.

Monounsaturated fatty acids are less prone to lipid peroxidation than PUFA due to fewer double bonds in the carbon chains.

Fish oil

Fish oil is characterized by a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both of which belong to the ω-3 LCFA family. DHA and EPA are important structural components of cell membranes, and EPA is also a precursor of eicosanoids such as prostaglandins, thromboxanes, and leukotrienes, which for example exhibit a lower inflammatory potential than those derived from ω-6 PUFA arachidonic acid (AA).

Increased intake of ω-3 fatty acids is followed by an increased ω-3/ω-6 fatty acid ratio in cell membranes of many cell populations. SMOFlipid contains 15% fish oil. After 5 days post- operative total parenteral nutrition with SMOFlipid ω-3 fatty acids as well as ω-3/ω-6 fatty acid ratio was significantly increased in plasma phospholipids and also in leucocytes and platelets compared to a soybean oil emulsion treatment. As a consequence, the EPA/AA ratio was increased resulting in a significantly higher leukotriene B5 (LTB5) release of neutrophils after stimulation vs control group. Leukotriene B4 (derived from AA) remained similar in both groups leading to a significant increased LTB5/LTB4 ratio in the SMOFlipid group only.

Parenteral fish oil has been successfully and safely used in postsurgical patients, pancreatitis patients, septic patients, patients with chronic plaque-type psoriasis.

10.3 Pharmacokinetics

Two phase I pharmacokinetics studies have been performed in healthy adult men to examine the intravascular metabolism of SMOFlipid 20% (study FE-SM-01-BE) and the elimination of triglycerides and the pharmacokinetics of other lipid parameters after administration of SMOFlipid 20% (study FE-SM-02-DE). The comparator in both studies was a soybean oil emulsion.

Both studies indicated that SMOFlipid 20% was well metabolized intravascularly and showed advantages over a soybean oil emulsion. Specifically, the less marked increase in triglycerides during infusion of SMOFlipid 20% and the faster elimination after stopping the infusion (i.e., shorter half-life) compared to a soybean oil emulsion are of potential benefit, particularly for patients with a limited triglyceride elimination capacity.

Distribution

Once SMOFlipid is administered intravenously it is distributed to all tissues by the vascular circulation.

Metabolism

The components of SMOFlipid are utilized in mainly three metabolic pathways, energy conversion, cell membrane incorporation, and elongation of free-fatty acids. All four lipids are used as energy. Medium chain fatty acids have only one pathway and that is to create energy. The other three components are both used as energy and also incorporated into cell membranes. Furthermore, fish oil has a high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA is precursor for mainly anti-inflammatory eicosanoids. The ω3 fatty acid in the soybean oil component (α-linolenic acid; C18:3ω3) is also elongated to EPA and DHA. The ω-6 fatty acid in soybean oil (linoleic acid; C18:2ω6) is converted to γ-linolenic acid and further elongated to arachidonic acid (C20:4ω6), which is precursor for mainly pro-inflammatory eicosanoids.

SMOFlipid is utilized as a nutrient and not excreted.

Elimination

The individual triglycerides have different clearance rate but SMOFlipid as a mixture is eliminated faster than LCT with lower triglyceride levels during infusion. Olive oil has the slowest clearance rate of the components (somewhat slower than LCT) and MCT the fastest. Fish oil in a mixture with LCT has the same clearance rate as LCT alone.

Special Populations and Conditions

- **Pediatrics**

Exploratory studies have been conducted but confirmatory pivotal studies have not been provided.

- **Geriatrics**

The metabolism of SMOFlipid does not appear to be affected by advanced age. The total need of energy supply may be lower than in younger patients.

- **Sex**

There are no differences between the genders regarding the metabolism of SMOFlipid.

- **Hepatic Insufficiency**

Overdosing of energy regardless of origin (glucose or lipids) may cause fat infiltration of the liver and result in further impairment of hepatic insufficiency.

- **Renal Insufficiency**

As SMOFlipid adds to the circulatory volume, it is important to have an adequate renal function. If the renal function is significantly impaired, it is recommended to have access to dialysis or hemofiltration due to the risk of fluid overload.

11 STORAGE, STABILITY AND DISPOSAL

Shelf life of the bag product in the overwrap: 24 months. For use once the overwrap is removed.

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. Store up to 25 °C. Do not freeze.

