LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Numeta G16E and Numeta G19E

Active substances:

alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, , methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil.

SE/H/918/02-03/DC

This module reflects the scientific discussion for the approval of Numeta. The procedure was finalised 2010-12-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Baxter Medical AB has applied for a marketing authorisation for Numeta, Emulsion for infusion. Numeta is a sterile, non-pyrogenic, single-use, ready-to-use product for infusion providing amino acids, electrolytes, glucose and lipids as drug substances. The active substances are Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil and refined olive oil.

The development of this product has complied with all measures in the agreed paediatric investigation plan EMEA-000112-PIP01-07-M01 (decision number P/191/2009).

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Numeta is presented in the form of emulsion for infusion containing a lipid emulsion, a paediatric amino acid solution with electrolytes, and a glucose solution in each of the respective chamber of a three chamber bag. Numeta is developed in 3 bag formats (300, 500 and 1000 ml), each for a specific segment of the paediatric population. The concentrations of amino acids (5.9 %), glucose (50 %), and lipid (12.5 %) are identical for all container sizes but the levels of electrolytes are different and have been set according to the requirement of the three related patient groups.
Before use the peel seals are opened and the three products are mixed together. If lipid administration is undesirable, the design of the bag allows the possibility to activate only the peel seal between the amino acids/electrolytes and glucose chambers, leaving the peel seal between the amino acids and lipid chambers intact.
The glucose solution contains glucose monohydrate as a single drug substance.
The amino acid solution with electrolytes contains: alanine, arginine, aspartic acid, cysteine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride dihydrate, magnesium acetate tetrahydrate, potassium acetate, sodium chloride, sodium glycerophosphate hydrated.
The lipid emulsion contains soya-bean oil (refined) and olive oil (refined) as drug substances.
The excipients in the glucose solution are hydrochloric acid and water for injections. The excipients in the amino acid solution with electrolytes are L-malic acid and water for injections. The excipients in the lipid emulsion are purified egg phosphatide, glycerol, sodium oleate, sodium hydroxide and water for injections.

II.2 Drug Substance

Most of the active substances are included in the Ph Eur, however for cysteine, taurine, lysine monohydrate and ornithine hydrochloride no Ph Eur monograph exists.

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 have been conducted and the data provided are sufficient to confirm the retest period for the respective drug substance.

II.3 Medicinal Product

Numeta emulsion for infusion is formulated using excipients described in the current Ph Eur, except for purified egg phosphatide and sodium oleate which are controlled according to acceptable in house specifications. All raw materials used in the product has 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 without freezing.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Numeta is indicated for i.v. parenteral nutrition in the pediatric population when oral or enteral nutrition is impossible, insufficient or contraindicated. Numeta is a ready-to-use nutritional product that contains amino acids/electrolytes, glucose, and lipids. The constituents of Numeta are found in already approved products in EU. The Applicant has not submitted any new primary or secondary pharmacodynamic studies, pharmacodynamic drug interaction studies or safety pharmacology studies with the final product Numeta. This is considered acceptable in view of published literature, previously performed studies on Primene and ClinOleic and clinical experience of these and similar products. Safety pharmacology studies with Primene revealed minimal cardiovascular acid-base changes, no hypotensive effects were observed in cats and/or dogs with neither Primene and ClinOleic.

III.2 Pharmacology

No studies of the primary and secondary pharmacodynamics of the amino acids have been performed. The safety pharmacology assessments of Primene 5 and 10% included cardiovascular and respiratory safety studies in dogs and/or cats. The lipid composition in

Numeta is a diluted formulation of the previously approved 20% ClinOleic to 12.5%. ClinOleic contains a mixture (approximately 80:20) of refined olive oil and refined soybean oil (15% saturated fatty acids (SFA), 65% monounsaturated fatty acids (MUFA), 20% polyunsaturated essential fatty acids (PUFA) and a phosphatides/triglycerides ratio of 0.06). Previous in vitro and in vivo primary pharmacodynamic studies have been performed to investigate the nutritional differences with soybean oil-based lipid emulsions. In addition a safety pharmacology study in cats has been performed compared to ClinOleic 20%. Studies on primary and secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions of the glucose compartment have not been conducted.

III.3 Pharmacokinetics

Numeta is intended for i.v. use only and therefore the bioavailability of the components is 100%. Glucose, amino acids and lipids provided by Numeta will undergo essentially the same metabolism as substrates ingested by diet. No new pharmacokinetic studies were performed by the Applicant. This is considered acceptable due to the nature of the active substances contained in Numeta and the clinical experience with similar medicinal products.

