PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for PERIOLIMEL/OLIMEL

This is a summary of the risk management plan (RMP) for PERIOLIMEL/OLIMEL. The RMP provides details on the important risks of PERIOLIMEL/OLIMEL, and how these risks can be minimized.

The summary of product characteristics (SmPC) and package leaflet (PL) for PERIOLIMEL/OLIMEL provide essential information to healthcare professionals and patients on how PERIOLIMEL/OLIMEL should be used.

Important new safety concerns and/or changes to the current safety concerns will be included in future updates of the RMP.

I. The medicine and what it is used for

PERIOLIMEL/OLIMEL is authorized for parenteral nutrition (PN) for adults and children greater than 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated; refer to the SmPC for complete indication wording. PERIOLIMEL/OLIMEL is given intravenously (IV), and it contains the following active substances:

Amino acid chamber: alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine (with or without sodium acetate trihydrate), sodium glycerophosphate hydrated, potassium chloride, magnesium chloride hexahydrate)

Glucose chamber: glucose monohydrate (with or without calcium chloride dihydrate)

Lipid chamber: refined olive oil and refined soya-bean oil

II. Risks associated with the medicine and activities to minimize or further characterize the risks

The important risks of PERIOLIMEL/OLIMEL, together with measures to minimize such risks and the activities performed in order to learn more about PERIOLIMEL/OLIMEL's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

- Important advice on the medicine's packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status – the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

The important risks of PERIOLIMEL/OLIMEL are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PERIOLIMEL/OLIMEL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine). The important risks and missing information for PERIOLIMEL/OLIMEL are listed in the table below.

Important identified risks	Severe infusion site reactions due to peripheral IV administration of an OLIMEL formulation indicated only for central IV administration
	Metabolic abnormalities due to incorrect drug administration rate
	Metabolic/electrolyte abnormalities, hypoglycemia due to failure to mix compartments of the triple chamber bag
Important potential risks	None
Missing information	None

II.B Summary of important risks and missing information

Severe infusion site reactions due to peripheral IV administration of an OLIMEL formulation indicated only for central IV administration	
Evidence for linking the risk to the medicine	Evidence source: medical literature and post-marketing reports. PERIOLIMEL N4E is indicated for either peripheral or central IV infusion, while the remaining OLIMEL formulations are indicated only for central IV infusion. Due to these differences in routes of administration, the possibility of peripheral IV administration of an OLIMEL formulation indicated only for central IV administration cannot be excluded; this can potentially result in AEs associated with administration of hypertonic solutions in a peripheral vein. The level of excess osmolarity of infusion solutions compared to serum osmolarity is considered one of the factors determining the risk of venous irritation and phlebitis associated with the administration of PN solutions (Bier 2000). As documented in medical literature, extravasation is a well-recognized occurrence associated with IV infusion of hypertonic solutions (Maki 1991, Wilkins 2004). Post-marketing reports of incorrect route of administration of PERIOLIMEL/OLIMEL associated with severe infusion site reactions have been received.
Risk factors and risk groups	Patients receiving PN treatment.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC sections 4.2 and 4.4. Adverse reactions representing severe infusion site reactions are listed in section 4.8 of SmPC. Discussed in PL section 2. Adverse reactions representing severe infusion site reactions are listed in section 4 of the PL. User Guide containing routine risk communication on proper drug preparation and administration, aligned to SmPC and PL. **Additional risk minimization measures:** None proposed.

Metabolic abnormalities due to incorrect drug administration rate	
Evidence for linking the risk to the medicine	Evidence source: medical literature and post-marketing reports. As with any PN solution, risk of an incorrect rate of administration cannot be excluded; this may result in AEs associated with administration of inadequate nutrients for the patient's needs. As documented in medical literature, medication errors associated with PN

	administration have been reported, particularly during the administration process (Sacks 2009). Post-marketing reports of metabolic abnormalities due to incorrect rate of administration of PERIOLIMEL/OLIMEL have been received.
Risk factors and risk groups	Patients receiving PN treatment.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC sections 4.2, 4.4 and 4.9. Discussed in PL section 3 and Part B. User Guide containing routine risk communication on proper drug preparation and administration, aligned to SmPC and PL. **Additional risk minimization measures:** None proposed.

Metabolic/electrolyte abnormalities, hypoglycemia due to failure to mix compartments of the triple chamber bag	
Evidence for linking the risk to the medicine	Evidence source: medical literature and post-marketing reports. PERIOLIMEL/OLIMEL is presented in a triple chamber bag, with the three compartments separated by non-permanent seals. Immediately prior to administration, manual pressure is used to break the seals, creating a homogenous solution. Non-activation or incomplete activation of the seals separating the chambers of the PERIOLIMEL/OLIMEL bag can result in the patient receiving only the compartment of the product containing amino acids and electrolytes, omitting the complete infusion of the glucose and/or lipid compartments. As documented in medical literature, medication errors associated with PN administration have been reported, particularly during the administration process (Sacks 2009). Reports of failure to mix compartments of the triple chamber bag have been received for PERIOLIMEL/OLIMEL in the post-marketing setting.
Risk factors and risk groups	Patients receiving PN treatment.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC sections 4.4 and 6.6. Discussed in PL section 2 and Part D. User Guide containing routine risk communication on proper drug preparation and administration, aligned to SmPC and PL. **Additional risk minimization measures:** None proposed.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligations of PERIOLIMEL/OLIMEL.

II.C.2 Other studies in post-authorization development plan

There are no studies required for PERIOLIMEL/OLIMEL.