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. Omegaflex plus is used to supply energy, essential FAs, amino acids, electrolytes and fluids for PN of patients. People of all ages receive PN. People can live well on PN for as long as it is needed.

Many hospitalised patients receive PN. 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 benefits

The standardised PN containing almost all compounds is suitable for most of the parenteral fed patients. The constituents of Omegaflex plus, are generally established for medicinal use, and are acknowledged as being both efficient and safe. The combination chosen in Omegaflex plus has positive effects on the body homeostasis.

The important objective of PN 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 PN regimen providing building blocks for protein synthesis and maintaining nitrogen balance (homeostasis). The amount of nitrogen administered during PN is crucial to reduce catabolism. The infusion of lipid emulsions allows a high energy supply and is indispensable for the supply of essential FAs, 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 FAs. Electrolytes administered with Omegaflex plus 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 Omegaflex plus.

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.	• Omegaflex plus must not be used in patients with known allergy to soy bean, egg, peanut or fish protein. • Previous allergic reactions to soybean, egg, peanut or fish or to any other substance should be reported to the physician before the beginning of the therapy.

Effective

Important identified risks		
Risk	**What is known**	**Preventability**
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 amino acid metabolism usually present in infancy and early childhood. However in some rare cases it can present in adulthood e.g. when patients are exposed to increased protein intake or certain medications and 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. Omegaflex plus 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.	• Omegaflex plus 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 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	• Recommended doses of Omegaflex plus should not be exceeded. • Blood lipids have to be controlled and dosage adjusted as necessary. • Overnutrition must be avoided.

Important identified risks		
Risk	**What is known**	**Preventability**
	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.	
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 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.	• Omegaflex plus 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.
High blood sugar (Hyperglycaemia)	High blood sugar may occur as a result of a high rate of administration or impaired utilisation 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. Omegaflex plus contains glucose and its	• 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 Omegaflex plus may be indicated if the blood glucose concentration

Important identified risks		
Risk	**What is known**	**Preventability**
	administration can lead to hyperglycaemia.	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.	• Omegaflex plus 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. Severe 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. 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).	• 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. • Sufficient amounts of electrolytes must be administered together with Omegaflex plus according to the patient's requirements.

Important identified risks		
Risk	**What is known**	**Preventability**
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 Omegaflex plus in pregnant women. Parenteral nutrition may become necessary during pregnancy. Omegaflex plus should only be given to pregnant women after careful consideration. Components/metabolites of Omegaflex plus 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 ofthe use of Omegaflex plus in patients with diabetes mellitus or renal failure. Like all large-volume infusion solutions, Omegaflex plus 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.
Paediatric patients	Due to its composition (amino acid composition, the relation of the macronutrients) Omegaflex plus is contraindicated in newborn infants, infants and toddlers under 2 years of age. Up to now there is no clinical experience with the use of Omegaflex plus in

	children > 2 years and adolescents.

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 EU-RMP for Omegaflex plus.

Part VI. Summary of activities in the risk management plan by product

Omegaflex special Emulsion for infusion

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity/anaphylactic reactions (rash, dyspnea) • Deterioration of amino acid imbalances and hyperammonemia in patients with inborn errors of amino acid metabolism • Fat overload syndrome including severe hypertriglyceridaemia particularly in patients with impaired lipid metabolism • Impairment of coagulation (severe coagulopathy, hypercoagulation) in patients with poor overall condition or in patients suffering from genetic disorders • Hyperglycaemia in patients with impaired glucose utilization or due to overdose • Cholestasis • Electrolyte disturbances (e.g. acidosis) including fluid overload (hyperhydration) associated with oedema (e.g. lung oedema) particularly in patients with impaired cardiac or renal function • Refeeding syndrome in malnourished patients
Important potential risks	-
Missing information	• Pregnancy and lactation • Patients with diabetes mellitus and renal failure • Paediatric patients