Do not use SMOFlipid after the expiry date printed on the container.

Shelf life after first opening the container

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 to 8 °C.

Storage after mixing

If additions are made to SMOFlipid, 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 °C to 8 °C, unless additions have taken place in controlled and validated aseptic conditions.

12 SPECIAL HANDLING INSTRUCTIONS

Instructions for use and handling

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

Intravenous (IV) emulsion

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

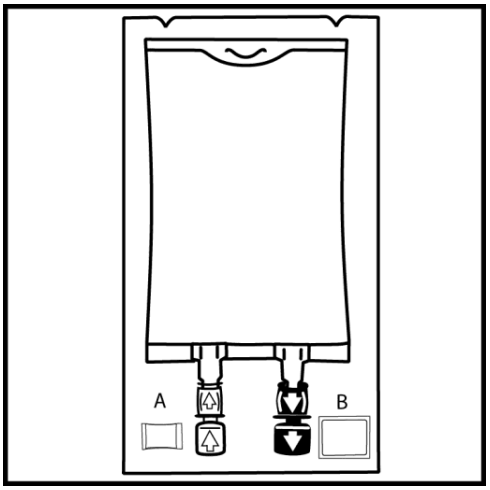


Figure 1

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.

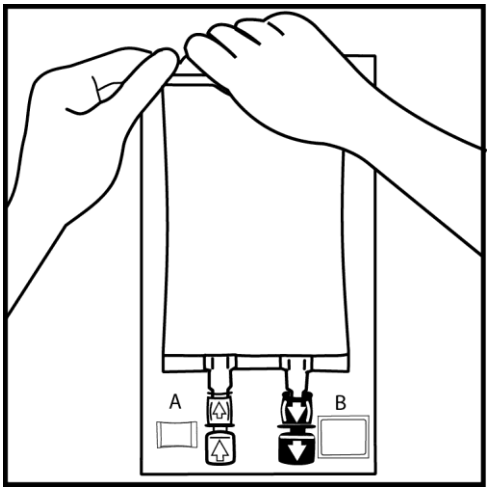


Figure 2

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.

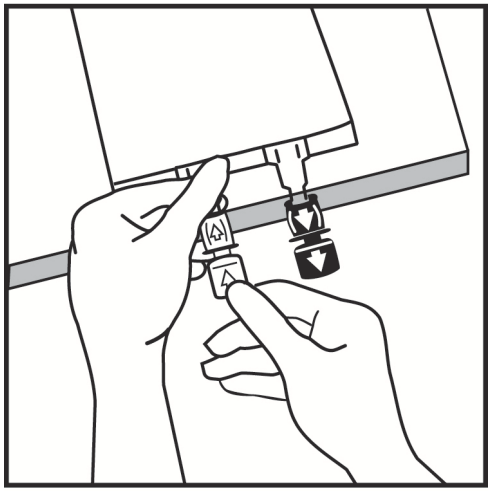


Figure 3

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

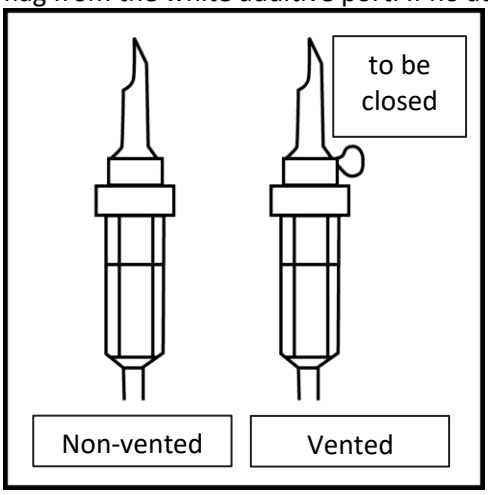


Figure 5.

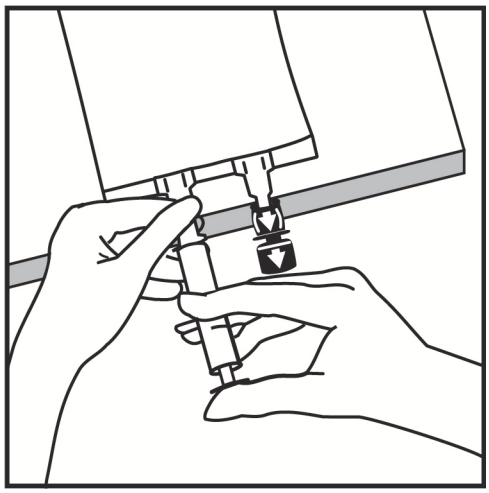


Figure 4

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.

