LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Quatriga extra Nitrogen

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

Quatriga extra Nitrogen Electrolyte free

(alanine, arginine, glycine, histadine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, glucose monohydrate, soya-bean oil refined, triglycerides medium chain, olive oil refined, fish oil rich in omega-3-acids)

SE/H/841/03-04/DC

This module reflects the scientific discussion for the approval of Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free. The procedure was finalised on 2018-09-18. 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

Fresenius Kabi AB has applied for a marketing authorisation for

Quatriga extra Nitrogen, emulsion and Quatriga extra Nitrogen Electrolyte free
The active substances
(alanine, arginine, glycine, histidine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride dehydrate, sodium glycerophosphate hydrate, magnesium sulfate heptahydrate, potassium chloride, sodium acetate trihydrate, zinc sulphate heptahydrate, glucose monohydrate, soya-bean oil refined, triglycerides medium chain, olive oil refined, fish oil rich in omega-3-acids), and (alanine, arginine, glycine, histadine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, glucose monohydrate, soya.bean oil refined, triglycerides medium chain, olive oil refined, fish oil rich in omega-3-acids),
are the same as in Quatriga, marketed by Fresenius Kabi AB since 2009-09-01.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a 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

The application is an extension, new strenghts, of the previously authorised product: Quatriga and Quatriga Elektrolytfri, emulsion for infusion (SE/H/841/01-02/DC). 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. Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free do not pose any significant environmental risks due to the nature of the products.

IV. CLINICAL ASPECTS

IV.1 Introduction

Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free are indicated for parenteral nutrition in adult patients when oral or enteral nutrition is impossible, insufficient or contraindicated. While enteral nutrition is generally preferred a number of conditions and situations necessitate parenteral nutritional support. In most cases this is a short-term need of a few days or weeks but in some situations, e.g. the short bowel syndrome and other chronic conditions with malnutrition, long-term support is needed.

The main focus of nutritional support is to maintain or optimise the function of important body functions, which might improve clinical outcomes (i.e. reduce likelihood for complications such as infections and promote earlier mobilisation), and ultimately lead to benefits in terms of patient-relevant long-term outcomes. Such hard outcomes benefits have, however, been difficult to establish and are not considered needed to characterise the efficacy of these products.

IV.2 Pharmacodynamics

The nutritional components in these products have been extensively used for many decades in clinical practice. The pharmacodynamic characterisation of Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free is based on available data for the individual components. This is mainly from bibliographic reports. No human clinical pharmacology studies have been performed since there is a significant body of clinical knowledge available for the individual components.

IV.3 Clinical efficacy

In general, all components of Quatriga and Quatriga Electrolyte Free and their combination can be considered well known and generally established for medicinal use. The efficacy of

similar products is well established. 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.

The dosing recommendations are compatible with relevant clinical guidelines. It should be recognised that there may be substantial individual variability, and the dose may need to be tailored to the individual patient depending on baseline nutritional status, response to nutrition, tolerability, illness severity, fluid tolerance and enteral nutrition provided.

The applicant has discussed the rationale for the line extension which is based mainly on guideline recommendations discussed in the publications, mostly related to ICU and critically ill patients.
Although guidelines by themselves cannot be considered as sufficient scientific evidence, the use of lower energy provision in patients who need parenteral nutrition is well recognised within the clinical community and supported by clinical experience.

IV.4 Clinical safety

Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free are composed of well-known components which are well-established in clinical use for parenteral nutrition. Accordingly, there is extensive experience concerning safety of the individual components and their combination.

The safety characterisation is based on data from a range of studies in adult as well as paediatric populations. Although the indication is from 2 years of age the data from preterm infants is considered valuable and supportive. No new safety information is provided. The findings are expected and in line with the established safety profile for parenteral nutrition.

The post marketing experience of the products related to this line extension procedure is extensive, without emerging safety signals that could have an impact on Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free.

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 Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free.

Safety specification

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, version 1.2 signed 07-Apr-2017 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 (PIL) has been performed on the basis of a bridging report making reference to the product

SmofKabiven and SmofKabiven Electrolyte Free. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefits from a balanced provision of major nutrients in line with current international guidelines, and the use of multi-compartment bags are considered sufficiently well described. The results from the studies presented are overall consistent.

There is a large clinical experience from parenteral nutrition, and many studies have been published covering a variety of patient populations and outcomes. While there is uncertainty regarding the frequency of specific uncommon adverse events, and room for further optimisation of therapy to e.g. reduce negative impact on hepatic biomarkers, this is not considered major limitations of the characterisation of the safety profile. No additional pharmacovigilance activities are considered needed.

The benefit/risk ratio is considered positive and Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free are 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 Quatriga extra Nitrogen and Quatriga extra Nitrogen Electrolyte free emulsion for infusion was positively finalised on 2018-10-15.

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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/xxxx/WS/499 (Quatriga extra Nitrogen Electrolyte free, SE/H/841/04)	To add information on dosing in intra-dialytic parenteral nutrition (IDPN) to the SmPC and Package Leaflet.	Yes	2022-03-18	Approval	Posology for intradialytic parenteral nutrition (IDPN) is provided.

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

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Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se