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable. No additional pharmacovigilance activities will be conducted.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable. No post authorisation efficacy development plan is in place.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity/ anaphylactic reactions (rash, dyspnea)	Proposed text in the SmPC: *4.3 Contraindications* • < hypersensitivity to the active substances, to egg, fish, peanut or soya protein or to any of the excipients listed in section 6.1 > *4.4 Special warnings and precautions for use* < Any sign or symptom of anaphylactic reaction (such as fever, shivering, rash or dyspnoea) should lead to immediate interruption of the infusion. > *4.8 Undesirable effects* ***Immune system disorders*** < Rare: Allergic reactions (e.g. anaphylactic reactions, dermal eruptions, laryngeal, oral and facial oedema) > Other routine risk minimisation measures Prescription only medicine	None proposed
Deterioration of amino acid imbalances and hyperammonemia in patients with inborn errors of amino acid metabolism	Proposed text in the SmPC: ***4.3 Contraindications*** • < inborn errors of amino acid metabolism > *4.4 Special warnings and precautions for use* < Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and renal function are necessary. > Other routine risk minimisation measures Prescription only medicine	None proposed
Fat overload syndrome including severe hypertriglyceridemia particularly in patients with impaired lipid metabolism	Proposed text in the SmPC: *4.3 Contraindications* • < severe hypertriglyceridaemia (≥ 1000 mg/dl or 11.4 mmol/l) >	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	4.4 Special warnings and precautions for use < The serum triglyceride concentration should be monitored when infusing Omegaflex special. > < Depending on the patient's metabolic condition, occasional hypertriglyceridaemia may occur. If the plasma triglyceride concentration exceeds 4.6 mmol/l (400 mg/dl) during administration of lipids it is recommended to reduce the infusion rate. The infusion must be interrupted if the plasma triglyceride concentration exceeds 11.4 mmol/l (1000 mg/dl), as these levels have been associated with acute pancreatitis.> *Patients with impaired lipid metabolism* < Omegaflex special should be administered cautiously to patients with disturbances of lipid metabolism with increased serum triglycerides, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired hepatic function, hypothyroidism (with hypertriglyceridaemia), sepsis and metabolic syndrome. If Omegaflex special is given to patients with these conditions, more frequent monitoring of serum triglycerides is necessary to assure triglyceride elimination and stable triglyceride levels below 11.4 mmol/l (1000 mg/dl). > < In combined hyperlipidaemias and in metabolic syndrome, triglyceride levels react to glucose, lipids and overnutrition. Adjust dose accordingly. Assess and monitor other lipid and glucose sources, and drugs interfering with their metabolism. > < The presence of hypertriglyceridaemia 12 hours after lipid administration also indicates a disturbance of lipid metabolism. > *4.8 Undesirable effects* **Metabolism and nutrition disorders** < Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, The frequency of	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	these undesirable effects is dose-dependent and may be higher under the condition of absolute or relative lipid overdose. > **General disorders and administration site conditions** < Very rare: Fat overload syndrome (details see below) > < Should the triglyceride level rise to above 11.4 mmol/l (1000 mg/dl) during infusion, the infusion must be stopped. With levels above 4.6 mmol/l (400 mg/dl), the infusion may be continued at a reduced dosage (see section 4.4). > < If the infusion is restarted, the patient should be carefully monitored, especially at the beginning, and serum triglycerides should be determined at short intervals. > **Information on particular undesirable effects** < *Fat overload syndrome* Impaired capacity to eliminate triglycerides can lead to 'fat overload syndrome', which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient's clinical condition such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipidaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leucopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	are usually reversible if the infusion of the fat emulsion is discontinued. > < Should signs of a fat overload syndrome occur, the infusion of Omegaflex special should be discontinued immediately. > *4.9 Overdose* *Symptoms of lipid overdose* < See section 4.8. > *Treatment* < Immediate cessation of infusion is indicated for overdose. Further therapeutic measures depend on the particular symptoms and their severity. When infusion is recommenced after the symptoms have declined, it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals. > <u>Other routine risk minimisation measures</u> Prescription only medicine	
