LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

SmofKabiven Low Osmo Peripheral

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

SE/H/861/02/DC

This module reflects the scientific discussion for the approval of SmofKabiven Low Osmo Peripheral. The procedure was finalised on 2018-10-10. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Fresenius Kabi AB has applied for a marketing authorisation for SmofKabiven Low Osmo Peripheral, emulsion for infusion. The active substances, see above, are the same as in SmofKabiven Perifer, emulsion for infusion (SE/H/861/01), marketed by Fresenius Kabi AB since 2007.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

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 present application concerns an extension application of the previously authorised product SmofKabiven Peripheral (SE/H/0862/001/MR). From a non-clinical perspective there are no changes to the products that would warrant new or additional data, and no such data of value for the assessment has been submitted.

Environmental Risk Assessment (ERA)
The applicant has not performed an ERA. The product is composed of vitamins, electrolytes, amino acids, carbohydrates, and lipids. In addition, the levels of the constituents are in the same range as in the previously authorised product SmofKabiven Peripheral (SE/H/0862/001/MR). Thus, no increased exposure to the environment is expected.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

N/A

IV.2 Pharmacodynamics

No data on pharmacodynamic properties of SmofKabiven Low Osmo Peripheral is available. PD data on the individual components, i.e. SMOFlipid 20%, Aminoven 10% with or without electrolytes, and Glucose 11.8% described by the applicant is considered acceptable provided that the new formulation of the products are line extensions to the existing approved SmofKabiven product range and the active substances of the products have been in well-established medicinal use.

IV.3 Clinical efficacy

The efficacy claim for 3CB SMOF LO is based on the evidence available for the nutritional efficacy of its individual components. The extensive experience of clinical use in PN with the individual compounds (lipids, amino acids, glucose, and electrolytes) and their combination is considered adequately documented in the clinical overview presented by the Applicant. In general, the effects of all components of SmofKabiven Low Osmo Peripheral and their combination are considered well known and generally established for clinical use.

The proposed dose and infusion rate for 3CB SMOF LO are primarily based on the data from clinical studies and post marketing data for SmofKabiven as well as the evidence relating to the components of SmofKabiven taking into account the similarities and differences in the composition between 3CB SMOF LO and its parent product SmofKabiven Peripheral.

The proposed dosage for adults and children of 3CB SMOF LO is considered as adequately justified in relation to nutritional requirements of adult and children patients in the proposed therapeutic indication. The dose should be individualised to the patient’s clinical condition, body weight (bw), nutritional and energy requirements, adjusting dosage based upon additional oral/enteral intake, which is adequately reflected in the SmPC section 4.2.

The applicant has discussed the rational for the line extension in relation to guideline recommendations discussed in the publications. Although guidelines by themselves cannot be considered as sufficient scientific evidence, based on the literature data, it is agreed that low osmolarity PN product has clinical utility as a therapeutic option to reduce possible infusion site reactions and thrombophlebitis during peripheral infusion. In general, the clinical utility of 3CB SMOF with the low osmolarity designed for peripheral use is considered sufficiently justified.

IV.4 Clinical safety

No additional studies have been conducted for 3CB SMOF LO. Maximum doses of the single components are within the limits of already registered products (i.e. SmofKabiven products, SMOFlipid 20%, and Aminoven 10%). The safety and tolerability claims for 3CB SMOF LO are made on the basis of the data available for the products of SmofKabiven, SmofKabiven Peripheral, Aminoven 10%, and SMOFlipid 20%.

The safety and tolerability of SmofKabiven and SmofKabiven Peripheral have been evaluated in six studies performed in adult patients, studies 03-3CB7-001, 03-3CB8-001, SMKV-008-CP3, SMKV-009-CP3, 00-3CB4-001 and AS-CS-01-FR. Post marketing data for SmofKabiven Peripheral, StructoKabiven and the individual already-marketed component Aminoven 10%, were also reviewed.

No new safety information is identified. Post marketing safety data from patients receiving doses within the limits specified in the respective SmPCs have not revealed any safety concerns related to dosing of either SmofKabiven or Aminoven 10%. There is no reason to believe that the safety profile of this line extension should be different compared to other marketed products of the class.

IV.5 Risk Management Plans

The MAH has submitted a risk management plan, 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 SmofKabiven Low Osmo Peripheral.

<u>The proposed Safety specification in RMP</u>

Table- 1 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Metabolic/electrolytes abnormalities
Important potential risk	• Refeeding syndrome
Missing information	• Use in pregnant and lactating women • Use in newborns or infants below 2 years of age

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

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

Summary of the RMP
The submitted Risk Management Plan 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

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 the user test of the SmofKabiven Perifer emulsion for infusion leaflet which was assessed and accepted in SE/H/861/01/MR. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present application concerns an extension application of the previously authorised product SmofKabiven Peripheral. SmofKabiven Low Osmo Peripheral were developed using identical active ingredients and excipients as those included in SmofKabiven Peripheral. The formulation of 3CB SMOF LO is formulated with an osmolarity of approximately 750mosmol/L by aiming to reduce possible complications during peripheral infusion. The extensive experience of clinical use in PN with the individual compounds (amino acids, lipids, glucose, and electrolytes) and their combination is considered adequately documented in the clinical overview. The applicant refers to post marketing experience available from other SmofKabiven products as marketed by the MAH, according to which the medicinal product is considered to be safe and effective with a positive benefit-risk ratio. In general, the effects of all components of SmofKabiven Low Osmo Peripheral and their combination are considered well known and generally established for clinical use. There is no reason to believe that the safety profile of this line extension should be different compared to other marketed products of the class.

To conclude, the benefit risk relation is considered favourable. The product information is acceptable. The application for SmofKabiven Low Osmo Peripheral is therefore recommended for approval.

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

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

VII. APPROVAL

The Decentralised procedure for SmofKabiven Low Osmo Peripheral, emulsion for infusion was positively finalised on 2018-10-10.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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