LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Nutriflex Omega plus and Nutriflex Omega special

Active substances:

glucose monohydrate, sodium dihydrogen phosphate dihydrate, zinc acetate dihydrate, triglycerides (medium-chain), soya-bean oil (refined), omega-3-acid triglycerides, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan, valine, arginine, histidine hydrochloride monohydrate, alanine, aspartic acid, glutamic acid, glycine, proline, serine, calcium chloride dihydrate, magnesium acetate tetrahydrate, sodium acetate trihydrate, sodium chloride, potassium acetate and sodium hydroxide

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This module reflects the scientific discussion for the approval of Nutriflex Omega plus and special. The procedure was finalised at 29 September 2010. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

B.Braun has applied for a marketing authorisation for Nutriflex Omega plus and Nutriflex Omega special, emulsion for infusion. The active substances are: glucose monohydrate, sodium dihydrogen phosphate dihydrate, zinc acetate dihydrate, triglycerides (medium-chain), soya-bean oil (refined), omega-3-acid triglycerides, isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan, valine, arginine, histidine hydrochloride monohydrate, alanine, aspartic acid, glutamic acid, glycine, proline, serine, calcium chloride dihydrate, magnesium acetate tetrahydrate, sodium acetate trihydrate, sodium chloride, potassium acetate and sodium hydroxide.

The ingredients in Nutriflex Omega special / Nutriflex Omega plus are separated in three sealed chambers. Before use the seals are broken for the components to mix. The products are intended for central venous infusion in adults.

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Nutriflex Omega plus and Nutriflex Omega special are presented in the form of emulsion for infusion containing a fat emulsion, an amino acid solution (with electrolytes) and a carbohydrate solution (with electrolytes) in each of the respective chamber of a three chamber bag. The contents in the three chambers are mixed prior to use.
The active substances in the amino-acid solution with electrolytes are isoleucine, leucine, lysine hydrochloride, methionine, phenylalanine, threonine, tryptophan, valine, arginine, histidine hydrochloride monohydrate, alanine, aspartic acid, glutamic acid, glycine, proline, serine, calcium chloride dihydrate, magnesium acetate tetrahydrate, sodium acetate trihydrate, sodium chloride, potassium acetate and sodium hydroxide.
The active substances in the carbohydrate solution are glucose monohydrate, sodium dihydrogen phosphate dihydrate and zinc acetate dihydrate.
The active substances in the lipid emulsion are triglycerides (medium-chain), soya-bean oil (refined) and omega-3-acid triglycerides.
The excipients in the amino acid solution with electrolytes are citric acid monohydrate and water for injections. The excipients in the carbohydrate solution are citric acid monohydrate and water for injections. The excipients in the lipid emulsion are α-tocopherol, egg lecithin, glycerol, sodium oleate, sodium hydroxide and water for injections.

II.2 Drug Substance

All the active substances 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 for some of the drug substances and the data provided are sufficient to confirm the retest periods, where applicable. Other drug substances are tested prior to use on conformity to the respective specification and in these cases no re-test period is applied.

II.3 Medicinal Product

Nutriflex Omega plus and Nutriflex Omega special emulsion for infusion are formulated using excipients described in the current Ph Eur, except for egg lecithin 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 below 25ºC, without freezing and kept in the outer carton in order to protect from light.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Lipid emulsions used in parenteral nutrition do not exert specific pharmacodynamic effects, but are intended to provide energy equivalents and essential fatty acids under conditions of inadequate oral intake and/or an increased energy demand. All constituents of Nutriflex Omega special and Nutriflex Omega plus are found in already approved lipid emulsions. The Applicant has not submitted any new primary or secondary pharmacology studies or pharmacodynamic drug interaction studies which is considered acceptable in view of published literature and the clinical experience of medium-chain triglycerides: long-chain triglycerides: (fractionated) fish oil ratio 5:4:1 (MLF541). The safety pharmacology studies conducted with medium-chain triglycerides: long-chain triglycerides: (fractionated) fish oil ratio 5:3:2 (MLF532) revealed a treatment related reduction in blood pH compared with controls, probably related to ketoacidosis caused by the formation of acetone bodies in the liver. This is considered acceptable. No other significant effects were reported.

III.2 Pharmacokinetics

Nutriflex Omega special and Nutriflex Omega plus are intended for intravenous use only and therefore the bioavailability of the components is 100%. Glucose, amino acids, and lipids provided by Nutriflex Omega special and Nutriflex Omega plus will undergo essentially the same metabolism as substrates ingested by diet. The pharmacokinetics of the active ingredients of the both emulsions is well-known. The dosage of formulations used in total parenteral nutrition are adjusted to provide adequate energy equivalents and to supplement the patient

with essential fatty acids. The dosages are already established in total parenteral nutrition. No pharmacokinetic studies testing the components of Nutriflex Omega special and Nutriflex Omega plus have been conducted by the Applicant which is considered acceptable.

