PRODUCT MONOGRAPH

SMOFlipid® 20%

Lipid Injectable Emulsion, Mfr. Std.
Soybean oil, medium chain triglycerides, olive oil and fish oil
(6%/ 6%/ 5%/ 3% w/v)

Lipid emulsion for intravenous nutrition.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Injectable emulsion</td>
<td>Purified egg phospholipids</td>
</tr>
<tr>
<td></td>
<td>20% (6% soybean oil / 6% medium chain triglycerides / 5% olive oil / 3% fish oil)</td>
<td>All-rac-α-tocopherol</td>
</tr>
</tbody>
</table>

For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

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.

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

SMOFlipid 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).

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 section 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.

**Hematologic**

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

**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 section ADVERSE REACTIONS).

**Special Populations**

**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.

**Nursing Women:** Parenteral nutrition may become necessary during lactation. SMOFlipid should only be given to breast-feeding women after careful consideration. There are no data available on exposure of SMOFlipid in breast-feeding women.

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

**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.
ADVERSE REACTIONS

Adverse Drug Reactions Overview
See 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 1  Frequency of Adverse Drug Reactions*

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

* 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:** 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.

**Clinical Trial Adverse Drug 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 Paraeesthesia” 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 2b.

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 2a. All adverse events classified under Gastrointestinal disorders came mainly from postoperative patients after abdominal surgery.

Table 2a  Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Patients

<table>
<thead>
<tr>
<th>System organ class</th>
<th>SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)</th>
<th>Comparator product n= 315* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (4.1)</td>
<td>13 (4.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13 (4.1)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>4 (1.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>10 (3.2)</td>
<td>10 (3.2)</td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>6 (1.9)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Liver function test abnormal</td>
<td>2 (0.6)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase increased</td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate increased</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic enzyme increased</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Glucosuria</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td>8 (2.5)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5 (1.6)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>3 (0.9)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Hyperchloremia</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>6 (1.9)</td>
<td>8 (2.5)</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>4 (1.3)</td>
<td>5 (1.6)</td>
</tr>
</tbody>
</table>
Table 2a  Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Patients

<table>
<thead>
<tr>
<th>System organ class</th>
<th>SMOFlipid 20% or Three-chamber bags containing SMOFlipid 20% n= 316* (%)</th>
<th>Comparator product n= 315* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestatis</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Cytolytic hepatitis</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>3 (0.9)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Tremor</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>2 (0.6)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Edema</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Infusion site erythema</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Infusion site swelling</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Pain</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Injury, poisoning and procedural complications</strong></td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Accidental overdose</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Post gastric surgery syndrome</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Enterobacter sepsis</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

Note that the numbers in each column can not be added because a subject may have had more than one adverse
event.
*Total number of the patients treated

Table 2b  Summary of Treatment-Emergent Adverse Drug Reactions in SMOFlipid Studies in Healthy Volunteers

<table>
<thead>
<tr>
<th>System organ class</th>
<th>SMOFlipid 20% n= 22* (%)</th>
<th>Comparator product n= 22* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>1 (4.5)</td>
<td>0</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>3 (13.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>1 (4.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

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

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

Not applicable. There are no other Adverse Drug Reactions reported in the clinical studies than the ones reported in Table 2.

**Abnormal Hematologic and Clinical Chemistry Findings**

See Table 2.

**Post-Marketing Adverse Drug 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.

**DRUG INTERACTIONS**

**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 3 Established or Potential Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Proper name</th>
<th>Ref</th>
<th>Effect</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>T</td>
<td>A possible transient decrease in triglyceride clearance</td>
<td>These findings are based on basic research and not reported as adverse events in clinical practice.</td>
</tr>
<tr>
<td>Coumarin derivatives</td>
<td>T</td>
<td>May decrease anticoagulant effect</td>
<td>Soybean 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.</td>
</tr>
</tbody>
</table>

Legend: T = Theoretical

**Drug-Food Interactions**
No SMOFlipid food interaction studies have been performed.

**Drug-Herb Interactions**
No SMOFlipid herb interactions studies have been performed.

**Drug-Laboratory Interactions**
High levels of lipids in plasma may interfere with some laboratory blood tests, e.g. hemoglobin.

