Public Assessment Report
Scientific discussion

Numeta G13E

(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 glycerophosphate, refined soybean oil, refined olive oil)

SE/H/918/04/DC

This module reflects the scientific discussion for the approval of Numeta G13E. The procedure was finalised on 2016-03-15. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Baxter Medical AB has applied for a marketing authorisation for Numeta G13E, emulsion for infusion. The application is a line extension application made according to Article 10b of Directive 2001/83/EC. The active substances are the same as in Numeta G19E, emulsion for infusion, marketed by Baxter Medical AB since 2011.

A referral procedure was initiated 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.

The applicant, Baxter Medical AB applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, CZ, DE, DK, EL, ES, FI, FR, IE, IT, LU, MT, NL, NO, PL, PT, UK as concerned member states (CMS).

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 Substances

The structures of the drug substances have been adequately proven and their physico-chemical properties are sufficiently described.

The manufacture of the drug substances has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substances specifications 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

III.1 Introduction

Numeta G13E is indicated for i.v. parenteral nutrition in the paediatric population when oral or enteral nutrition is impossible, insufficient or contraindicated. Numeta G13E is a ready-to-use nutritional product that contains amino acids/electrolytes, glucose, and lipids. The constituents of Numeta G13E 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 G13E. 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 G13E 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 G13E is intended for i.v. use only and therefore the bioavailability of the components is 100%. Glucose, amino acids and lipids provided by Numeta G13E 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 G13E 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 G13E 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 G13E is therefore considered acceptable.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics
This product contains a mixture of amino acids, salts and glucose naturally occurring in the human body and lipids. These components need no pharmacokinetic profiling and therefore the lack of clinical pharmacokinetic data is acceptable.

IV.2 Pharmacodynamics
No studies investigating the pharmacodynamics of Numeta in humans were conducted; however, studies investigating the pharmacodynamics of the individual components of Numeta (Primene, ClinOleic, and glucose) have been performed. Those studies of interest to the pediatric population were identified for inclusion in this dossier.

Numeta mimics individually compounded PN admixtures and combines well known compounds (ie, Primene, ClinOleic, and glucose) which have been registered for IV parenteral nutrition in neonatal and pediatric patients for many years.

IV.3 Clinical efficacy
The Clinical Study Reports included in this application have already been assessed by the authorities as part of the initial submission when Numeta was approved in 2010.

Reformulation of Numeta 13E formulation

During the reformulation process, the most recent guidelines and the literature for Mg intake in preterm infants were reviewed by the MAH for information on the Mg content of nutrient admixtures which are used to feed parenterally nourished preterm infants. The current published recommendations for parenteral Mg intake for preterm neonates are quite varied and range from 0.15 to 0.5 mmol/kg/day.The joint ESPEN/ESPGHAN guidelines and the ASPEN are considered the gold standards for pediatric nutrition. ASPEN guidelines specify a daily Mg requirement for preterm neonates ranging from 0.15 to 0.25 mmol/kg/day, while the ESPGHAN/ESPEN guidelines do not specify the needs of preterm infants with regards to parenteral Mg intake.

Tsang et al, authored another frequently consulted guide to nutritional requirements for the preterm infant which details a parenteral Mg intake of 0.2 to 0.3 mmol/kg/day for extremely low birth weight and very low birth weight infants.

A review of literature for Mg intake provided during PN to preterm infants indicates that the Mg content of PN solutions for preterm infants varies between 0 to 0.41 mmol per 100 mL and the Mg intake per kg/day in the majority of cases was approximately 0.2 mmol/kg/day.

Table 1.

Recommendations for Parenteral Magnesium Intake in Neonatal Patients

Guidelines for Parenteral Mg Intake	**Preterm Infants**	**Infants and Children (0 to 6**
ESPGHAN/ESPEN (2005)	Not specified	0.2 mmol/kg/day
ASPEN (2004) [2]	0.15 – 0.25 mmol/kg/day	
Tsang et al (2005)	ELBW and VLBW: 0.2 – 0.3 mmol/kg/day	

ELBW=extremely low birth weight
VLBW=very low birth weight

Based on the current guidelines and the literature, Numeta G13E has been reformulated to a Mg content of 0.47 mmol per 300 mL which corresponds to a Mg concentration of 0.16 mmol/100 mL when the bag is activated as a 3CB. When delivered at a maximum daily dose of 127.9 mL/kg/day, a Mg intake of 0.2 mmol/kg/day is provided. When the reformulated Numeta G13%E is activated as a 2CB, the Mg content is 0.2 mmol per 100 mL of the binary, lipid-free solution. The magnesium intake with the maximum daily dose of this lipid-free solution of 102.3 mL/kg/day is also 0.2 mmol/kg/day.

