LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pedismof Preterm, Pedismof Infant, Pedismof

(isoleucine, serine, histidine, threonine, lysine acetate, sodium glycerophosphate, anhydrous, magnesium sulfate heptahydrate, zinc sulfate heptahydrate, valine, proline, potassium chloride, fish oil, rich in omega-3-acids, alanine, zinc sulfate anhydrous, lysine, leucine, tyrosine, calcium chloride dihydrate, tryptophan, calcium chloride anhydrous, sodium acetate anhydrous, olive oil, refined, soya-bean oil, refined, methionine, phenylalanine, sodium acetate trihydrate, magnesium sulfate, anhydrous, arginine, glucose (anhydrous), triglycerides, medium-chain, glucose monohydrate, glycine, taurine)

SE/H/2430/01-03/DC

This module reflects the scientific discussion for the approval of Pedismof Preterm, Pedismof Infant, Pedismof. The procedure was finalised on 2025-06-26. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Pedismof Preterm, Pedismof Infant, Pedismof, Emulsion for infusion.

The active substance is aspartic acid, sodium glycerophosphate, anhydrous, tryptophan, lysine, phenylalanine, alanine, histidine, magnesium sulfate, anhydrous, calcium gluconate (monohydrate), methionine, soya-bean oil, refined, leucine, serine, isoleucine, magnesium sulfate heptahydrate, fish oil, rich in omega-3-acids, sodium glycerophosphate, hydrated, taurine, potassium chloride, olive oil, refined, valine, calcium gluconate, anhydrous, glutamic acid, arginine, proline, threonine, cysteine, glucose (anhydrous), glucose monohydrate, glycine, triglycerides, medium-chain, tyrosine, lysine monohydrate, sodium acetate trihydrate, sodium acetate anhydrous. A comprehensive description of the indication and posology is given in the Summary of product characteristics (SmPC).

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Pedismof Preterm, Pedismof Infant, Pedismof, Emulsion for infusion, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IS, IT, LT, LV, NL, NO, PL, PT, RO, SI, SK as concerned member states (CMS).

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Potential similarity with orphan medicinal products
N/A.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
The product is composed of glucose, lipids, amino acids, and electrolytes intended to be used for nutrition. Pharmacodynamic, pharmacokinetic and toxicological properties of these are well known. As these nutrients are widely used, well-known substances, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
The components in all three Pedismof solutions are naturally occurring natural substances the use will not alter the concentration or distribution of the substances in the environment. Therefore, Pedismof is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
There are no clinical pharmacokinetics (PK) data generated for Pedismof, and this WEU application is supported only by literature references. The Applicant has presented several literature references in the Summary of Clinical Pharmacology to describe distribution and elimination of lipids, amino acids and carbohydrates. In addition, a review of electrolyte metabolism in paediatric patients is also included by the Applicant. The product contains only nutrients/endogenous compounds.

Overall, the absence of clinical PK data together with the presented literature references are considered acceptable. Information provided by the Applicant is sufficient to support proposed SmPC claims in 5.2 PK section.

Pharmacodynamics
The primary innovation is the use of a balanced lipid emulsion, Smoflipid, composed of soybean oil (SO), medium-chain triglycerides (MCT), olive oil (OO), and fish oil (FO). The known properties of these lipid components and their relevance to growth, development, and serum lipid profile in paediatric populations are presented. The document compares the effects of pure SO-based emulsions with balanced combinations (SO, MCT, OO, FO) in the context of parenteral nutrition (PN).

Risk factors, development, symptoms and treatment of essential fatty acid deficiency (EFAD) are described. Long term benefit of mixed LE supplementation in preterm neonates with regard to EFAD is shown in small studies and it is in accordance with the current clinical widely accepted recommendations. It is considered approved from the RMS perspective.