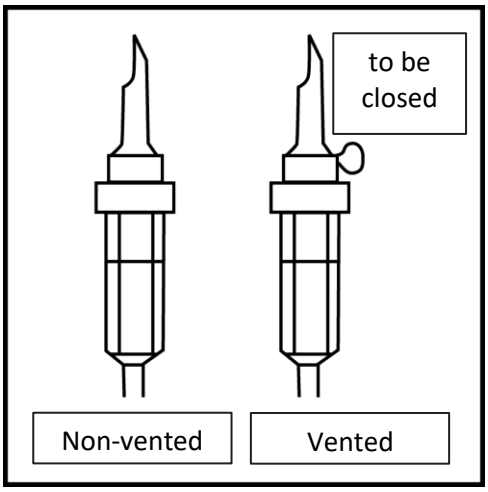


Figure 5

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.

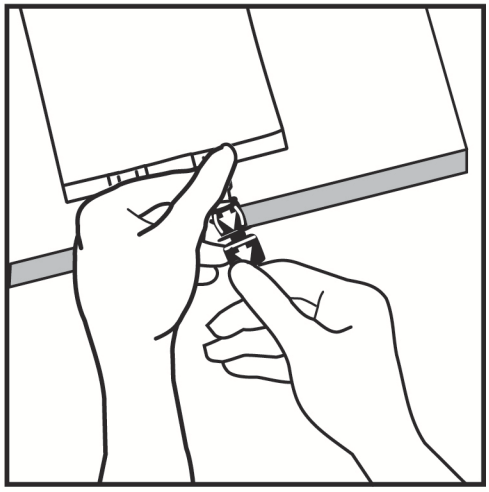


Figure 6

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

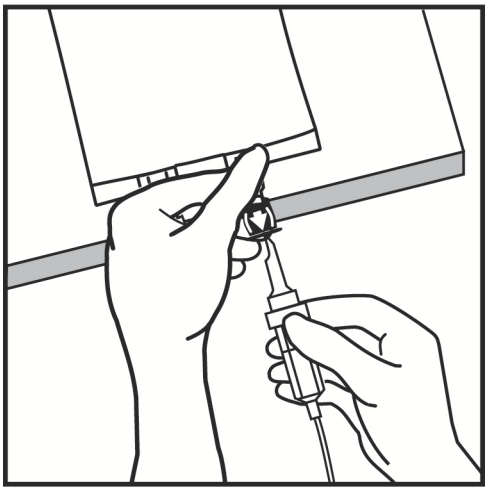


Figure 7

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.

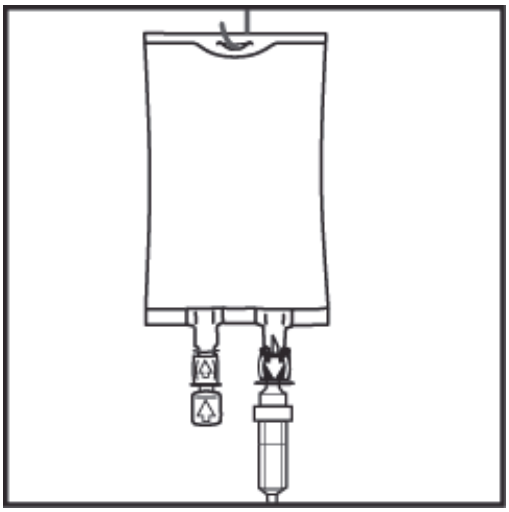


Figure 8

Hang the bag in the hanger cut and start infusion.

Additives

SMOFlipid can be mixed with drugs or vitamins especially formulated for addition to lipid emulsions. SMOFlipid should not be mixed with electrolyte or nutrient solutions, nor should drugs or vitamins be added to the emulsion in the infusion bag unless compatibility of the resulting infusion is evaluated and ensured prior to administration to the patient.

The simultaneous administration of SMOFlipid and amino acid solutions or carbohydrate can be also achieved, using separate infusion sets where the two liquids are allowed to mix in a Y- tube just before the intravenous needle.