III.4 Toxicology

In addition to bibliographic data, the Applicant has submitted preclinical studies for Primene 5 and 10% and ClinOleic 20%. No preclinical studies have been conducted with the glucose compartment which is considered acceptable in view of the clinical experience of glucose.

Primene

Single dose toxicity studies with Primene 5 and 10% were conducted in mice and rats and repeated dose toxicity studies in rats and dogs. In single and repeated dose toxicity studies maximum tolerated doses (MTD) were limited by the route of administration and were exaggerated by means of infusion rate. There were no observed toxic effects attributed to Primene. In addition, neonatal rats were dosed sc three times daily with either Primene 10% or Vamine N for 28 days. Primene was equivalent to Vamine N and supported acceptable growth and behaviour during treatment. No specific local tolerance studies were conducted, however, no injection site findings attributable to test article were found in any of the toxicology studies. No genotoxicity, carcinogenicity, reproductive and development toxicity studies were performed by the Applicant. In view of the nature of the product, published literature and clinical experience with amino acids this is considered acceptable.

ClinOleic

Single dose toxicity studies with ClinOleic were conducted in mice and rats, repeated dose toxicity studies in rats, rabbits and dogs and local tolerance studies in rats. The general signs of toxicity noted in these studies were mild hemolytic anemia, transitory thrombocytopenia, hypercholesterolemia, hepatic pathology of lipid and pigmentary overload, all well known effects after infusion of high doses of lipids. At doses close to the therapeutic dose (15 mL/kg/day corresponding to 3 g/kg/day), only very slight lipid and pigmentary overload of the liver was observed. At doses up to 30 mL/kg/day (6 g/kg/day) in rats and dogs, toxic effects were limited and reversible with the exception of the persistence of pigments in the cells of the reticuloendothelial system. The effects of ClinOleic in repeat-dose toxicity studies were generally comparable to the reference emulsion Intralipid®. Tissue necrosis did not occur following sc or id administration of the lipid emulsion, absorption from injection sites was complete by 14 days post administration. No chronic toxicity, genotoxicity, carcinogenicity studies, or reproductive and developmental toxicity studies were conducted on the lipid emulsion. In view of the nature of the product, published literature and clinical experience with lipids this is considered acceptable.

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

Container closure system
The same container closure system as in Numeta is used for similar registered products. Satisfactory specifications and certificates of analysis have been provided for packaging components. There are no toxicological concerns.

III.5 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 any significant risk to the environment. The absence of environmental risk assessment for Numeta is therefore considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Clinical efficacy

Presently, the amino acid component Primene is registered in the following EU countries: AU, BE, BU, CR, DK, FI, FR, DE, HL, IE, IT, LU, NL, PL, ES, and UK, in most since the 1990-ties. The product is also registered in 17 non-EU countries.
Presently, the component ClinOleic is registered in the following EU countries: AU, BE, BU, CY, CR, FR, DE, HL, IE, IT, LI, LU, NO, NL, PL, ES, SE, and UK, in most since the 1990-ties. The product is also registered in 21 non-EU countries.
The efficacy of each of these products, and also of glucose, in treating paediatric patients > 28 weeks of gestational age can be concluded to be well established. This is also the position of the RMS in the present DCP.
The knowledge in paediatric parenteral nutrition has gradually increased and the advice by (ESPEN-ESPGHAN) is presently the state of art. Numeta Ped has been composed to fulfil the nutritional recommendations as listed in their joint 2005 (most recent) publication. As the needs in the span from premature infants to adolescents differ, in some aspects substantially, the Applicant has composed three infusion bags with profiles according to these different needs.

According to the submitted data, mainly from the Ped3CB/P01/06/Mu.B study, there are no indications that Numeta should not deliver an adequate amount of macronutrients and electrolytes. Even if additions to Numeta bag occurred in approximately 60% of the patients to adjust the nutritional treatment to the individual needs, Numeta formulation could be used without adjustment in approximately 50% of the days of treatment.
Overall, subjective impressions of the pharmacists and the nurses handling the bags were positive, more mildly in preterm wards. The opinions of the prescribing physicians are not addressed in the study.

IV.2 Clinical safety
In addition to metabolic complications, parenteral nutrition may be associated with both technical and septic adverse events. The introduction of a three chamber bag with amino acids, lipids, glucose, and electrolytes will solve some problems and may create new ones.