Soybean Oil (SO) and medium chain triglycerides (MCTs)
SO is a traditional lipid source, rich in long-chain triglycerides (LCTs). MCT/LCT (1:1) emulsions, or those with ≤50% MCT, improve energy utilisation compared to LCT alone, it is described in various target patient categories in the adult population. Evidence from small studies supports improved energy delivery in all paediatric subgroups, including Preterm neonates (2 g/kg/day), Infants/Neonates (up to 3–4 g/kg/day), Children aged 2–6 years (up to 1.5 g/kg/day), Children/adolescents aged 1.5–17

years (up to 2.5 g/kg/day). In preterm neonates (gestational age 25–37 weeks), MCT/LCT emulsions may also reduce β-oxidation of EFAs and long-chain polyunsaturated fatty acids (LC-PUFAs).

Olive Oil (OO)

Olive oil provides a high content of monounsaturated fatty acids (MUFAs), which are less susceptible to lipid peroxidation compared to polyunsaturated fatty acids (PUFAs). The use of OO in parenteral nutrition (PN) supports membrane integrity and reduces oxidative stress. MUFAs are not essential fatty acids but serve as a stable energy source and help modulate the structural and functional properties of cell membranes.
A 4:1 mixture of SO:OO has demonstrated clinical benefits comparable to pure SO-based emulsions in both extremely preterm (<28 weeks) and preterm neonates (28–37 weeks). These benefits include maintenance of essential fatty acid status and improved antioxidant profiles, as indicated by higher α-tocopherol/total lipid and α-tocopherol/cholesterol ratios.
In broader paediatric populations, OO-based emulsions were well tolerated, maintained normal EFAD markers, and may offer superior protection against lipid peroxidation compared to SO-based emulsions. Theoretical considerations regarding the role of fatty acid saturation in modulating immune function are discussed, though conclusive clinical evidence is not presented.

Fish Oil (FO)

The immunomodulatory components of FO are outlined, including mechanisms observed in vitro and in animal models, particularly concerning inflammation and membrane fluidity. The applicant discusses the roles of arachidonic acid (AA) and docosahexaenoic acid (DHA) in brain and retinal development during late gestation and early neonatal life. The impact on neurodevelopmental outcomes is theoretically supported by preclinical and human data.

Amino Acids solution

The general importance of amin acids, its properties and substitution with regard to definitions of amino acid requirements; available techniques to assess requirements; recommendations; factors influencing requirements and requirements in acute and chronic wasting diseases are described. Conditionally essential amino acids, in the paediatric population, with emphasis on cystein and the amino acid-like substance taurine.

Glucose

Glucose is the obligate energy source for the brain, renal medulla, and erythrocytes and during foetal life it is the main source of energy. During the last trimester approximately 5 mg/kg/min (7 g/kg/d) glucose cross the placenta. It is the main source of energy and accounts for a major part of the osmolarity in PN solutions. Total osmolality is sufficiently addressed in the SmPC.

Electrolytes (for Pedismof Infant and Pedismof)

The electrolytes are well known.

Conclusion

From the RMS perspective the basic pharmacodynamics for the content of 3CB and 2CB Pedismof Preterm, Pedismof Infant and Pedismof respectively is considered sufficiently described.

Clinical efficacy

Literature search Study population

The applicant's categorisation of studies based on comparator type is considered adequate and acceptable. Studies involving amino acids other than Vaminolact or similar are regarded as supportive; all others are classified as main studies. Limited findings on glucose and electrolytes are noted and accepted from the RMS perspective. The decision not to perform an integrated pooled analysis is acknowledged, as is the chosen format for data presentation.
The study population is adequately described and reflects the intended target group. In total, data from 5044 paediatric patients were included across the referenced publications, comprising 3899 preterm neonates, 137 term neonates, and 1008 children across various age groups, to support the clinical

efficacy of all three 3CB Pedismof solutions.

Efficacy
Anthropometric parameters indicate acceptable growth, organ development, and overall maturation, comparable to reference comparators and consistent with expected age-related outcomes. Short-term variations in lipid and amino acid profiles, as well as nitrogen balance, are appropriately correlated with the dose and composition of the administered lipid emulsions and amino acid solutions.

