EU RISK MANAGEMENT PLAN (EU-RMP)

Lipoflex peri emulsion for infusion
Lipoflex plus emulsion for infusion
Lipoflex special emulsion for infusion
Lipoflex special without electrolytes emulsion for infusion

Active substances (INN or common name):	**Lipoflex peri emulsion for infusion** **Lipoflex plus emulsion for infusion** **Lipoflex special emulsion for infusion** Glucose monohydrate, sodium dihydrogen phosphate dehydrate, zinc acetate dehydrate, soya-bean oil (refined), medium-chain triglycerides, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan, valine, arginine, histidine hydrochloride monohydrate, alanine, aspartic acid, glutamic acid, glycine, proline, serine, sodium hydroxide, sodium chloride, sodium acetate trihydrate, potassium acetate, magnesium acetate tetrahydrate, calcium chloride dihydrate **Lipoflex special without electrolytes emulsion for infusion** Glucose monohydrate, soya-bean oil (refined), medium-chain triglycerides, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan, valine, arginine, histidine, alanine, aspartic acid, glutamic acid, glycine, proline, serine
Pharmaco-therapeutic group (ATC Code):	Solutions for parenteral nutrition, combinations (B 05BA10)
Name of Marketing Authorisation Holder or Applicant:	B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen Germany
Number of medicinal products to which this RMP refers:	4
Products concerned (brand names):	Lipoflex peri emulsion for infusion Lipoflex plus emulsion for infusion Lipoflex special emulsion for infusion Lipoflex special without electrolytes emulsion for infusion

Data lock point for this RMP

30.04.2014

Version number

03

Date of final sign off

Please see effective date in the header

B. Braun Melsungen AG

VI.2. Elements for a Public Summary

VI.2.1. Overview of disease epidemiology

Patients may need parenteral nutrition (PN) for any variety of diseases or conditions that impair food intake, nutrient digestion or absorption. Lipoflex is used to supply energy, essential fatty acids, amino acids, electrolytes and fluids for parenteral nutrition of patients. People of all ages receive parenteral nutrition. People can live well on parenteral nutrition for as long as it is needed.

Many hospitalised patients receive parenteral nutrition. In the U.S. for example, patients received PN in almost 360,000 hospital stays in 2009. About 33% of those were for children and newborns. Individuals can also receive this therapy at home and in long-term care facilities.

VI.2.2. Summary of treatment benefit

The standardised parenteral nutrition containing almost all compounds is suitable for most of the parenteral fed patients. The constituents of Lipoflex, are generally established for medicinal use, and are acknowledged as being both efficient and safe. The combinations chosen in the Lipoflex versions have positive effects on the body homeostasis.

The important objective of parenteral nutrition is to meet energy requirements and to maintain vital organ structure and function. Protein degradation (catabolism) should be decreased and protein synthesis promoted. Thus amino acid solutions are an essential part of a complete parenteral nutrition regimen providing building blocks for protein synthesis and maintaining nitrogen balance (homeostasis). The amount of nitrogen administered during parenteral nutrition is crucial to reduce catabolism. The infusion of lipid emulsions allows a high energy supply and is indispensable for the supply of essential fatty acids, components of each cell membrane and tissue. In addition, it balances the energy provision by glucose, thereby reducing an overdose of each other. Glucose is the most important energy source for all organs and tissues, and is used exclusively in the brain and nervous tissue, erythrocytes and renal medulla. Additionally, glucose is required for normal metabolism of fatty acids. Electrolytes administered with Lipoflex help to maintain the blood levels necessary for the physiological processes of the cell, for which rather constant electrolyte levels are prerequisite.

VI.2.3. Unknowns relating to treatment benefits

There are no unknown related to treatment benefits for Lipoflex.

VI.2.4. Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
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 parenteral nutrition have been reported by patients with soybean, peanut or egg allergies as skin eruption and urticaria. They are considered to be fairly rare.	• Lipoflex special must not be used in patients with known allergy to soy bean or egg protein. • Previous allergic reactions to soybean or egg or to any other substance should be reported to the physician.
Intolerance in patients with inborn errors of amino acid metabolism	There are some rare, genetic disorders of the metabolism of one or a group of amino acids. Inborn errors of aminoacid metabolism usually present in infancy and early childhood. However in some rare cases it can present in adulthood e.g. when patients are	• Lipoflex special must not be used in patients with inborn errors of amino acid metabolism. • The existence of such a disorder must be immediately brought to the attention of the treating