III.3 Toxicology

In addition to bibliographic data, the Applicant has submitted single-dose toxicity, repeat-dose toxicity, local tolerance, antigenicity and immunotoxicity studies for the lipid emulsion MLF532 (one single dose study with MLF541). No preclinical studies were conducted with the combined 3-component medicinal product or with the other two components glucose and amino acids. The safety profile of glucose and amino acids is well-established. The toxic effects observed with MLF532 are attributed to fat overload. Side effects of lipid emulsions mostly concern basal metabolism (particular fat metabolism and reticuloendothelial system). Activation of reticuloendothelial system, accompanied with an increased phagocytotic activity and proliferation of Kupffer cells, has been observed in the liver and other organs after excessive fat exposure, generally characterised by fat embolism caused by fat overload.

Repeat dose toxicity studies showed no significant differences between MLF532 and the reference lipid emulsion Lipofundin. The toxic effects observed in rat and dog with MLF532 were attributed to fat overload, which is well characterised in the clinic. In addition, a 15 day dog study revealed an increased bleeding time, which is a well-known effect for omega-3-fatty acids.

Genotoxicity and carcinogenicity studies were not performed by the Applicant. Due to the nature of the active substances the lack of these studies is considered acceptable.

No *reproductive and developmental toxicity studies* were conducted with MLF541. In view of the nature of the active substances the lack of reproductive and developmental toxicity studies is acceptable. Previous studies on MLF532 tested for embryotoxic, foetotoxic and teratogenic effects in rabbit did not reveal any effects.

Local tolerance studies in rabbit revealed local reactions but these were reversible and the vascular tolerability was considered good.

All ingredients were checked for *impurities* and there are no toxicological concerns.

The plastic in the 3-chamber bag is made of a co-extruded film of polyamide 11 and polypropylene and is in accordance with Ph. Eur. recommendations for sterile plastic containers for aqueous solutions for parenteral infusion. The plastic bag used in Nutriflex Lipid has been tested in toxicology studies for potential effects of substances that may leach from the plastic with no signs of toxicological effects. The Applicant confirmed that the same plastic bag is used in Nutriflex Omega special and Nutriflex Omega plus.

III.4 Ecotoxicity/environmental risk assessment

According to the guideline on the *environmental risk assessment* of medicinal products for human use (EMEA/CHMP/SWP/4447/00), electrolytes, amino acids, carbohydrates and lipids are unlikely to result in significant risk to the environment and the absence of risk assessment of Nutriflex Omega special and Nutriflex Omega plus is considered acceptable.

III.5 Discussion on the clinical aspects

The non-clinical data on Nutriflex Omega plus and Nutriflex Omega special is judged to be sufficient.

IV. CLINICAL ASPECTS

IV.1 Introduction

The basis for the products concerned in the present applications concerns a further development of the already approved products Nutriflex Lipid special and Nutriflex Lipid plus in that 10 % of the long-chain triglycerides are replaced with omega-3 acid triglycerides. The remaining constituents have not been changed in Nutriflex Omega special / plus in comparison with the Nutriflex Lipid products. The lipid content of the applied products is also marketed by the applicant as Lipoplus or Lipidem.

IV.2 Pharmacokinetics

No new pharmacokinetic studies were provided by the Applicant. This is considered acceptable due to the nature of the active substances contained in Nutriflex Omega special and Nutriflex Omega plus and the clinical experience with similar medicinal products.

IV.3 Pharmacodynamics

All ingredients in Nutriflex Omega special and Nutriflex Omega plus are known substrates in human nutrition. Metabolic pathways of lipids, glucose, aminoacids, electrolytes, zinc and acetate are described in publications on biochemistry and nutrional biochemistry.

IV.4 Clinical efficacy

The results of the studies referred to in the clinical overview support that efficacy of the lipid part of Nutriflex Omega plus / special is similar to conventional lipid emulsions for energy supplementation. The lipid emulsion is already regulatory approved and marketed as Lipoplus or Lipidem.

There are no efficacy studies submitted on the new products Nutriflex Omega special / Nutriflex Omega plus. However, the ingredients, apart from the lipid emulsion, are identical with the contents of the already approved products Nutriflex Lipid special / Nutriflex Lipid plus. The efficacy of these products is well established. Consequently, no new studies are deemed necessary for the evaluation of this nutrition product.

IV.5 Clinical safety

Inclusion of omega-3 triglycerides in emulsions for parenteral nutrion is in line with general nutrition recommendations. No new safety studies have been performed on the combined product containing the lipid emulsion Lipoplus and the glucose solution and amino acids from the Nutriflex Lipid products. However, there are no safety concerns identified for each separate component of Nutriflex Omega plus and Nutriflex Omega special and there are no reasons to believe that the new combination would alter the safety profile in adults. Inclusion of omega-3 triglycerides in emulsions for parenteral nutrion is in line with general nutrition recommendations. The safety profile of the lipid emulsion Lipoplus and the Nutriflex Lipid products are well known in adults.

IV.6 Discussion on the clinical aspects

The clinical data on Nutriflex Omega plus and Nutriflex Omega special is judged to be sufficient.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 NuTRIflex Lipid plus, DE/H/164/01/II/005. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Nutriflex Omega plus and Nutriflex Omega special, emulsion for infusion is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Nutriflex Omega plus and Nutriflex Omega special, emulsion for infusion was successfully finalised on 29 September 2010.

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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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