Impairment of coagulation (severe coagulopathy, hypercoagulation) in patients with poor overall condition or in patients suffering from genetic disorders	<u>Proposed text in the SmPC:</u> *4.3 Contraindications* • < severe coagulopathy > • < aggravating haemorrhagic diatheses > • < acute thrombo-embolic events, lipid embolism > *4.4 Special warnings and precautions for use* < Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and renal function are necessary. > *4.8 Undesirable effects* **Blood and lymphatic system disorders** < <u>Rare:</u> Hypercoagulation > **Information on particular undesirable effects** <u>Fat overload syndrome</u>	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	Impaired capacity to eliminate triglycerides can lead to "fat overload syndrome", which may be caused by overdose. Possible signs of metabolic overload must be observed. The cause may be genetic (individually different metabolism) or the fat metabolism may be affected by ongoing or previous illnesses. This syndrome may also appear during severe hypertriglyceridaemia, even at the recommended infusion rate, and in association with a sudden change in the patient's clinical condition such as renal function impairment or infection. The fat overload syndrome is characterised by hyperlipidaemia, fever, fat infiltration, hepatomegaly with or without icterus, splenomegaly, anaemia, leucopenia, thrombocytopenia, coagulation disorder, haemolysis and reticulocytosis, abnormal liver function tests and coma. The symptoms are usually reversible if the infusion of the fat emulsion is discontinued. Should signs of a fat overload syndrome occur, the infusion of Omegaflex special should be discontinued immediately. <u>Other routine risk minimisation measures</u> Prescription only medicine	
Hyperglycaemia in patients with impaired glucose utilization or due to overdose	<u>Proposed text in the SmPC:</u> *4.3 Contraindications* • < hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour> *4.4 Special warnings and precautions for use* < Like all solutions containing carbohydrates, the administration of Omegaflex special can lead to hyperglycaemia. The blood glucose level should be monitored. If there is hyperglycaemia, the rate of infusion should be reduced or insulin should be administered. If the patient is receiving other intravenous glucose solutions concurrently, the amount of additionally administered glucose has to be taken into account. >	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	< 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. > *4.8 Undesirable effects* ***Metabolism and nutrition disorders*** < Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, The frequency of these undesirable effects is dose-dependent and may be higher under the condition of absolute or relative lipid overdose. > *4.9 Overdose* *Symptoms of glucose overdose* < Hyperglycaemia, glucosuria, dehydration, hyperosmolality, hyperglycaemic-hyper-osmolar coma. > *Treatment* < Immediate cessation of infusion is indicated for overdose. Further therapeutic measures depend on the particular symptoms and their severity. When infusion is recommenced after the symptoms have declined, it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals. Other routine risk minimisation measures Prescription only medicine	
Cholestasis	Proposed text in the SmPC: *4.3 Contraindications* • < intrahepatic cholestasis > *4.4 Special warnings and precautions for use* < Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	renal function are necessary. > *4.8 Undesirable effects* ***Hepatobiliary disorders*** < Not known: Cholestasis > Other routine risk minimisation measures Prescription only medicine	
Electrolyte disturbances (e.g. acidosis) including fluid overload (hyper-hydration) associated with oedema (e.g. lung oedema) particularly in patients with impaired cardiac or renal function	Proposed text in the SmPC: *4.2 Posology and method of administration* *Patients with renal/hepatic impairment* < The doses should be adjusted individually in patients with hepatic or renal insufficiency (see also section 4.4). > *4.3 Contraindications* • < acidosis > • < disturbances of electrolyte and fluid balance > • < acute pulmonary oedema > • < decompensated cardiac insufficiency > *4.4 Special warnings and precautions for use* < Caution should be exercised in cases of increased serum osmolarity. > < Disturbances of the fluid, electrolyte or acid-base balance must be corrected before the start of infusion. > < Too rapid infusion can lead to fluid overload with pathological serum electrolyte concentrations, hyperhydration and pulmonary oedema. > < Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and renal function are necessary. > *Elderly patients* < Basically the same dosage as for adults applies, but caution should be exercised in	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
	patients suffering from further diseases like cardiac insufficiency or renal insufficiency that may frequently be associated with advanced age. > *<u>Patients with diabetes mellitus, impaired cardiac or renal function</u>* < Like all large-volume infusion solutions, Omegaflex special should be administered with caution to patients with impaired cardiac or renal function. > < There is only limited experience of its use in patients with diabetes mellitus or renal failure. > *4.8. Undisarable Effects* ***Metabolism and nutrition disorders*** < <u>Very rare:</u> Hyperlipidaemia, hyperglycaemia, metabolic acidosis, The frequency of these undesirable effects is dose-dependent and may be higher under the condition of absolute or relative lipid overdose. > *4.9 Overdose* *Symptoms of fluid and electrolyte overdose* < Hyperhydration, electrolyte imbalance and pulmonary oedema. > *Treatment* < Immediate cessation of infusion is indicated for overdose. Further therapeutic measures depend on the particular symptoms and their severity. When infusion is recommenced after the symptoms have declined, it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals. > <u>Other routine risk minimisation measures</u> Prescription only medicine	

