EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report for Numeta G13%E and Numeta G16%E emulsions for infusion, and associated names

Procedures under Article107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1373

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.

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1. Background information on the procedure

Numeta G13%E and Numeta G16%E are industrially manufactured, heat sterilised parenteral nutrition solutions (glucose, lipids, amino acids and electrolytes). Numeta G13%E is specifically designed for preterm newborn infants for whom oral or enteral nutrition is not possible, insufficient or contraindicated. Numeta G16%E is indicated for parenteral nutrition in term newborn infants and children up to two years when oral or enteral nutrition is not possible, insufficient or contraindicated. Numeta has been registered through the decentralised procedure (DCP) in Europe in 18 countries.

In March 2013, the marketing authorisation holder (MAH) for Numeta (Baxter Healthcare Ltd) became aware of case reports of hypermagnesemia in three preterm neonates receiving Numeta G13%E. No associated adverse events (AEs) were reported in conjunction with the hypermagnesemia episodes in these patients.

The MAH continued to monitor Numeta case reports for hypermagnesemia and on 10 June 2013, following further reports of hypermagnesaemia in preterm neonates using Numeta G13%E, the MAH informed the European national competent authorities of a decision to enact a recall of the product from the market to prevent any potential harm to premature infants. A Direct healthcare professional communication (DHPC) was sent out in agreement with the European Medicines Agency to inform relevant healthcare professionals of the recent reporting of cases of hypermagnesemia and of the decision of the MAH to recall Numeta G13%E from the market.

On 13 June 2013, considering uncertainties regarding the appropriateness of the levels of magnesium in Numeta G13%E and the clinical consequences of this, along with uncertainties regarding the availability of adequate alternatives across the EU member states, the Swedish competent authority notified the EMA, in accordance with Article 107i of Directive 2001/83/EC, of the urgency to undertake a review and requesting the PRAC to give a recommendation on the benefit-risk balance of Numeta G13%. Although no reports had been received for Numeta G16%E at that time, the PRAC decided at its June 2013 meeting that this product would also be included in the scope of the referral because of its magnesium content and because of its use in neonates and infants/toddlers up to the age of 2 years, who may also be at risk of developing hypermagnesaemia.

2. Scientific discussion

Parenteral nutrition (PN) is the use of intravenous macronutrients, electrolytes, micronutrients and fluids to provide nutritional support in patients who cannot be fed by oral or enteral nutrition. PN solutions are delivered through a peripheral or central venous catheter. Parenteral nutrition is essential in certain situations, and there are various methods available for preparation and delivery.

Numeta G13%E is a 300 mL bag with a PN formulation which has been specifically designed for preterm neonates when oral or enteral nutrition is not possible, insufficient, or contraindicated. Examples for such clinical conditions of preterm infants in which Numeta G13%E has been administered are low birth weight infants, preterm infants with respiratory distress syndrome, necrotizing enterocolitis or other gastrointestinal problems (*Rigo et al*, 2012).

Numeta G16%E is a 500 ml bag with a PN formulation which has been specifically designed for term newborn infants and children up to two years of age when oral or enteral nutrition is not possible, insufficient, or contraindicated. Numeta G16%E has been administered to neonates and infants with primary digestive diseases, respiratory disease, oncologic and hematologic disease and following digestive tract surgery (*Colomb et al*, 2012).

All or parts of the Numeta bags may be infused. The prescribed volume of Numeta G13%E and Numeta G16%E is based on the body weight of the patient and the nutrient requirements which need to be covered parenterally. When no oral or enteral nutrition is possible, all nutrient needs will be covered by Numeta. When some oral or enteral nutrition is possible, Numeta will complement the oral/enteral nutrient intake.

The initial application for Numeta G13%E and Numeta G16%E was supported by a prospective, multicentre, non-comparative, open-label phase 3 study (Ped3CB/P01/06/MuB). The primary objective of this study was to provide daily information on the performance safety of the range of Numeta products in practical therapeutic use for the 5 days of the study and during an optional treatment period in preterm newborn infants. Overall Numeta was found to be acceptable to paediatric clinical staff in terms of handling, ease of use and time from prescription to infusion. In terms of efficacy measurements, the different Numeta formulations were able to maintain or increase body weight.