Dose studies
The primary components of Smoflipid, Vaminolact, carbohydrates, and fluid volumes fall within clinical recommendation dosage ranges across all paediatric subgroups, including preterm and term neonates, as presented in the application. Electrolyte content is not addressed in Pedismof Preterm, as electrolytes are not part of its formulation. In Pedismof Infant and Pedismof, individual component doses align with, or are close to, established clinical guideline recommendations. Minor deviations are acknowledged and addressed in the Summary of Product Characteristics Section 4.2.

Methods
The studied population is clinically heterogeneous, varying in age, weight, physiological status, and comorbid conditions. Additionally, differences in levels of care, regional treatment practices, complication rates, and time-point comparisons may influence clinical outcomes. The applicant has adequately described the majority of these variables. Study objectives, outcome measures/endpoints, and statistical methodologies are clearly presented and appropriate. While limitations in sample size and randomisation are noted in individual studies, the overall dataset provides a sufficiently robust and comprehensive assessment of the intervention.

Conclusion Clinical Efficacy
Recruitment strategies and study conduct differ across the included studies but are generally well documented by the applicant. Baseline characteristics, sample sizes, statistical analyses, and outcomes are presented in sufficient detail. Overall, the evidence demonstrates that all three Pedismof solutions supports appropriate growth and developmental maturation across the studied paediatric age groups.

The applicant has not provided a dedicated analysis for the most vulnerable subpopulations—specifically, extremely premature neonates, neonates with extremely low birth weight, or those classified as small for gestational age. Given known pharmacokinetic and physiological distinctions in these groups, clinically relevant variability cannot be excluded. Nevertheless, the data submitted are considered sufficiently detailed to guide informed clinical use by healthcare professionals experienced in managing this vulnerable patient group.

Clinical safety
A total of more than 6,500 paediatric patients received treatment with Smoflipid, Vaminolact, or their combination. This included over 5,000 preterm neonates, between one and two hundred term neonates, and almost a thousand paediatric patients across various age groups. Due to heterogeneity in the definitions of adverse events (AEs) and overall safety outcomes across the included publications, a pooled safety analysis was not conducted.

The applicant identified and summarised over 50 studies involving the use of Smoflipid, and 20 studies involving Vaminolact or comparable amino acid solutions in paediatric populations.

The published studies included patients from all paediatric age categories. The majority of study populations consisted of preterm neonates, which aligns with clinical practice, where parenteral nutrition (PN) is most commonly used in neonatal care. Due to inconsistent reporting across studies, it was not possible to quantify the exact number of patients within each paediatric age subgroup.

The main clinical indications for PN included prematurity, gastrointestinal disorders, and surgical interventions. In neonatal populations, PN is typically administered until sufficient enteral or oral intake is established, with discontinuation usually occurring within 2 to 4 weeks. In contrast, older paediatric patients often require prolonged PN due to chronic underlying conditions.

Comparator solutions' lipid and amino acid compositions are described. They should be assessed together with primary pharmacology for lipids and amino acids, in particular content of cystein and, taurine for neonates and preterm neonates and essential amino acids.

Although dose regimens and treatment durations vary across studies, they are adequately described and summarised by the applicant. Relevant data and comparisons are presented, with detailed discussion.

Adverse events
Clinical outcomes, including adverse events (AEs) and neonatal morbidities, were assessed across the published studies. A summary of commonly reported AEs is provided, maintaining the same stratification by type of parenteral nutrition (PN) and age group as outlined previously.

In neonatal studies, reported AEs were consistent with the expected clinical profile of preterm populations and primarily reflected complications associated with prematurity, such as necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and patent ductus arteriosus (PDA). In contrast, in older paediatric patients, AEs were predominantly related to the underlying medical conditions or to PN administration in general.