Effective

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Refeeding syndrome in malnourished patients	Proposed text in the SmPC: *4.4 Special warnings and precautions for use* < Refeeding or repletion of malnourished or depleted patients may cause hypokalaemia, hypophosphataemia and hypomagnesaemia. Close monitoring of serum electrolytes is mandatory. Adequate supplementation of electrolytes according to deviations from normal values is necessary. > < Controls of the serum electrolytes, the water balance, the acid-base balance, and of blood cell counts, coagulation status, hepatic and renal function are necessary. > < Substitution of electrolytes, vitamins and trace elements may be necessary as required. As Omegaflex special contains zinc, magnesium, calcium and phosphate, care should be taken when it is co-administered with solutions containing these substances. > Other routine risk minimisation measures Prescription only medicine	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
Pregnancy and lactation	Proposed text in the SmPC: *4.6 Fertility, pregnancy and lactation* Pregnancy < There are no or limited amount of data from the use of Omegaflex special in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Parenteral nutrition may become necessary during pregnancy. Omegaflex special should only be given to pregnant women after careful consideration.> Breast-feeding < Components/metabolites of Omegaflex special are excreted in human milk, but at	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
	therapeutic doses no effects on the breastfed newborns/infants are anticipated. Nevertheless breast-feeding is not recommended for mothers on parenteral nutrition. > *5.3 Preclinical safety data* < Non-clinical studies have not been performed with Omegaflex special. > < Toxic effects of mixtures of nutrients given as substitution therapy at the recommended dosage are not to be expected. > <u>Other routine risk minimisation measures</u> Prescription only medicine	
Patients with diabetes mellitus and renal failure	<u>Proposed text in the SmPC:</u> *4.2 Posology and methods of administration* <u>Posology</u> < The dosage should be adapted to the patients' individual requirements. > < It is recommended that Omegaflex special be administered continuously. A stepwise increase of the infusion rate over the first 30 minutes up to the desired infusion rate avoids possible complications.> *Patients with renal/hepatic impairment* < The doses should be adjusted individually in patients with hepatic or renal insufficiency (see also section 4.4). > *4.3 Contraindications* • < hyperglycaemia not responding to insulin doses of up to 6 units insulin/hour > • < acidosis > • < severe renal insufficiency in absence of renal replacement therapy > • < unstable metabolic condition (e.g. severe postaggression syndrome, coma of unknown origin) > *4.4 Special warnings and precautions for use* *Patients with impaired lipid metabolism*	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
	< Omegaflex special should be administered cautiously to patients with disturbances of lipid metabolism with increased serum triglycerides, e.g. renal insufficiency, diabetes mellitus, pancreatitis, impaired hepatic function, hypothyroidism (with hypertriglyceridaemia), sepsis, and metabolic syndrome. If Omegaflex special is given to patients with these conditions, more frequent monitoring of serum triglycerides is necessary to assure triglyceride elimination and stable triglyceride levels below 11.4 mmol/l (1000 mg/dl). In combined hyperlipidaemias and in metabolic syndrome, triglyceride levels react to glucose, lipids and overnutrition. Adjust dose accordingly. Assess and monitor other lipid and glucose sources, and drugs interfering with their metabolism. > < Like all solutions containing carbohydrates, the administration of Omegaflex special can lead to hyperglycaemia. The blood glucose level should be monitored. If there is hyperglycaemia, the rate of infusion should be reduced or insulin should be administered. If the patient is receiving other intravenous glucose solutions concurrently, the amount of additionally administered glucose has to be taken into account. > < 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. > *Elderly patients* < Basically the same dosage as for adults applies, but caution should be exercised in patients suffering from further diseases like cardiac insufficiency or renal insufficiency that may frequently be associated with advanced age.> *Patients with diabetes mellitus, impaired cardiac or renal function* < Like all large-volume infusion solutions	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
	Omegaflex special should be administered with caution to patients with impaired cardiac or renal function. > < There is only limited experience of its use in patients with diabetes mellitus or renal failure. > *4.8 Undesirable effects* ***Metabolism and nutrition disorders*** < Very rare: Hyperlipidaemia, hyperglycaemia, metabolic acidosis, The frequency of these undesirable effects is dose-dependent and may be higher under the condition of absolute or relative lipid overdose. > *4.9 Overdose* *Symptoms of fluid and electrolyte overdose* < Hyperhydration, electrolyte imbalance and pulmonary oedema.> *Symptoms of glucose overdose* < Hyperglycaemia, glucosuria, dehydration, hyperosmolality, hyperglycaemic-hyperosmolar coma. > < *Treatment* Immediate cessation of infusion is indicated for overdose. Further therapeutic measures depend on the particular symptoms and their severity. When infusion is recommenced after the symptoms have declined, it is recommended that the infusion rate be raised gradually with monitoring at frequent intervals. > Other routine risk minimisation measures Prescription only medicine	
Paediatric patients	Proposed text in the SmPC: *4.1 Therapeutic indication* Omegaflex special is indicated in adults.	none proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		
	4.2 Posology and method of administration Posology *Paediatric population* < Omegaflex special is contraindicated in newborn infants, infants and toddlers < 2 years of age (see section 4.3). The safety and efficacy in children > 2 years have not been established yet. No data are available. > *4.3 Contraindication* < On account of its composition Omegaflex special must not be used in newborn infants, infants and toddlers under 2 years of age. > Other routine risk minimisation measures Prescription only medicine	