**DOSAGE AND ADMINISTRATION**

**Dosing Considerations**
The patient’s ability to eliminate the fat infused should determine the dosage and infusion rate.

**Recommended Dose and Dosage Adjustment**
The standard dose is 1.0 – 2.0 g lipid/kg body weight (b.w.)/day, corresponding to 5 – 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>
<thead>
<tr>
<th>Standard daily dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per kg of body weight</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Usual lipid dose</td>
</tr>
<tr>
<td>Infused volume of SMOFlipid 20%</td>
</tr>
</tbody>
</table>
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.

**Administration**

Intravenous infusion into a peripheral or central vein.

**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 patients clinical conditions e.g. renal function impairment or infection.

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

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

**ACTION AND CLINICAL PHARMACOLOGY**

**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 (approx. 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.

**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 (see section DETAILED PHARMACOLOGY).

**Pharmacokinetics**

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.

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

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. (see section DETAILED PHARMACOLOGY).

**Special Populations and Conditions**

**Pediatrics:** Exploratory studies have been conducted but confirmatory pivotal studies have
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.

Gender: 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.

STORAGE AND STABILITY

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 - 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 - 8°C, unless additions have taken place in controlled and validated aseptic conditions.
SPECIAL HANDLING INSTRUCTIONS

Instructions for use and handling

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

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

1. 

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

2. 

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

The Oxalert™ sachet A and the oxygen absorber B should be discarded.
3. Place the bag on the clean, flat surface. If additives are to be used break off the tamper-evident arrow flag from the white additive port. If no additives are to be used go to figure 5.

4. Place the bag on the clean, flat surface. Insert the needle horizontally through the centre of the septum of the additive port and inject the additives (with known compatibility). Use syringes with needles of 18-23 gauge and a length of max. 40 mm.
5. Use a non-vented infusion set or close the air vent on a vented set. Follow the instructions for use for the infusion set. Use a spike with diameter as specified in ISO 8536-4, 5.6 +/- 0.1 mm.

6. Place the bag on the clean, flat surface. Break off the tamper-evident arrow flag from the blue infusion port.
7. Place the bag on the clean, flat surface. Hold the base of the infusion port. Insert the spike through the infusion port, by rotating your wrist slightly until the spike is inserted.

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

**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.
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.
DOSAGE FORMS, COMPOSITION AND PACKAGING

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-\textsuperscript{rac}-\textalpha-\text{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: approx. 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.

The packaging consists of an inner bag (primary package) with an oxygen barrier overpouch. An oxygen absorber and an integrity indicator (Oxalert\textsuperscript{TM}) 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.
### PHARMACEUTICAL INFORMATION

#### Drug Substance

<table>
<thead>
<tr>
<th>Proper name:</th>
<th>Soybean oil</th>
<th>Medium chain triglycerides (MCT)</th>
<th>Olive oil</th>
<th>Fish oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical name:</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Molecular formula:</td>
<td>Triacylglycerol (triglyceride) with fatty acid chains mainly C16:0, C18:0, C18:1, C18:2, C18:3</td>
<td>Triacylglycerol (triglyceride) with fatty acid chains mainly C8:0, C10:0</td>
<td>Triacylglycerol (triglyceride) with fatty acid chains mainly C16:0, C18:1, C18:2</td>
<td>Triacylglycerol (triglyceride) rich in the omega-3 fatty acids EPA and DHA (C20:5, C22:6)</td>
</tr>
<tr>
<td>Structural formula:</td>
<td><img src="image" alt="Structural formula" /></td>
<td><img src="image" alt="Structural formula" /></td>
<td><img src="image" alt="Structural formula" /></td>
<td><img src="image" alt="Structural formula" /></td>
</tr>
<tr>
<td></td>
<td>R₁, R₂, R₃ represents the chain of the fatty acids linked to the glycerol backbone.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physicochemical properties:</td>
<td>Liquid at room temperature.</td>
<td>Practically insoluble in water, very soluble in acetone and in heptane while slightly soluble in ethanol.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## CLINICAL TRIALS

### Study demographics and trial design

Table 1 Summary of patient demographics for clinical trials in specific indication