The applicant concludes that the overall incidence of AEs was comparable between treatment groups. However, patients receiving Smoflipid generally exhibited a lower frequency of neonatal morbidities and AEs compared to comparator groups, with the exception of late-onset sepsis, which was reported more frequently in Smoflipid-treated patients.

Mortality
Mortality outcomes were reported in more than 40 studies. Overall, the reported mortality rate was low and comparable across treatment groups. No deaths were attributed to the study treatment in any of the included studies.

Laboratory
Laboratory parameters are discussed individually for each study by the applicant. In several studies, direct bilirubin (dBil) levels were lower in the Smoflipid-treated groups compared to controls, while a few studies reported higher cholesterol levels in patients receiving Smoflipid.
Electrolyte disturbances were commonly observed across studies; however, due to inconsistent reporting and heterogeneous study designs, the overall frequency could not be reliably quantified across all paediatric age groups. Additionally, the composition of electrolytes in the proposed solution for the youngest age group is not representative.

Intrinsic Patient Factors:
Parenteral nutrition (PN) should be used with caution in patients presenting with renal impairment, cardiovascular disorders, hepatobiliary dysfunction, or other unstable clinical states. Close monitoring of fluid balance, electrolyte levels, and organ function parameters is recommended, as appropriate for the individual patient's condition. Significant abnormalities, including fluid, electrolyte, or metabolic imbalances, should be corrected prior to initiation of PN. These precautions are appropriately reflected in the Summary of Product Characteristics, section 4.4.

Excess of fat, amino acid solution and glucose substitution
Fat overload syndrome is a rare but recognised complication, resulting from excessive lipid accumulation in the serum and/or impaired lipid metabolism. It is characterised by hyperlipidaemia,

fever, hepatomegaly, anaemia, leukopenia, thrombocytopenia, coagulopathy, abnormal liver function tests, and in severe cases, coma. These symptoms are typically reversible upon discontinuation of lipid infusion. The condition is most commonly observed when lipid doses or infusion rates exceed recommended levels or in the context of altered metabolic capacity due to changes in clinical status.

Exceeding the recommended infusion rate of amino acids may lead to adverse effects such as shivering, nausea, vomiting, and sweating. In some cases, this may be associated with impaired renal function, evidenced by elevated nitrogenous waste products (e.g., creatinine, urea). Infusion should be stopped immediately if such reactions occur. Reinitiation at a reduced dosage or rate may be considered, depending on the clinical situation.

Hyperglycaemia, defined as blood glucose >8 mmol/L (145 mg/dL), should be avoided in neonatal and paediatric intensive care settings. Glucose infusion rates should be adjusted accordingly, and insulin therapy initiated as required. Close monitoring, particularly in the postoperative period, is essential. It is noted that neonates generally recover from hyperglycaemic episodes more rapidly than adult postoperative patients.

Refeeding syndrome is a potentially life-threatening condition that may occur in malnourished or metabolically stressed patients upon the initiation of nutritional support. It is characterised by profound shifts in fluid and electrolyte balance, most notably hypophosphataemia. Other common features include hypokalaemia, hypomagnesaemia, thiamine deficiency, disturbances in sodium and fluid homeostasis, and alterations in glucose, protein, and fat metabolism. While well documented in adult populations, refeeding syndrome is less clearly defined in neonates.
In preterm neonates, the risk of refeeding syndrome may be mitigated by ensuring an adequate supply of calcium and phosphate and by initiating parenteral nutrition (PN) gradually. Close monitoring of fluid and electrolyte status is essential during the initiation and progression of nutritional therapy.

Relevant warnings and guidance on management of fat overload, amino acid overdose, and hyperglycaemia are included in sections 4.4, 4.8, and 4.9 of the proposed SmPC.

Extrinsic factors
When used in neonates and children below 2 years of age, the solution should be protected from light exposure until administration is completed. Especially after admixture with trace elements and/or vitamins, due to generation of peroxides and degradation products. This is reflected in the SmPC.

