LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Nutriflex Omega 56/144/40 elektrolytfri

Active substances:

(Glucose monohydrate, Soya-bean oil, refined, Medium-chain triglycerides, Omega-3-acid triglycerides, Isoleucine, Leucine, Lysine monohydrate, Methionine, Phenylalanine, Threonine, Tryptophan, Valine, Arginine, Histidine, Alanine, Aspartic acid, Glutamic acid, Glycine, Proline, Serine)

SE/H/1414/01/DC

This module reflects the scientific discussion for the approval of Nutriflex Omega 56/144/40 elektrolytfri. The procedure was finalised on 2016-06-13. 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.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

B. Braun Melsungen AG has applied for a marketing authorisation for Nutriflex Omega 56/144/40 elektrolytfri, emulsion for infusion. The active substances are Glucose monohydrate, Soya-bean oil, refined, Medium-chain triglycerides, Omega-3-acid triglycerides, Isoleucine, Leucine, Lysine monohydrate, Methionine, Phenylalanine, Threonine, Tryptophan, Valine, Arginine, Histidine, Alanine, Aspartic acid, Glutamic acid, Glycine, Proline, Serine.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 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 structures of the drug substances have been adequately proven and their physico-chemical properties are sufficiently described.

The manufactures of the drug substances have been adequately described and satisfactory specifications have been provided.

The drug substance specifications include 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

III.1 Pharmacology

All constituents of Nutriflex Omega 56/144/40 elektrolytfri are the same as found in already approved products. The pharmacology of lipid emulsions in parenteral nutrition in general and the pharmacology of fish oil are already well known from published literature. The pharmacology of Glucose, commonly used for caloric replacement, and amino acids, used to limit nitrogen losses or to treat a negative nitrogen balance, in parenteral nutrition is also well established.

No new pharmacology studies have been conducted and the Applicant refers to published literature and clinical experience with similar products. The absence of new primary and secondary pharmacology studies, safety pharmacology and pharmacodynamic drug interaction studies is considered acceptable.

III.2 Pharmacokinetics

Pharmacokinetics of Glucose, amino acids, and lipids provided by Nutriflex Omega 56/144/40 elektrolytfri is well known and the components are expected to undergo essentially the same metabolism as substrates ingested by diet. The information provided in the Non-Clinical Overview is considered sufficient.

III.3 Toxicology

The safety profile of glucose, amino acids and mixtures of MCTs and LCTs derived from soybean oil is well established and no new toxicological studies have been performed. The information provided in the Non-clinical Overview is considered sufficient, especially considering the nature of the active substances contained in Nutriflex Omega 56/144/40 elektrolytfri and the extensive clinical experience with similar medicinal products.

III.4 Ecotoxicity/environmental risk assessment

The components of Nutriflex Omega 56/144/40 elektrolytfri are unlikely to result in any significant risk to the environment.

III.5 Discussion on the non-clinical aspects

The non-clinical data on Nutriflex Omega 56/144/40 elektrolytfri is judged to be sufficient.

IV. CLINICAL ASPECTS

IV.1 Introduction

The basis for “Nutriflex Omega 56/144/40 elektrolytfri” concerns a further development of the already approved medicinal product “Nutriflex Lipid special elektrolytfri” in that 10% of the fat component is replaced by OAT. This is obtained by replacing 20% of the LCT fraction, i.e. soybean oil, by fish oil.

IV.2 Clinical efficacy

In general, all constituents of “Nutriflex Omega 56/144/40 elektrolytfri” are claimed to be generally established for medicinal use. The extensive experience of clinical use in PN with the individual compounds (lipids, amino acids, glucose and fluid) and their combination is adequately documented in the clinical overview presented by the Applicant.

The proposed dosage for adults of ”Nutriflex Omega 56/144/40 elektrolytfri” is adequate to cover the daily nutritional requirements of adult patients according to the proposed therapeutic indication.

However, concerning the use of OAT in PN in children and adolescents, the safety and efficacy in children and adolescents has not been established. Therefore, the proposed indication for use in children aged 2 to 14 years and adolescents were not approvable and subsequently the Applicant has withdrawn this indication.

IV.3 Clinical safety

“Nutriflex Omega 56/144/40 elektrolytfri” is composed of well-known constituents which are well-established in clinical use for PN. Accordingly, there is extensive experience concerning safety of the individual components and their combination. Furthermore, the Applicant refers to post marketing experience available from the other OAT containing emulsions for infusion marketed by the MAH, according to which these medicinal products are considered to be safe and effective with a positive benefit-risk ratio. There is no reason to believe that the safety profile of the applied product should be different.

Safety and efficacy in children over 2 years of age and adolescents has not been established.

IV.4 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 Nutriflex Omega 56/144/40 elektrolytfri.

Safety specification

Risk Management Plan

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

Summary of the RMP

The RMP is approved.

V. USER CONSULTATION

The package leaflet 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 PIL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clinical aspects

Concerning use of Nutriflex Omega 56/144/40 elektrolytfri in the adult population according to the indication, the benefit risk ratio is considered positive.

The initial application included a paediatric indication. As the safety and efficacy in children and adolescents has not been established, the Applicant has withdrawn this indication during this procedure.

Overall conclusion
The quality of the product, Nutriflex Omega 56/144/40 elektrolytfri, is found adequate. There are no objections to approval of Nutriflex Omega 56/144/40 elektrolytfri, from a non-clinical and clinical point of view.
The product information is acceptable.

The application is therefore recommended for approval.

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

Quality: The applicant commits to test the first 3 commercial scale batches for levels of aluminium and to present and discuss the results, as well as to test 3 commercial batches manufactured after each change that may impact the aluminium levels.

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

N/A

VII. APPROVAL

The Decentralised procedure for Nutriflex Omega 56/144/40 elektrolytfri, emulsion for infusion was positively finalised on 2016-06-13.

LÄKEMEDELSVERKET
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
SE/H/1414/II/20/G	The age group 2-18 years is added in 4.1. Dosage recommendation in the SmPC Chapter 4 is in agreement with the current clinical knowledge based on the joint 2018 guidelines on paediatric parenteral nutrition by the ESPGHAN/ESPEN/ESPR/CSPEN international clinical societies (abbreviated ESPEN 2018 in this document). The update contains more specific recommendations, including stage of illness: acute, stable and recovery phase, in the affected age group. The age intervals for dose	Yes	2024.01.19	Approval	The proposed posology in children and adults 2-18 years is in agreement with current knowledge and the joint 2018 guidelines on paediatric parenteral nutrition by the ESPGHAN/ESPEN/ESPR/CSPEN international clinical societies. Updates are performed in the SmPC, sections 4 and 6. Scientific support for efficacy and safety in the proposed age group, 2-18 years, is sparse. However, evidence for efficacy of adequate nutrition in general is robust. The applicant has provided a clinical overview and no safety concerns can be observed in the provided data to expect a compromised benefit-risk ratio for the proposed lipid composition compared to standard lipid profile. This is in line with two previously EMA authorised PN solutions 20% composite ILEs which include FO as well as other oils have been marketed in Europe for the proposed age group (Vlaardingerbroek H, van Goudoever JB. Intravenous lipids in

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.mpa.se E-mail: registrator@mpa.se

	recommendations are adjusted to EMEA guidelines. Dose recommendations for intradialytic parenteral nutrition (IDPN) are added in the SmPC Chapter 4, section 4.2.				preterm infants: impact on laboratory and clinical outcomes and long-term consequences. World Rev Nutr Diet 2015; 112:71-80.) The level of evidence is considered low. The benefit-risk assessment is favourable. No conditions to the Marketing authorisation are applicable.

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