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Trial design</th>
<th>Dosage (g fat/kg bw/h)</th>
<th>Route of administration</th>
<th>Duration (h)</th>
<th>Study subjects (n=number)</th>
<th>Age (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy volunteers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE-SM-01-BE Pharmacokinetics</td>
<td>open-label, randomized, active-controlled, crossover</td>
<td>0.15</td>
<td>IV</td>
<td>4</td>
<td>10</td>
<td>18-45</td>
</tr>
<tr>
<td>FE-SM-02-DE Pharmacokinetics</td>
<td>double-blind, randomized, active-controlled, crossover</td>
<td>0.125</td>
<td>IV</td>
<td>6</td>
<td>12</td>
<td>18-45</td>
</tr>
<tr>
<td><strong>Adult patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FE-SM-03-DE Efficacy/Safety</td>
<td>double-blind, randomized, active-controlled, parallel-group</td>
<td>1.5</td>
<td>IV</td>
<td>5</td>
<td>249</td>
<td>≥18</td>
</tr>
<tr>
<td>FE-SM-04-CH Safety</td>
<td>double-blind, randomized, active-controlled, parallel-group</td>
<td>up to max 2</td>
<td>IV</td>
<td>10-14</td>
<td>32</td>
<td>≥18</td>
</tr>
<tr>
<td>03-3CB7-001* Safety</td>
<td>open-label, randomized, active-controlled, parallel-group</td>
<td>Day 1: 0.6 Days 2-4: 0.9–1.2 Days 5-7: 0.6-1.2</td>
<td>IV</td>
<td>5-7</td>
<td>53</td>
<td>≥18</td>
</tr>
<tr>
<td>03-3CB8-001** Safety</td>
<td>open-label, randomized, active-controlled, parallel-group</td>
<td>max 1.1 for test product and 1.4 for reference product</td>
<td>IV</td>
<td>5-7</td>
<td>52</td>
<td>≥18</td>
</tr>
<tr>
<td>05-SMOF-006 Safety</td>
<td>double-blind, randomized, active-controlled, parallel-group</td>
<td>max 1-2</td>
<td>IV</td>
<td>4 weeks</td>
<td>73</td>
<td>≥18</td>
</tr>
</tbody>
</table>

Note:
* 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

Comparative Bioavailability Studies
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-6/ω-3 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.

DETAILED PHARMACOLOGY

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.

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 6%, MCT 6%, olive oil 5%, and fish oil 3% 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 $\omega$-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 $\omega$-6 or $\omega$-3 PUFA in parenteral lipid emulsions may be immunosuppressive. The more balanced the $\omega$-6 to $\omega$-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 $\omega$-6:$\omega$-3 ratio is in the range of 2:1 to 4:1. The ratio of $\omega$-6:$\omega$-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 (C18:1\(\omega9\)) 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 \(\omega-3\) 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 \(\omega-6\) PUFA arachidonic acid (AA).

Increased intake of \(\omega-3\) fatty acids is followed by an increased \(\omega-3/\omega-6\) fatty acid ratio in cell membranes of many cell populations. SMOFlipid contains 15% fish oil. After 5 days postoperative total parenteral nutrition with SMOFlipid \(\omega-3\) fatty acids as well as \(\omega-3/\omega-6\) fatty acid ratio were 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\(^24\).

Parenteral fish oil has been successfully and safely used in postsurgical patients\(^25,26,27,28,29,30,31,32,33\), pancreatitis patients\(^34\), septic patients\(^30,35,36\), patients with chronic plaque-type psoriasis\(^37\).

**MICROBIOLOGY**
Not applicable.
TOXICOLOGY

The following toxicological studies have been performed with SMOFlipid

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Species</th>
<th>SMOFlipid Doses g TG/kg bw/day</th>
<th>Observations and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-Dose Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>9, 18, 36</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Repeat-Dose Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-week Dog</td>
<td>9</td>
<td></td>
<td>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 pneumonia) and kidney (interstitial nephritis). At the end of the 4-week recovery period all afore described drug substance-related changes had subsided.</td>
</tr>
<tr>
<td>13-week Dog</td>
<td>3, 6**</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genotoxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial gene mutation</td>
<td><em>S. typhimurium</em></td>
<td>Up to 40 mg/plate</td>
<td>No mutagenic effects were observed.</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Human lymphocytes</td>
<td>Up to 5 mg/ml</td>
<td></td>
</tr>
<tr>
<td>HPRT-test</td>
<td>V79 cells</td>
<td>Up to 10 mg/ml</td>
<td></td>
</tr>
<tr>
<td>In vivo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow cytogenetic test</td>
<td>Rat</td>
<td>10</td>
<td>No mutagenic effect was observed.</td>
</tr>
</tbody>
</table>
### Local Tolerance

