LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Quatriga

Active substances:

Fish oil (rich in omega-3-acids), olive oil, 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 $2H_2O$, sodium glycerophosphate, magnesium sulphate $7H_2O$, potassium chloride, sodium acetate $3\ H_2O$ and zinc sulphate $7H_2O$

SE/H/841/01-02/MR

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This module reflects the scientific discussion for the approval of Quatriga. The procedure was finalised at 2009-09-01. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Fresenius-Kabi AB has applied for a marketing authorisation for Quatriga emulsion for infusion in a three chamber bag containing a lipid emulsion, an amino acid solution with electrolytes and a glucose solution. The contents in the three chambers are mixed prior to use. The active substances are fish oil (rich in omega-3-acids), olive oil, 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 $2H_2O$, sodium glycerophosphate, magnesium sulphate $7H_2O$, potassium chloride, sodium acetate 3 H_2O and zinc sulphate $7H_2O$. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Quatriga is presented in the form of emulsion for infusion in a three chamber bag containing a lipid emulsion, an amino acid solution with electrolytes and a glucose solution. The contents in the three chambers are mixed prior to use. The active substances in the lipid emulsion are: fish oil (rich in omega-3-acids), olive oil, soya-bean oil (refined) and medium-chain triglycerides. The active substance the glucose solution is glucose monohydrate. The active substances in the amino acid solution with electrolytes are alanine, arginine, glycine, histidine, isoleucine, leucine, lysine acetate, methionine, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride $2H_2O$, sodium glycerophosphate, magnesium sulphate $7H_2O$, potassium chloride, sodium acetate 3 H_2O and zinc sulphate $7H_2O$.
The excipients in the lipid emulsion are all-*rac*-α-tocopherol, purified egg phospholipids, anhydrous glycerol, sodium oleate, sodium hydroxide and water for injections. The excipient in the glucose solution is water for injections. The excipients in the amino acid solution with electrolytes are acetic acid glacial and water for injections.

II.2 Drug Substance

All the drug substances, except taurin, have a monograph in the Ph Eur.

The structures of drug substances have been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specifications include relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest periods.

II.3 Medicinal Product

Quatriga emulsion for infusion is formulated using excipients described in the current Ph Eur, except for purified egg phospholipids and sodium oleate which are controlled according to

acceptable in house specifications. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01) or viral safety.

The product development has taken into consideration the physico-chemical characteristics of the active substances.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored in the overpouch below 25ºC, without freezing.

III. NON-CLINICAL ASPECTS

The Non Clinical Overview was written by Prof. Dr Joachim Lindena. Non-clinical studies with Quatriga were not performed. The non-clinical evaluation was based on the data submitted to support market authorisation of the lipid component SMOFLipid® 20 %, the amino acid component Aminoven® 10 % and on the amino acid solutions of the Vamin® series (Vamin® 18, Vamin® 18 EF, Vamin® 18 Novum). Vamin® 18 Novum closely resemble the composition of Aminoven ® 10 % except for the exclusion of aspartic- and glutamic acid and inclusion of taurine in Aminoven. This approach is considered adequate and no additional studies are required.

An additional Non Clinical Overview on the safety of the three chamber bag biofine packaging concept was written by Dr Per Sjöberg, Eureda. This overview was submitted as it is well established that substances from polymers used in packaging material can migrate into the emulsion/solutions. Therefore, there is a need to assess the risks associated with such migration from new packaging material. Of the components included in the 3-CB Biofine, the inner bag film Biofine, fill-port and septum are in direct contact with the parenteral solution. The view of the expert that there should be no safety concern with potential migrants from the alternative 3-CB Biofine packaging system into the Quatriga, Quatriga Electrolyte Free and Quatriga Peripheral products nor into the Kabiven, Kabiven Peripheral, StructoKabiven, StructoKabiven EF, StructoKabiven Peripheral products is endorsed. This conclusion is based on documentation showing that the 3-CB packaging system conforms to the relevant stipulations in the Ph. Eur. It is also based on an in depth review of the possible migration and toxicity of components of the 3-CB Biofine packaging system (container, septum and printing inks) as well as migration/extraction experiments on selected components with perceived or documented toxicity (aluminium, antioxidants, 2-EHA, accelerators and plastic monomer). Finally, a large number of biological/toxicity tests have been conducted on extracts from components of the 3-CB container system and on saline and Intralipid stored in the new packaging system without any significant effects.

An environmental risk assessment in accordance with the 6th draft of the Guideline for Environmental Risk assessment (III 5509/94, December 1994) was provided. Considering the

nature of the active substances (i.e lipids, aminoacids, glucose, and electrolytes) no environmental risk is anticipated.

From a preclinical point of view, Quatriga can be recommended for market authorisation.

IV. CLINICAL ASPECTS

Clinical efficacy

The clinical part of this application for a medicinal product containing a new combination of known active substances is bibliographic.
The Applicants justification for the new composition is in summary:

> *"The most recently published guidelines recommend a lipid/carbohydrate ratio < 40/60 and a lipid/total energy ratio < 30/70. These recommendations are valid for products meant for infusion in central veins. The versions for peripheral infusion must by necessity contain higher amount of fat. Quatriga fulfils the lipid/glucose ratio at the border line and almost reaches the line for the lipid/total calories ratio. The improved n-6/n-3 fatty acid ratio (approx. 2.5:1) in Quatriga compared with StructoKabiven is of potential benefit regarding the interaction with inflammatory processes. Olive oil has been included in Quatriga to decrease the total proportion of polyunsaturated fatty acids.*
> *The nitrogen/calorie ratio has for many years been aimed to 1/150 (1 g N/150 kcal). More recent opinions have made a trend to aim for a ratio closer to 1/100. StructoKabiven was modified to apply to both recommendations concerning the relative fraction of fat, glucose and protein and Quatriga was further changed to come closer to the recent experiences concerning an optimized composition of fatty acids."*

The adjustments in the composition for Quatriga compared with StructoKabiven are based on recent research in parenteral nutrition.

The Applicant's arguments for the new composition (based on relevant submitted bibliographic references) are accepted.

Clinical safety

The safety data from the limited study on Quatriga must be seen in the context of the already known safety profiles of its components and the very similar products StructoKabiven/Kabiven. The submitted data on a small study can only support these earlier safety data.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet for SmofKabiven has been performed and is acceptable.

As Quatriga is a duplicate application to SmofKabiven (SE/H/792/01-02/MR), the applicant has submitted the same application dossier which means that the user test for SmofKabiven also applies for Quatriga. For further information please see the RMS's assessment of the user testing from procedure SE/H/792/01-02/MR.

The risk/benefit ratio is considered positive and Quatriga emulsion for infusion is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Quatriga was successfully finalised on 2009-09-01.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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