Use a 1.2 micron in-line filter during administration.

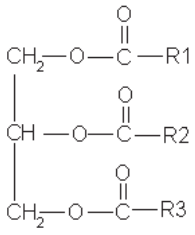
When infused alone, SMOFlipid can be administered via central or peripheral vein. When administered as a component of parenteral nutrition (with dextrose and amino acids), the osmolarity of the final infusion will dictate whether the central or peripheral venous route should be used.

The remaining contents of a partly used bag must be discarded and should not be stored for later use. To avoid damaging the spike port, use spike conforming to ISO 8536-4, diameter 5.6 mm ± 0.1 mm.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	**Soybean oil**	**Medium chain triglycerides (MCT)**	**Olive oil**	**Fish oil**
Chemical name:	Not applicable	Not applicable	Not applicable	Not applicable
Molecular formula:	Triacylglycerol (triglyceride) with fatty acid chains mainly C16:0, C18:0, C18:1, C18:2, C18:3	Triacylglycerol (triglyceride) with fatty acid chains mainly C8:0, C10:0	Triacylglycerol (triglyceride) with fatty acid chains mainly C16:0, C18:1, C18:2	Triacylglycerol (triglyceride) rich in the omega-3 fatty acids EPA and DHA (C20:5, C22:6)
Structural formula:	 R_1, R_2, R_3 represents the chain of the fatty acids linked to the glycerol backbone.			
Physicochemical properties:	Liquid at room temperature. Practically insoluble in water, very soluble in acetone and in heptane while slightly soluble in ethanol.			

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Intravenous nutrition

Table 7 Summary of patient demographics for clinical trials in specific indication

Study No.	**Trial design**	**Dosage (g fat/kg bw/h)**	**Route of administration**	**Duration (h)**	**Study subjects (n=number)**	**Age (Range)**
Healthy volunteers						
FE-SM-01-BE Pharmacokinetics	open-label, randomized, active-controlled, crossover	0.15	IV	4	10	18-45

Study No.	Trial design	Dosage (g fat/kg bw/h)	Route of administration	Duration (h)	Study subjects (n=number)	Age (Range)
FE-SM-02-DE Pharmacokinetics	double-blind, randomized, active-controlled, crossover	0.125	IV	6	12	18-45
Adult patients						
FE-SM-03-DE Efficacy/Safety	double-blind, randomized, active-controlled, parallel- group	1.5	IV	5	249	≥18
FE-SM-04-CH Safety	double-blind, randomized, active-controlled, parallel- group	up to max 2	IV	10-14	32	≥18
03-3CB7-001* Safety	open-label, randomized, active-controlled, parallel- group	Day 1: 0.6 Days 2-4: 0.9–1.2 Days 5-7: 0.6-1.2	IV	5-7	53	≥18
03-3CB8-001** Safety	open-label, randomized, active-controlled, parallel- group	max 1.1 for test product and 1.4 for reference product	IV	5-7	52	≥18
05-SMOF-006 Safety	double-blind, randomized, active-controlled, parallel-group	max 1-2	IV	4 weeks	73	≥18

* Test product: Three-chamber bags containing SMOFlipid 20% (in study 03-3CB7-001 named 3CB SMOF EL): SMOFlipid 20% in one chamber of a three-chamber bag (3CB) delivery system (the two other chambers contained 10% amino acids solution and glucose) composed for central infusion.
** Test product: Three-chamber bags containing SMOFlipid 20% (in study 03-3CB8-001 named 3CB SMOF
Peri EL): SMOFlipid 20% in one chamber of a 3CB delivery system (the two other chambers contained 10% amino acids solution and glucose) composed for peripheral infusion.

Study Results

Seven clinical studies comparing the safety and tolerance of SMOFlipid 20% with soybean oil-based lipid emulsions have been conducted in a total of 22 healthy volunteers and 459 adult patients. Safety and

tolerance were assessed by adverse event profile, laboratory safety parameters and vital signs. Of these seven clinical studies, efficacy was compared in addition to safety in five studies.

In two randomised, two-period crossover studies in healthy volunteers, the elimination of triglycerides appeared to be faster for SMOFlipid 20% compared to a standard soybean oil emulsion.