If the handling of the bags will introduce less risks for bacterial contamination this will of course be an improvement. Also, if the risks for miscalculations for additions are reduced, this would be welcomed.

None of these aspects are demonstrated in the Ped3CB/P01/06/Mu.B study as no comparator was used.

Additional macronutrients or electrolytes were needed for approximately 60% of the studied patients but in approximately 50% of the study days. Pretested additions seem to have worked satisfactorily for all types of bags.

Since laboratory values only are required as part of the study design for preterm infants (no values were required for term infants, toddlers, children and adolescents) and that only at baseline, day 5 and day 10/or end of study the safety assessment will be limited. However, in addition to the protocol-specified safety laboratory assessments, clinicians ordered additional tests, as needed, to adequately monitor and care for the patients. Abnormal results were to be reported as adverse events. The ESPEN paediatric nutrition guidelines have been followed and no major safety problems should be expected in the non-preterm infants.

Initially RMS had a negative opinion for the 300 ml bag of Numeta. This was aimed for treatment of preterm newborn infants.

The Applicant's response to this negative opinion has exhaustively addressed the RMS's concerns regarding a single PN bag for all preterm newborn infants.
The response highlights the discrepancy in nutritional support administered in published studies (e.g. Iacobelli and Lenclen) and the ESPEN Guidelines. The Applicant's presentation and interpretation of these data admittedly support that a single bag of Numeta (300 ml) in this population at least is not inferior to "in house" designed multiple PN bags each aimed for infants of a certain day after birth.
The observed weight gain after Numeta treatment is fully acceptable.
The ongoing instability in electrolyte homeostasis in preterm newborn infants is acknowledged. As noted by the Applicant, low concentrations of certain electrolytes are of less importance than high concentrations. Most of the abnormal values were of the former kind.

The proposed additions to the SPC text will inform a potential subscribing physician of the limitations of Numeta in this special population of patients and also the lack of firm informative data for infants less than 28 weeks of gestational age.

Posology:
The following statement will be added: *Numeta may not be appropriate for some preterm infants, as the clinical condition of the patient may require administration of individualized formulations to meet the specific needs of the patient as assessed by the clinician.*
Precautions:
The following statement will be added: *There are limited data on the administration of Numeta in preterm infants less than 28 weeks gestational age.*

IV.3 Discussion on the clinical aspects

The RMS revised its earlier opinion of a "Potential serious risk to public health" for the Numeta 300 ml bag. With the presented justification of a positive benefit/risk submitted in the Applicant's response combined with the proposed additions to the SPC text the RMS has the opinion that the benefit-risk for all three Numeta bags (300 ml, 500 ml and 1000 ml) are positive.

IV.4 Risk management Plan

Six identified risks, [drug administration errors, use of Numeta in patients with hypersensitivity to one of the components, use of Numeta in patients with severe metabolic disorders, catheter-related infection and sepsis, re-feeding syndrome, and use of Numeta in patients with certain organ impairments], one potential risk [extravasation and thrombophlebitis], and one piece of important missing information [pregnant or lactating females were not studied] have been discovered. All six identified risks were discussed in the SmPC or CTD and will not require additional risk minimization activities. Extravasation and thrombophlebitis have been witnessed in other parenteral nutrition products, however it was not witnessed in the Numeta study and is dependent on route of administration, therefore, it is labelled as a potential risk and will not require additional risk minimization activities at this time. Based on the well-established safety profile for this product, there is no need for additional risk minimization activities. Information about the appropriate use of the product and adverse events are thoroughly presented in the product SmPC. If any new safety concerns arise, the need for risk minimization activities will be re-evaluated and the RMP will be updated.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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.

The risk/benefit ratio is considered positive and Numeta, Emulsion for infusion is recommended for approval.

The applicant has committed to follow up the GMP status for the amino acid mixture based on the outcome of discussion at the QWP meeting.

VI. APPROVAL

The Decentralised procedure for Numeta, Emulsion for infusion was successfully finalised 2010-12-15.

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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
A referral procedure was initiated for Numeta G13E and following the conclusion of the Article 107i referral (procedure number EMA/H/A-107i/1373), the Marketing Authorisation of Numeta G13E (SE/H/918/01) was suspended. The PRAC recommendations and the CMDh agreement requested that the MAH reformulated the product, to include a level of magnesium which is justified based on the most recent knowledge in the area.	EMEA/H/A-107i/1373	Numeta G13%E emulsion for infusion	13/06/2013	18/09/2013	Suspension	No

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