Drug-drug Interactions
Drug–drug interactions are adequately addressed, cross referenced and presented in proper order in the SmPC.

Effect on fertility, pregnancy and breastfeeding
The product contains glucose, amino acids, and lipids; based on the nature of these components, adverse effects on fertility are considered unlikely. Adequate nutritional support is essential for normal reproductive function. PN during pregnancy is typically reserved for cases such as hyperemesis gravidarum, where prolonged nutritional deficiency, weight loss, and fluid or electrolyte imbalance may pose risks to both mother and foetus. Clinical use of PN in such settings has been associated with reduced perinatal morbidity. The information provided in section 4.6 of the SmPC is considered appropriate and acceptable.

Conclusion Clinical Safety
The totality of clinical safety data from published studies supports the favourable safety profile of Smoflipid and Vaminolact in the paediatric population, including preterm and term neonates.
Identified risks are consistent with the underlying clinical conditions and expected effects of parenteral nutrition components. Adequate monitoring and risk mitigation strategies, as reflected in the SmPC, ensure safe use in clinical practice.
The benefit-risk balance is considered positive for the intended patient groups when administered

according to the recommended dosing and precautions.

Risk Management Plan
The MAH has submitted a risk management plan, version 0.1, with DLP 01-Aug-2023, signed 28-Sep-2023 in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pedismof Preterm, Pedismof Infant and Pedismof.

Part II Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Part III Pharmacovigilance Plan
Routine pharmacovigilance and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The submitted Risk Management Plan, Pedismof Preterm, Pedismof Infant, Pedismof RMP version 0.1, with DLP01-Aug-2023, signed 28-Sep-2023 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted: At the request of the RMS; Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

Pedismof
The package leaflet of Pedismof has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

Pedismof Infant

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Pedismof (SE/H/2430/03/DC). The bridging report submitted by the applicant has been found acceptable.

Pedismof Preterm
A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Pedismof (SE/H/2430/03/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The clinical efficacy of Pedismof Preterm, Pedismof Infant, and Pedismof is supported by data from > 5.000 paediatric patients, including almost 4.000 preterm neonates, between one and two hundred term neonates, and around 1.000 older children. The applicant’s classification of studies and decision not to pool data are accepted. Anthropometric and biochemical endpoints consistently demonstrate age-appropriate growth and developmental outcomes across treatment groups. Dosing regimens of Smoflipid and Vaminolact, as well as carbohydrate and fluid volumes, align with established clinical guidelines, with acknowledged deviations appropriately addressed in the SmPC. Although extremely premature and small-for-gestational-age neonates were not analysed separately, the available evidence supports informed clinical use by experienced professionals.

Safety data more than 6,500 paediatric patients (including over 5,000 preterm neonates, between one and two hundred term neonates, and around one thousand paediatric patients across various age groups) reveal no new safety signals. Adverse events were consistent with the expected morbidity profile of the respective age groups, and no treatment-related mortality was reported. Late-onset sepsis was observed more frequently in Smoflipid-treated neonates in isolated cases, though no consistent pattern of increased risk was established. Laboratory data indicate occasional elevations in cholesterol with common but variably reported electrolyte disturbances. Identified risks such as fat overload syndrome, amino acid overdose, hyperglycaemia, and refeeding syndrome are rare, manageable, and appropriately addressed in the SmPC. Use in high-risk subpopulations requires enhanced clinical monitoring.

The overall benefit–risk balance is considered positive for all intended paediatric subgroups, including preterm and term neonates, when Pedismof is used in accordance with the recommended dosing, monitoring, and precautions outlined in the SmPC

The applicant's pharmacovigilance system is deemed acceptable.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A.

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A.

VII. APPROVAL

The decentralised procedure for Pedismof Preterm, Pedismof Infant, Pedismof, Emulsion for infusion was positively finalised on 2025-06-26.

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SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se