Out of 5 randomised, double-blind studies, one study was conducted in 249 patients post-surgery. Over 5 days of efficacy evaluation revealed that both treatment groups were equivalent with respect to triglyceride concentration in serum. Due to different composition of the two lipid emulsions, SMOFlipid 20% was associated with higher mean concentrations of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and lower mean concentrations of the ω-6 fatty acid linoleic acid compared to a soybean oil emulsion in plasma free fatty acids and in plasma, leukocyte and platelet phospholipids. The ω-3/ω-6 ratio increased significantly in the SMOFlipid 20% group compared to the soybean oil emulsion group.

The efficacy was also investigated in the long-term study in 73 patients. Regarding the ratio of ω- 6/ω-3 fatty acids in red blood cells (RBC) phospholipids and plasma lipoproteins, differences in favour of SMOFlipid were observed which reflected the composition of SMOFlipid 20% compared to Intralipid 20%.

In the five clinical studies performed in adult patients plus the two studies in healthy volunteers, safety and tolerability was considered comparable in the SMOFlipid 20% and comparator groups.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

The following toxicological studies have been performed with SMOFlipid

Type of study	**Species**	**SMOFlipid Doses g TG/kg bw/day**	**Observations and conclusions**
Single-Dose Toxicity			
	Rat	9, 18, 36	There was no significant toxicity associated with SMOFlipid up to a dose level of 18 g TG/kg bw (90 ml/kg bw). At 36 g TG/kg bw. toxic signs were observed due to the excessive administration of fluid volume
Repeat-Dose Toxicity			
4-week	Dog	9*	A good tolerance was demonstrated. An adjustment to the intravenous supply of energy was indicated by a dose-related reduction in food intake over time. A dose- and time-related reduction in lymphocytes and thrombocytes was found after high doses, i.e., 9 and 6 g TG/kg bw/day, respectively. Serum cholesterol and phospholipids were increased roughly in proportion to the molar dose of TG and reversed completely within 4 weeks of recovery. Significant morphological changes observed were fatty changes in hepatocytes (fat in the centriacinar region); lungs (foci of granulomatous
13-week	Dog	3, 6**	

Type of study	Species	SMOFlipid Doses g TG/kg bw/day	Observations and conclusions
			pneumonia) and kidney (interstitial nephritis). At the end of the 4-week recovery period all afore described drug substance-related changes had subsided.
Genotoxicity			
In vitro			
Bacterial gene mutation	S. typhimurium	Up to 40 mg/plate	No mutagenic effects were observed.
Chromosomal aberration	Human lymphocytes	Up to 5 mg/ml	
HPRT-test	V79 cells	Up to 10 mg/ml	
In vivo			
Bone marrow cytogenetic test	Rat	10	No mutagenic effect was observed
Local Tolerance			
	Rabbit (iv,ia,pv,sc, im)		SMOFlipid 20% revealed a good local compliance in rabbits after intravenous infusion and following intra-arterial, paravenous and subcutaneous administration. Moderate local changes, which had disappeared after 14 days, were observed after intramuscular administration.
	Dog		In the 4-week and 13-week repeat dose toxicity intravenous infusion studies in peripheral veins with SMOFlipid 20%, a similar slight to moderate reaction, mainly characterized by induration and swelling, was seen at the infusion sites in dogs from the test, reference and control groups at similar incidence and severity. The vascular changes were consistent with the anticipated response to repeated venipuncture. The osmolality of SMOFlipid 20% is approximately 270 mosmol/kg water and similar that of human serum (281-297 mosmol/kg water).

* Reference Soybean oil emulsion

**Reference: 0.9% NaCl solution

Note: ia (intraarterial), pv (vaginal), sc (subcutaneous), im (intramascular))

No reproductive toxicity studies have been performed with SMOFlipid. However, studies have been performed with the components of SMOFlipid (LCT, MCT, Olive oil and Fish oil) and did not reveal any toxic potential.

Safety pharmacology studies have not been performed with SMOFlipid. However, SMOFlipid repeat dose toxicity studies did not reveal any adverse effects on any organ system or function.

In toxicological studies performed with SMOFlipid no other effects than those expected after high doses of lipids were observed, based on single dose and repeat dose toxicity. No signs of genotoxic potential were detected in the respective studies. In a local tolerance study in rabbits a good local compliance was

observed after intravenous infusion and following intra-arterial paravenous and subcutaneous administration. Moderate local changes, which disappeared after 14 days, were observed after intramuscular administration.