The initially proposed Mg content of the earlier Numeta G13%E formulation contained 1.3 mmol Mg per 300 mL instead of 0.47 mmol Mg per 300 mL in the reformulated Numeta 13E.

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Table 2 Numeta Composition of 300 mL Bag with or without Activation of the Lipid Compartment

Ingredients/Nutritional Content	**Without Lipids**		**With Lipids**	
	240 mL	**240 mL** (per 100 mL)	**300 mL**	**300 mL** (per 100 mL)
Nitrogen (g)	1.4	0.59	1.4	0.47
Amino Acids (g)	9.4	3.9	9.4	3.1
Glucose (g)	40.0	16.7	40.0	13.3
Lipids (g)	n.a.	n.a.	7.5	2.5
Total Calories (kcal)	198	82	273	91
Nonprotein Calories (kcal)	160	67	235	78
Glucose Calories (kcal)	160	67	160	53
Lipid Calories (kcal) [a]	n.a.	n.a.	75	25
Nonprotein Calories/Nitrogen Ratio (kcal/g N)	113	113	165	165
Lipid calories (% non-protein calories)	n.a.	n.a.	32	32
Lipid calories (% total calories)	n.a.	n.a.	28	28
Sodium (mmol)	6.4	2.7	6.6	2.2
Potassium (mmol)	6.2	2.6	6.2	2.1
Magnesium (mmol)	0.47	0.20	0.47	0.16
Calcium (mmol)	3.8	1.6	3.8	1.3
Phosphate (mmol) [b]	3.2	1.3	3.8	1.3
Acetate (mmol)	7.2	3.0	7.2	2.4
Chloride (mmol)	9.3	3.9	9.3	3.1
Malate (mmol)	3.2	1.3	3.2	1.1
pH (approximately)	5.5	5.5	5.5	5.5
Osmolarity (mOsm/L, approximately)	1400	1400	1150	1150

The MAH has submitted the same clinical study reports as assessed during the procedure when Numeta was approved in 2010. The study results have not reanalyzed within this procedure.

Additionally the MAH has justified the new Mg content in the reformulated Numeta G13E and presented a review of clinical guidelines and published literature.

It is acknowledged that the need of magnesium is essential during parenteral nutrition and that the recommended daily dose differs between guidelines and experts.

The new Mg content in the reformulated Numeta G13E is aimed at providing a daily intake of 0.2 mmol/kg/day of Mg, corresponding to the center of the ranges of internationally published experiences (see Table 1). However, the delivery of 0.2 mmol/kg/day of Mg is reached with a maximum daily dose of 127.9 mL/kg/day of Numeta G13E. If there are other reasons to decrease the total volume, every reduction in total volume will lower the magnesium dose accordingly to a relatively higher degree. However, it is foreseen that electrolytes including Mg will be followed during the clinical care and therefore in case of hypomagnesaemia, Mg intake will be adjusted.

The new Mg content is acceptable.

IV.4 Clinical safety

No formulation development studies have been conducted, or are planned, for Numeta as it mimics individually compounded PN products and combines well known compounds which have been registered for intravenous (IV) parenteral nutrition in neonatal and pediatric patients for many years. Additionally, in the reformulated Numeta G13E, the reduced magnesium (Mg) level reflects the most recent international recommendations for daily Mg intake as well as current clinical practice concerning Mg provision to preterm infants reported in the literature. Numeta is administered via the intravenous (IV) route, thus its bioavailability is considered to be 100 percent. Therefore, no studies of the bioavailability of Numeta are planned or have been conducted.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan (Version 4.0 dated 25 Feb 2015), 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 Numeta.