<table>
<thead>
<tr>
<th>Animal</th>
<th>Route</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit (iv, ia, pv, sc, im)</td>
<td>SMOFlipid 20%</td>
<td>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. 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).</td>
</tr>
<tr>
<td>Dog</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reference Soybean oil emulsion  
**Reference: 0.9% NaCl solution

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.
REFERENCES


39. Leuschner J. 4-week subchronic toxicity study of SMOF 20% by daily 6-hour intravenous infusion to Beagle dogs. Hamburg: LPT, Laboratory of Pharmacology and Toxicology, LPT Report No. 9358/1/95 (1996b).


45. Leuschner J. Local tolerance test of SMOF 20% in rabbits after a single intravenous, intraarterial, paravenous, intramuscular and subcutaneous administration. Hamburg: LPT, Laboratory of Pharmacology and Toxicology, LPT Report No. 9802/1/96 (1996d).
PART III: CONSUMER INFORMATION

SMOFlipid® 20%
Lipid Injectable Emulsion, Mfr. Std.
Soybean oil, medium chain triglycerides, olive oil and fish oil (6%/ 6%/ 5%/ 3% w/v)
Lipid Emulsion for Intravenous Nutrition

This leaflet is part III of a three-part "Product Monograph" published when SMOFlipid 20% was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SMOFlipid 20%. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is 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.

A healthcare professional will recommend you SMOFlipid when you are unable to take food by mouth or other forms of feeding have not worked (e.g. nasogastric tube, direct catheter).

What SMOFlipid 20% does:
SMOFlipid 20% helps to ensure adequate intake of calories and essential fatty acids and thus helping to prevent or treat malnutrition.

When SMOFlipid 20% should not be used:
It is contraindicated to administer SMOFlipid if:
- you are allergic (hypersensitive) to fish, eggs or any of the ingredients of SMOFlipid. (See What the important nonmedicinal ingredients are)
- you are allergic to peanuts or soya. SMOFlipid contains soybean oil.
- you have especially high levels of fats in your blood (severe hyperlipidemia).
- you have severe reduced liver function (severe liver insufficiency).
- you have severe blood clotting disorders.
- you have severe impaired kidney function (severe renal insufficiency) without access to hemofiltration or dialysis.
- you are in an acute shock.
- you have the following general contraindications to infusion therapy: critical fluid accumulation in your lungs (acute pulmonary edema), excess water content of your body (hyperhydration), and decompensated heart failure (decompensated cardiac insufficiency).
- 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 conditions.

What the medicinal ingredient is:
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

What the important nonmedicinal ingredients are:
Purified egg phospholipids 1.2 g
All-rac-α-tocopherol 16-23 mg
Glycerol 2.5 g
Sodium oleate 30 mg
Sodium hydroxide to adjust pH

What dosage forms it comes in:
SMOFlipid 20% is a white homogeneous lipid emulsion. You will receive your medicine by infusion.

WARNINGS AND PRECAUTIONS

BEFORE you use SMOFlipid 20% talk to your doctor or pharmacist if:
You have any diseases/conditions listed in contraindications section (see When it should not be used)

Care should be taken when administrating SMOFlipid 20%, therefore inform you doctor if:
- you are pregnant or planning to become pregnant.
- you are breast feeding or planning to breastfeed.
- you are taking any other medications.
- you have high level of lipids in your blood.
- you have allergy to soybean, fish or eggs, which may rarely cause allergic reactions. Peanut may also cause reactions to patients, who are allergic to soybean.
- any sign or symptom of allergic reaction (such as fever, shivering, rash or breathlessness) occurs during the treatment.
- you have impaired metabolism, which may occur if you have kidney or liver problems, diabetes, pancreatitis (inflammation of the pancreas), thyroid problems (hypothyroidism), and sepsis (infection).
INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with SMOFlipid 20%

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Soybean oil has a natural content of vitamin K1. The amount in SMOFlipid however is minimal and not expected to significantly counteract the blood-thinning (anticoagulant) activity of coumarin derivates.