In a test in guinea pigs (Maximisation test) fish oil showed moderate dermal sensitization. A systemic antigenicity test gave no indication of evidence of anaphylactic potential of fish oil.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

SMOFlipid ® 20%

Lipid Injectable Emulsion

Read this carefully before you start taking **SMOFlipid 20%** 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 **SMOFlipid 20%**.

What is SMOFlipid 20% used for?

SMOFlipid 20% is used in adults to provide energy, essential fatty acids and omega-3 fatty acids from fish oil. It is administered into your blood by a drip or an infusion pump.

SMOFlipid 20% is used when you are unable to take food by mouth or when other forms of feeding have not worked (e.g., nasogastric tube, direct catheter).

How does SMOFlipid 20% work?

SMOFlipid 20% helps to ensure adequate intake of calories and essential fatty acids. This helps to prevent or treat malnutrition.

What are the ingredients in SMOFlipid 20%?

Medicinal ingredients: fish oil, olive oil, soybean oil, triglycerides.

Non-medicinal ingredients: all-*rac*-α-tocopherol, glycerol, purified egg phospholipids, sodium hydroxide, sodium oleate.

SMOFlipid 20% comes in the following dosage forms:

Emulsion; 20% (6% soybean oil / 6% medium chain triglycerides / 5% olive oil / 3% fish oil)

Do not use SMOFlipid 20% if:

- you are suffering from a heart attack, acute stroke, metabolic acidosis (too much acid in the blood), severe infection (sepsis), dehydration or a blockage in the arteries.
- you have an unstable medical condition.
- you are allergic (hypersensitive) to fish, fish oil, eggs, olive oil, triglycerides or any of the non-medicinal ingredients in SMOFlipid 20% (See **What are the ingredients in SMOFlipid 20%?**).
- you are allergic to peanuts or soya. SMOFlipid 20% contains soybean oil.
- you have especially high levels of fats in your blood (severe hyperlipidemia).
- you have severe liver problems.
- you have severe blood clotting disorders.
- you have severe kidney problems without access to hemofiltration or dialysis.
- you are in an acute shock.
- you have any of the following serious conditions: fluid accumulation in your lungs, excess water content in your body, heart failure.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take SMOFlipid 20%. Talk about any health conditions or problems you may have, including if you:

- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed.
- have high level of lipids (fats) in your blood.
- have trouble metabolizing (breaking down) fats, which may happen if you have:
    - kidney or liver problems
    - diabetes
    - pancreatitis (inflammation of the pancreas)
    - thyroid problems
    - serious infection

Other warnings you should know about:

Blood tests and monitoring: Your healthcare professional will perform regular blood tests while you are taking SMOFlipid 20%. They will check your blood glucose, electrolyte, and fat levels as well as the health of your blood cells and liver and your body's fluid balance. Your healthcare professional will decide when to perform these tests and will interpret the results.

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

The following may interact with SMOFlipid 20%:

- medicines used to prevent blood clots, such as coumarin derivatives or heparin

SMOFlipid 20% may interfere with certain laboratory tests. It is important to tell any healthcare professional doing tests that you are using SMOFlipid 20%.

How to take SMOFlipid 20%:

- SMOFlipid 20% will be given to you in a hospital or clinic setting by a healthcare professional.
- In some cases, after appropriate training, you might be able to administer SMOFlipid 20%, that has been prepared by your pharmacist, to yourself at home.
- In all cases aseptic techniques must be followed when administering SMOFlipid 20% to reduce the possibility of infection.
- SMOFlipid 20% will be given directly into a vein as an infusion over 12 to 24 hours.
- SMOFlipid 20% may be mixed by your healthcare professional with carbohydrates, amino acids, salts, vitamins and trace elements which together provide your complete nutritional needs.

Usual dose:

- Your healthcare professional will decide on the dose and flow rate that are right for you based on your medical needs.

Instructions for use and handling:

Before using SMOFlipid 20% inspect the emulsion and the bag. The emulsion should appear milk-like. If there are particles in the emulsion, it is discoloured or the bag is leaking or damaged discard the bag and use a new one.

Each bag should be used only once. If there is any emulsion left in the bag after you have given yourself your dose throw it away. Do not use a partially used bag.