Important identified risks		
Risk	**What is known**	**Preventability**
	exposed to increased protein intake or certain medicationsand infections. The most common amino acid disorders are phenylketonuria, urea cycle disorders, nonketonic hyperglycinaemia, tyrosinaemia and maple syrup disease. Treatment includes severe restriction of natural protein intake, combined with an amino acid supplement which substitutes all necessary amino acids, excluding the one(s) affected by the metabolic defect. Lipoflex special is a standard product with an amino acid composition of a natural high quality protein. The different inborn errors of amino acid metabolism require specific, different adaptions of the amino acid composition that a standard product cannot provide.	physician. This is part of the careful evaluation of each patient's medical history before treatment is started.
Fat overload syndrome	'Fat Overload Syndrome' results when the lipid infusion rate exceeds the ability of the body to utilize 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 utilization, 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 Lipoflex special should not be exceeded. • Blood lipids have to be controlled and dosage adjusted as necessary. • Overnutrition must be avoided.
Disturbance of blood coagulation (bleeding)/or tendency to form blood clots (thrombosis)	Blood clotting (coagulation) may be impaired in patients in poor overall condition putting them into an increased risk of bleeding. Also patients suffering from genetic disorders like haemophilia or patients treated with drugs decreasing blood coagulation (anticoagulants) or antiplatelet agents (e.g. aspirin) are exposed to a higher risk of bleeding. Blood clotting should be under control before parenteral nutrition via intravenous catheter should be started. On the other hand patients with in a poor state of health as well as bedridden patients are	• Lipoflex special must not be used in patients with severely impaired blood clotting function. • Coagulation status should be continuously monitored especially, in patients treated concomitantly with anticoagulants or antiplatelet drugs.

Important identified risks		
Risk	**What is known**	**Preventability**
	also often exposed to a higher risk of development of blood clots in the blood stream, which theoretically may be increased after infusion of soybean oil emulsion.	
High blood sugar (Hyperglycaemia)	High blood sugar may occur as a result of a high rate of administration or impaired utilization of glucose. Glucose is excreted in urine when the blood glucose level reaches a critic level (renal threshold). Excretion of glucose is accompanied by increased urination. If untreated, this can lead to excessive loss of fluid which may be life-threatening. Increased blood sugar can be transformed into triglycerides which may cumulate in the liver leading to the development of fatty liver. Lipoflex special contains glucose and its administration can lead to hyperglycaemia.	• The rate of infusion should be reduced or insulin should be administered in case that hyperglycaemia occurs. • If the patient is receiving other glucose solutions concurrently, this amount has to be taken into account. • Blood levels of glucose should be monitored. • An interruption of administration of Lipoflex special may be indicated if the blood glucose concentration reaches a critical level during administration and cannot be controlled by appropriate amounts of insulin.
Impaired bile flow (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.	• Lipoflex special must not be used in case of intrahepatic cholestasis. Liver function must be monitored during parenteral nutrition.
Fluid deficit or water excess in the body/ disturbances of the body salt composition	Administration of intravenous solutions may cause disturbances of the body salt and fluid balance. The risk of such undesirable effects is enhanced in case of infusion of too large volumes (hyperhydration) or a too rapid infusion as well as in severely ill and pediatric patients or patients with impaired cardiac or renal function who all have limited ability to maintain the fluid balance. In patients with pre-existing disturbances of fluid and salt balance, the disorder may be aggravated by infusion of intravenous solutions. Severer salt imbalances can lead to shifts in the body fluids with the accumulation of fluid in certain tissues like the lungs (lung oedema) or the brain. Untreated these conditions can result in serious complications and permanent damage.	• Disturbances of the fluid and salt balance must be corrected before the start of infusion. • The infusion rate should be appropriately dosed. • Regular controls of the blood composition are necessary.

Important identified risks		
Risk	**What is known**	**Preventability**
	A special kind of a body salt imbalance (acidosis) is when the body produces too much acid (e.g. decompensated diabetes or glucose utilization 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).	
Refeeding syndrome	Refeeding syndrome is a disturbance that occurs as a result of reinstitution of nutrition to patients who are starved or severely malnourished. Refeeding or repletion of such patients may lead to deficiency of some essential salts in the body, i.e. potassium, phosphorus and magnesium.	• In starved or severely mal-nourished patients the nutrition must be reinstituted slowly and gradually. • An adequate supplementation of salts according to deviations from normal values is necessary. • Regular controls of the blood composition is necessary.

Missing information	
	What is known
Pregnancy and lactation	There are no or limited amount of data from the use of Lipoflex special in pregnant women. Parenteral nutrition may become necessary during pregnancy. Lipoflex special should only be given to pregnant women after careful consideration. Components/metabolites of Lipoflex special are excreted in human milk, but at therapeutic doses no effects on the breastfed newborns/infants are anticipated. Nevertheless, breast-feeding is not recommended for mothers on parenteral nutrition.
Patients with diabetes mellitus and renal failure	There is only limited experience of its use in patients with diabetes mellitus or renal failure. Like all large-volume infusion solutions, Lipoflex special should be administered with caution to patients with impaired renal function. The doses should be adjusted individually in patients with renal insufficiency. Patients with diabetes mellitus are particularly prone to hyperglycemia. Therefore the dosage should be adopted to the patients' individual needs and glucose tolerance. A slow and stepwise increase of the infusion rate to the desired infusion rate avoids possible complications. The blood glucose level should be monitored. If there is hyperglycaemia the rate of infusion should be reduced or insulin should be administered. An interruption of administration of the emulsion may be indicated if the blood glucose concentration rises to above 14 mmol/l (250 mg/dl) during administration. If the patient is receiving other intravenous glucose solutions concurrently, the amount of additionally administered glucose has to be taken into account.

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

Not applicable. No additional risk minimisation measures are planned.

VI.2.6. Planned post authorisation development plan

Not applicable.

VI.2.7. Summary of changes to the Risk Management Plan over time

Not applicable, as this is the first RMP for the product.