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. Omegaflex special is used to supply energy, essential FAs, amino acids, electrolytes and fluids for PN of patients. People of all ages receive PN. People can live well on PN for as long as it is needed.

Many hospitalised patients receive PN. 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 benefits

The standardised PN containing almost all compounds is suitable for most of the parenteral fed patients. The constituents of Omegaflex special, are generally established for medicinal use, and are acknowledged as being both efficient and safe. The combination chosen in Omegaflex special has positive effects on the body homeostasis.

The important objective of PN 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 PN regimen providing building blocks for protein synthesis and maintaining nitrogen balance (homeostasis). The amount of nitrogen administered during PN is crucial to reduce catabolism. The infusion of lipid emulsions allows a high energy supply and is indispensable for the supply of essential FAs, 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 FAs. Electrolytes administered with Omegaflex special 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 Omegaflex special.

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	• Omegaflex special must not be used in patients with known allergy to soy bean, egg, peanut or fish protein. • Previous allergic reactions to soybean, egg, peanut or fish or to any other substance should be reported to the physician before the beginning of the

Important identified risks		
Risk	**What is known**	**Preventability**
	fairly rare.	therapy.
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 amino acid metabolism usually present in infancy and early childhood. However in some rare cases it can present in adulthood e.g. when patients are exposed to increased protein intake or certain medications and 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. Omegaflex 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.	• Omegaflex 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 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,	• Recommended doses of Omegaflex special should not be exceeded. • Blood lipids have to be controlled and dosage adjusted as necessary. • Overnutrition must be avoided.

Important identified risks		
Risk	**What is known**	**Preventability**
	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.	
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 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.	• Omegaflex 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.
High blood sugar (Hyperglycaemia)	High blood sugar may occur as a result of a high rate of administration or impaired utilisation 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	• 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

Important identified risks		
Risk	**What is known**	**Preventability**
	may cumulate in the liver leading to the development of fatty liver. Omegaflex special contains glucose and its administration can lead to hyperglycaemia.	administration of Omegaflex 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.	• Omegaflex 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. Severe 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. 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	• 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. • Sufficient amounts of electrolytes must be administered together with Omegaflex special according to the patient's requirements.

Important identified risks		
Risk	**What is known**	**Preventability**
	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 Omegaflex special in pregnant women. Parenteral nutrition may become necessary during pregnancy. Omegaflex special should only be given to pregnant women after careful consideration. Components/metabolites of Omegaflex 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 ofthe use of Omegaflex special in patients with diabetes mellitus or renal failure. Like all large-volume infusion solutions, Omegaflex 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

Missing information	
	What is known
	administered glucose has to be taken into account.
Paediatric patients	Due to its composition (amino acid composition, the relation of the macronutrients) Omegaflex special is contraindicated in newborn infants, infants and toddlers under 2 years of age. Up to now there is no clinical experience with the use of Omegaflex special in children > 2 years and adolescents.

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 EU-RMP for Omegaflex special.