Use SMOFlipid 20% immediately after the overwrap has been removed.

The medicine must be at room temperature to be administered.

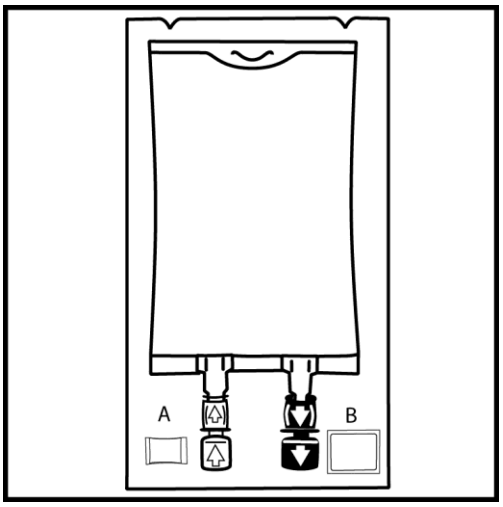


Figure 1

Before removing the overwrap from the bag, look at the integrity indicator (Oxalert™). This is the sachet labelled as “A” in Figure 1. If the indicator is black the overwrap is damaged, and the product should be discarded.

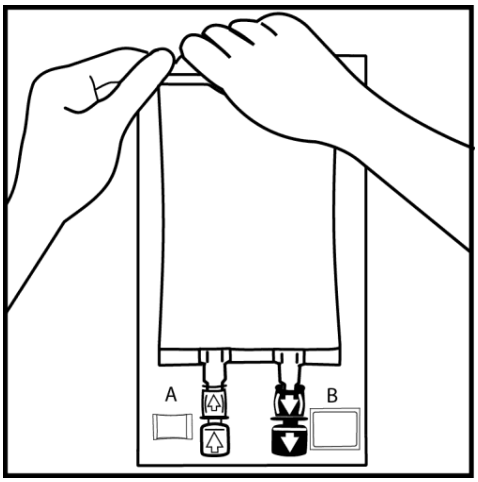


Figure 2

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.

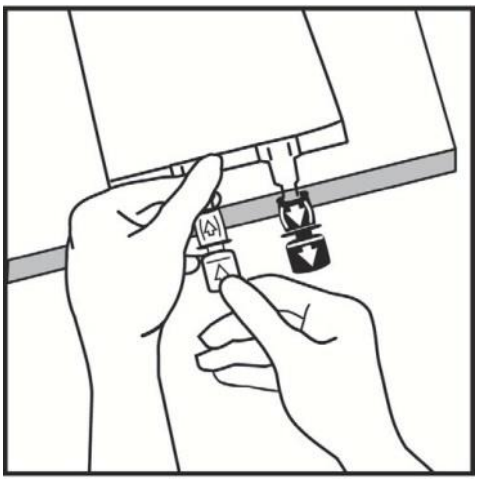


Figure 9

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 .

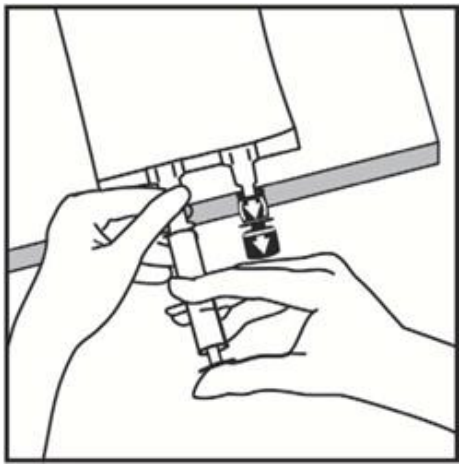


Figure 4

Insert the needle horizontally through the centre of the septum of the additive port and inject the additives as instructed by your healthcare professional. Use syringes with needles of 18-23 gauge and a length of max. 40 mm.