There may also be interaction between SMOFlipid 20% and heparin.

Inform your doctor if you are taking any anticoagulants to help prevent blood clots, e.g. heparin or coumarin derivates.

Drug-Laboratory Interactions
This medicine may interfere with certain laboratory tests. It is important to tell any doctor doing tests that you are using SMOFlipid 20%.

PROPER USE OF THIS MEDICATION

SMOFlipid 20% may be mixed by health care professionals with carbohydrates, amino acids, salts, vitamins and trace elements which together provide your complete nutritional needs.

SMOFlipid can be given in a hospital or managed care facility, or at home under the supervision of a doctor or other health care professional.

After appropriate training and with the agreement of your health care team, you may be able to administer yourself a compounded TPN admixture containing SMOFlipid prepared by pharmacy professionals under aseptic conditions. Use only if the compounded emulsion is homogeneous and milk-like. Use only if the bag is not damaged. Aseptic conditions must be followed. The bag should only be used once. Discard unused portion. Do not use a partially used bag.

Usual adult dose:
You will receive your medicine by intravenous infusion. The amount and rate at which the infusion is given depends on your individual requirements and your medical condition (please also see section “WARNINGS AND PRECAUTIONS”).

Your doctor will decide on the correct dose for you.

Your doctor will also specify a flow rate corresponding to your needs and medical condition.

Instructions for use and handling

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

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

1.

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

2.

Place the bag on the clean, flat surface. Remove the overwrap by tearing at the notch and pulling down along the container. The Oxalert™ sachet A and the oxygen absorber B should be discarded.

3.

Place the bag on the clean, flat surface. If additives are to be used break off the tamper-evident arrow flag from the white additive port. If no additives are to be used go to figure 5.
4. Place the bag on the clean, flat surface. Insert the needle horizontally through the centre of the septum of the additive port and inject the additives (with known compatibility). Use syringes with needles of 18-23 gauge and a length of max. 40 mm.

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

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

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

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

The medicine must be at room temperature to be administered.

Your doctor may monitor your condition and periodically test your blood and urine.

**Overdose:**
If you think that you have received too high dose or SMOFlipid 20% was infused too quickly, inform your doctor or nurse immediately. In case of 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 dosage. See section “SIDE EFFECTS” for more information.

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

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.
SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SMOFlipid 20% can cause side effects, although not everybody gets them.

If any symptoms of an allergic reaction develop, for example such as breathing difficulties, skin rash, urticaria, flush, headache, stop the infusion immediately and contact your doctor. Occasional redness and stinging may occur at the injection site.

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

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or nurse</th>
<th>Stop taking drug and call your doctor or nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Only if severe</td>
<td>NA</td>
</tr>
<tr>
<td>- Nausea, Vomiting, - Chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>In all cases</td>
<td></td>
</tr>
<tr>
<td>- low blood pressure, (hypotension)</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>- high blood pressure (hypertension)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- allergic reaction (e.g. breathing difficulties,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>skin rash, urticaria, flush, headache)</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>

This is not a complete list of side effects. For any unexpected effects while taking SMOFlipid, contact your doctor or pharmacist.

Fat overload syndrome
Possible symptoms of fat overload are fever, yellowing of the skin and eyes, abdominal pain, vomiting, anemia, fall in the number of white blood cells and platelets, troubles in blood clotting, liver and spleen enlargement and coma. Stop the medication if these symptoms occur. These symptoms usually disappear when the medication is stopped.

If you suffer such side effects, tell your doctor.

HOW TO STORE IT

Store up to 25 °C. Do not freeze.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- online at MedEffect (www.healthcanada.gc.ca/medeffect)
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to:  Canada Vigilance Program
             Health Canada
             Postal Locator 0701E
             Ottawa, ON
             K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

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.

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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer’s website (http://www.fresenius-kabi.ca), or by calling 1-877-821-7724 (toll-free-telephone).

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