VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Artificial nutrition might be necessary as a supportive medical therapy among certain medical conditions in many different underlying diseases. The primary purpose for nutritional support is generally to maintain or improve the nutritional status of patients who, for a critical period of time are not able to eat adequately. These patients have an increased risk to become malnourished. Malnutrition is defined as a state of nutrition in which a deficiency or excess (or imbalance) of energy, protein, and other nutrients causes measurable adverse effects on the patient and his health. Body reserves can normally make up for short fasting periods, however in patients at-risk of malnutrition or who are already malnourished even short periods without adequate nutrition present an additional hazard which could lead to a negative impact on his health.

The main risk groups who bare an increased risk for malnutrition and are prone to need artificial nutrition are severely ill patients who have to be treated in an ICU (extensive surgery, severe accidents, large-area and/or severe burns), geriatric patients, cancer patients and patients with gastrointestinal diseases like inflammatory bowel diseases (Crohn Disease), intestinal failure or short

bowel syndrome (SBS). Patients suffering from severe intestinal failure or SBS may need artificial nutrition support for the rest of their lives.

VI.2.2 Summary of treatment benefits

Parenteral nutrition (PN) as a special kind of artificial nutrition refers to the direct infusion of specialised nutrition solutions into a vein bypassing the gastrointestinal tract. This method of feeding may be required when other routes like normal oral nutrition or tube feeding are not effective or cannot be used.

For patients with severe gastrointestinal failure and SBS PN provides the only ability to sustain and maintain quality of life, promote rehabilitation support and was proven to be mandatory for long-term survival.

The standardised parenteral nutrition containing all compounds is suitable for most of the parenterally fed patients. However, some critically ill patients or patients with severe intestinal failure like SBS may require patient-tailored nutrition because their nutrient requirements are very specific and tend to vary significantly from standard requirements.

In general intravenous lipid emulsions as part of PN are known for over 40 years and today are widely used as a caloric source in both adult and infant populations requiring parenteral nutrition support.

Lipoplus is such an injectable intravenous fat emulsion providing energy and essential fatty acids especially as part of patient-tailored PN regimes.

VI.2.3 Unknowns relating to treatment benefits

No data from the use of Lipoplus in pregnant and lactating women are in place and there is as yet only limited experience of the use of Lipoplus for periods longer than seven days.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Abnormally elevated levels of blood lipids (Hypertriglyceridaemia)	Hypertriglyceridaemia refers to high blood levels of triglycerides, the most abundant fatty molecule in most organisms. Elevated blood levels are often linked to overdose, either by a too high daily dose or by a too quick infusion. There are also disorders of lipid metabolism were blood lipids cannot be utilised efficiently which also lead to increased blood level, for example in diabetes, impaired function of the kidneys, liver or the thyroid gland, inflammation of the pancreas or sepsis. Also, combined disorders are fairly common which may e.g. develop in patients with obesity or diabetes. In these cases, overnutrition leads to increased blood levels of glucose and lipids. Very high blood triglyceride level may cause an acute inflammation of the pancreas (acute pancreatitis) and must therefore be avoided.	Lipoplus should be given in appropriate amounts, and over appropriate period of time. Blood lipids have to be controlled. If Lipoplus is given to patients with impaired fat metabolism, more frequent monitoring of blood lipids (triglycerides) and glucose is necessary. Overfeeding must be avoided. When blood triglycerides exceed a critical level the infusion must be stopped.
Abnormally high acid levels in the blood (Acidosis)	Acidosis occurs when the body produces too much acid (e.g. decompensated diabetes or glucose utilisation with lack of oxygen in the tissues), or when the elimination of acids from the body is impaired (e.g. renal insufficiency or inadequate ventilation).	Lipoplus must not be used in case of acidosis. Acidosis should be treated and controlled before PN is started. Control of acid-base balance is necessary during PN.
Allergic reactions (Hypersensitivity)	Most allergic reactions are minor, such as rash. But in some cases, an allergic reaction can be life-threatening and can present with dyspnoea, hypotension and shock. Hypersensitivity reactions to the lipid emulsion of PN have been reported by patients with soybean, peanut or egg allergies as skin eruption and urticaria. They are considered to be fairly rare.	Lipoplus must not be used in patients with known allergy to any of the active substances, to egg, fish, peanut or soya protein or to any of the excipients. Previous allergic reactions to soybean or egg or to any other substance should be reported to the physician.
Tendency to form blood clots (Hypercoagulation)	Patients with a poor state of health as well as bedridden patients are often exposed to a higher risk of development of blood clots in the blood stream, which theoretically may be increased after infusion of soya-bean oil emulsion.	Lipoplus should not be used in patients with acute thrombo-embolic events like heart attack, stroke, pulmonary or fat embolism. Coagulation status should be continuously monitored.

Effective

Important identified risks		
Risk	**What is known**	**Preventability**
Fat overload syndrome	'Fat Overload Syndrome' results when the lipid infusion rate exceeds the ability of the body to utilise the lipids. The clinical symptoms of 'Fat Overload Syndrome' are complex. They include elevation of blood lipid levels, fever, enlarged liver with or without jaundice, enlarged spleen, decreased number of red and white blood cells, decreased platelets in blood, blood clotting disorders, break-up of red blood cells, abnormal liver function tests and coma. Fat overload syndrome has been described for dosages of parenteral lipids higher than recommended in the product information. Patients with impaired lipid utilisation, e.g. diabetes, impaired function of the kidneys, liver or the thyroid gland, inflammation of the pancreas or sepsis are at risk for fat overload syndrome.	Recommended doses of Lipoplus should not be exceeded. Blood lipids have to be controlled and dosage adjusted as necessary. Overnutrition must be avoided.
Impaired bile flow (Intrahepatic cholestasis)	Cholestasis is a condition in which bile cannot be sufficiently drained into the intestine. As a result, bile stagnates in the gallbladder and eventually also within the liver, impairing liver function (intrahepatic cholestasis). Infusion of fat emulsions may further enhance cholestasis.	Lipoplus must not be used in case of intrahepatic cholestasis. Liver function must be monitored during PN.

Important potential risks	
Risk	**What is known**
Incompatibility	Lipoplus may only be mixed with other medicinal products for which compatibility has been documented. Compatibility data for different additives/nutrients (e.g. electrolytes, trace elements, vitamins) and the corresponding shelf life of such admixtures can be provided on demand by the manufacturer.

Risk	**What is known**
Use in pregnant and lactating women	There are no or limited data from the use of Lipoplus in pregnant women. No evidence of embryotoxicity or teratogenicity (to cause malformation of an embryo or foetus) was seen in a reproductive study. Components/metabolites of Lipoplus are excreted in human milk.
Use for periods longer than seven days	There is as yet only limited experience of the use of Lipoplus for periods longer than seven days.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Table 5: Major changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
2.0	05-Dec-2014	Identified Risks: • Hypertriglyceridaemia • Acidosis • Hypersensitivity • Hypercoagulation • Intrahepatic cholestasis • Fat overload syndrome Potential Risks • Incompatibility Missing information • Use in pregnant and lactating women • Use for periods longer than seven days	None
1.0	09-Apr-2013	Identified Risks: • Hyperlipidaemia • Metabolic acidosis • Allergic reactions • Hypercoagulation Potential Risks • None Missing information • Use in pregnant and lactating women • Use for periods longer than seven days	None