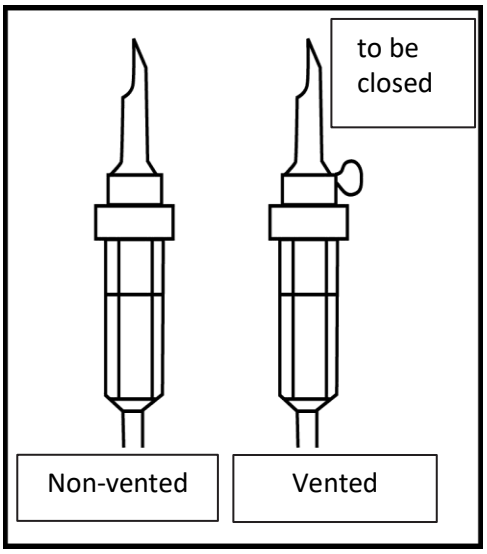


Figure 5

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.

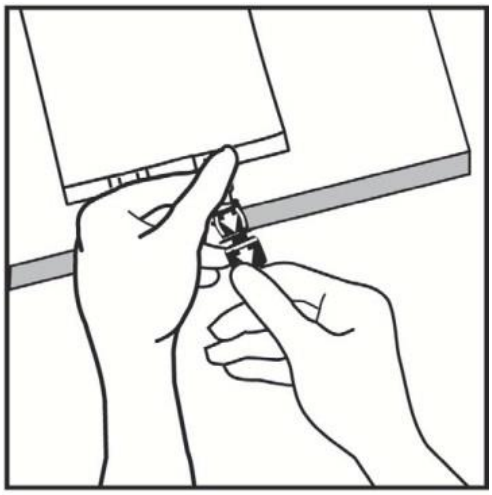


Figure 6

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

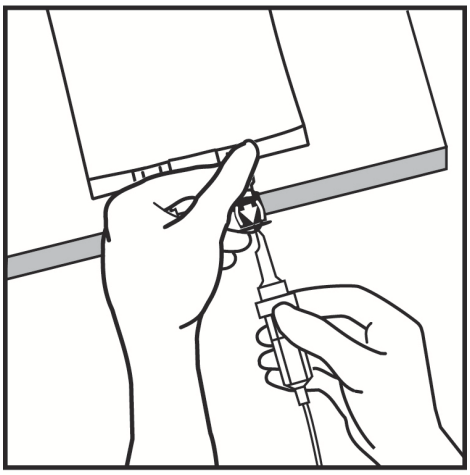


Figure 7

Hold the base of the infusion port. Insert the spike through the infusion port, by rotating your wrist slightly until the spike is inserted.

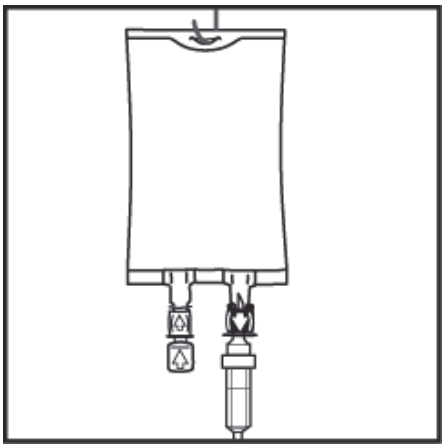


Figure 8

Hang the bag in the hanger cut and start the infusion.

Overdose:

If you think that you have received too high a dose or that SMOFlipid 20% was infused too quickly, talk to your healthcare professional immediately. In the case of an overdose there is a risk of receiving too much fat. This is called "**fat overload syndrome**". In these cases, the fat infusion should be stopped or, if necessary, continued at a reduced dose. See the **Serious side effects and what to do about them** table, below for more information.

If you think you, or a person you are caring for, have taken too much SMOFlipid 20%, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using SMOFlipid 20%?

These are not all the possible side effects you may have when taking SMOFlipid 20%. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea, vomiting
- lack of appetite
- chills
- shortness of breath

Serious side effects and what to do about them			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	
Allergic reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, nausea, vomiting, hives or rash, flushing, headache, swelling of the face, lips, tongue or throat			√
Fat overload syndrome: fever, yellowing of the skin and eyes, abdominal pain, vomiting, pale skin, fatigue, loss of energy, shortness of breath, weakness, swollen lymph nodes, frequent infections, bruising or bleeding for longer than usual if you hurt yourself, coma		√	
VERY RARE			
Priapism: Long-lasting (greater than 4 hours in duration) and painful erection of the penis			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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:

Store up to 25 °C. Do not freeze.
Keep out of reach and sight of children.

If you want more information about SMOFlipid:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.fresenius-kabi.ca), or by calling 1-877-821-7724 (toll-free-telephone).

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