Safety specification

Summary table of safety concerns as approved in RMP

Important Identified Risks	Drug administration error – peripheral infusion with insufficient or no dilution
	Metabolic/electrolyte abnormalities
Important Potential Risks	Hypersensitivity reactions
	Refeeding syndrome
	Drug administration error – failure to mix compartments of 3-chamber bag
	Hypermagnesemia (specific to NUMETA G16%E formulation)
	Pulmonary vascular precipitates
	Ceftriaxone-calcium salt precipitation
Missing Information	Lack of data on use of NUMETA G19%E in pregnant or lactating females
	Lack of data in patients with certain organ impairments

Pharmacovigilance Plan

There is currently one ongoing Post Authorization Safety study in the European Union to evaluate blood Mg levels in term newborn infants and children up to 2 years following the use of Numeta G16%E in routine clinical practice. Moreover, there is a planned study with ClinOleic in children per FDA to fulfill PMR requirements.

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (planned, started)	Date For Submission Of Interim Or Final Reports (planned or actual)
Study 7032-001: A Multicenter, Non-interventional, Uncontrolled, Open- label, Observational Study in Children (up to Age 24 Months) to Evaluate Serum Mg Levels Associated with the Intake of NUMETA G16%E (Category 1)	To evaluate serum magnesium levels observed in term newborn infants and children up to two years of age treated with NUMETA G16%E in routine clinical practice.	Potential risk of hypermagnesemia specific to NUMETA G16%E formulation	On-going FPI: 16 Dec 2014	Targeted : Q3/2017

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 Risk Minimisation Plan

Summary of Safety Concerns and Planned Risk Minimisation Activities as approved in RMP

Safety concern	***Routine/Additional pharmacovigilance activities***	***Routine/Additional riskminimisation activities***
Important identified risk		
• *Drug administration error – peripheral infusion with insufficient or no dilution*	*Routine*	*Routine*
• *Metabolic/electrolyte abnormalities*	*Routine*	*Routine*
Important potential risks		
• *Hypersensitivity reactions*	*Routine*	*Routine*
• *Refeeding syndrome*	*Routine*	*Routine*
• *Drug administration error – failure to mix compartments of 3-chamber bag*	*Routine*	*Routine*
• *Hypermagnesemia (specific to NUMETA G16%E formulation)*	*Routine* *Additional PASS*	*Routine* *DHPC (done)*
• *Pulmonary vascular precipitates*	*Routine*	*Routine*
• *Ceftriaxone-calcium salt precipitation*	*Routine*	*Routine*
Missing information		
• *Lack of data on use of NUMETA G19%E in pregnant or lactating females*	*Routine*	*Routine*
• *Lack of data in patients with certain organ impairments*	*Routine*	*Routine*

The MAH has updated the RMP (Version 4.0 dated 25 Feb 2015) including the new formulation of Numeta G13E . No new safety concern has been proposed driven by the new formulation and this is acceptable. The MAH will continue to closely monitor this risk in the post-marketing setting and provide discussions in future PSURs if relevant data emerges.

The Pharmacovigilance plan includes as before an imposed PASS concerning Numeta G16E.

No additional raisk minimization measures is proposed.

The updated RMP is approved.

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.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

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 Numeta G13%E/G16%E/G19% E emulsion for infusion.
The user test of the Numeta G13%E/G16%E/G19%E emulsion for infusion leaflet was assessed and accepted in SE/H/918/01-03/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Following a discussion in the CMDh the benefits and risk of parenteral nutrition with multi-chambered bag in paediatric has been assessed previously and Numeta G16%E and Numeta G19%E is approved.

Based on cases with hypermagnesaemia a referral procedure was initiated in June 2013, 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 reformulate the product Numeta G13E, to include a level of magnesium which is justified based on the most recent knowledge in the area.

Based on clinical guidelines and published literature, the MAH has proposed the new formulation which results in maximum daily intake of 0.2 mmol/kg Mg. The earlier Numeta G13%E formulation contained 1.3 mmol Mg per 300 mL and the reformulated Numeta G13E contains 0.47 mmol Mg per 300 mL; i.e. a 60% reduction. The proposed Mg content is reasonable.

The SmPC has been updated with minor changes.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 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 Numeta G13E, emulsion for infusion was positively finalised on 2016-03-15.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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