The safety concerns of Numeta G13%E outlined in the initial application and risk management plan include drug administration errors (peripheral infusion with insufficient dilution, failure to mix compartments of triple chamber bag), use of Numeta in patients with hypersensitivity to one of the components, use of Numeta in patients with severe metabolic disease, catheter-related infection and sepsis, re-feeding syndrome, use of Numeta in patients with certain organ impairment and extravasation and thrombophlebitis when peripherally administered. These risks are shared by the other range of Numeta products including Numeta G16%E and are considered to be complications of PN use in general as outlined in the joint paper on paediatric PN the European society of paediatric gastroenterology, hepatology and nutrition (ESPGHAN) and the European society for clinical nutrition and metabolism (ESPEN).

Following several reports of cases of hypermagnesemia in preterm neonates infants using Numeta G13%E, the MAH has informed the European national competent authorities of its decision to enact a voluntary recall of the product from the market to prevent any potential harm to premature infants. A Direct healthcare professional communication (DHPC) was sent out in agreement with the European Medicines Agency to inform relevant healthcare professionals of the recent reporting of cases of hypermagnesemia of the decision of the MAH to recall Numeta G13%E from the market.

In view of the MAH's decision to withdraw the product from the market, the PRAC initiated a review of the benefit-risk balance of Numeta G13% and Numeta G16%. The latter product was also included in the scope of the referral because of its magnesium content and because of its use in neonates and infants/toddlers up to the age of 2 years of age, who may also be at risk of developing hypermagnesaemia.

2.1. Clinical safety

In the context of this referral procedure, the PRAC reviewed all available data from clinical studies, published literature, post-marketing experience on the safety of Numeta G13%E and Numeta G16%, as well as stakeholders' submissions in particular with regards to the hypermagnesaemia or elevated magnesium events. Available guidelines with recommendations for magnesium intake were also considered. A relevant summary of the findings is described hereinafter.

Published literature on hypermagnesemia

Magnesium, one of the mineral components of Numeta G13%E and Numeta G16%E, is the fourth most abundant metal in the body and is a predominantly intracellular ion (representing 99% of corporal magnesium) and the second most abundant intracellular cation after potassium (*Delucas et al*, 2000).

The physiological importance of magnesium lies in its role in skeletal development and in the maintenance of electrical potential in nerves and muscle membranes.

Although some limitations may apply, serum magnesium concentration is still used as the standard for evaluating magnesium status in patients and it has proven helpful in detecting rapid extracellular changes; however total serum magnesium is rarely measured in clinical practice and not typically measured in preterm neonates during the first days of life (*Jahnen-Dechent et al*, 2012).

There is not one universal reference interval for serum magnesium in preterm infants, neonates or children up to two years as reference intervals differ depending on laboratory, analytical technique, reagent and equipment. In addition, the continuously changing physiology of growing children makes their laboratory values a moving target. Numerous other factors such as age, gender, or ethnic differences affect laboratory parameters. Consequently, only large populations of healthy individuals are ideal for development of adequate reference intervals for diagnostic tests (*Ceriotti et al*, 2012).

Studies investigating levels of magnesium in preterm infants have reported higher levels of magnesium as compared to more mature newborn infants indicating that plasma magnesium may be inversely related to somatic maturity (*Ariceta et al*, 1995; *Tsang et al*, 1970). According to *Ariceta et al*, a number of extrinsic and intrinsic factors may contribute to this relative hypermagnesemia of very preterm infants including greater capacities for intestinal absorption and also alterations in the internal magnesium balance with shifts occurring from the intracellular to the extracellular compartment (*Ariceta et al*, 1995). In a study involving 2188 healthy children and adolescents it was found that magnesium levels were initially increased in the neonatal period but then declined quickly after 14 days *(Colantonio et al*, 2012). Overall, the majority of studies which have reported measured levels of serum magnesium in preterm neonates, full term neonates and children have reported levels below 1 mmol/L.

A review of the literature showed that moderate elevation of plasma concentration is accompanied by only a few signs such as nausea and vomiting but marked hypermagnesaemia is followed by severe neurological and cardiovascular impairment. Early recognition and treatment of hypermagnesemia may prevent or minimise life-threatening events, however the vast majority of mild hypermagnesaemia patients may be missed (*Ali et al*, 2003), as measurement of magnesium levels is not routine in clinical practice. Hypotension, electrocardiographic changes and evidence of sedation appeared at serum magnesium concentrations of 3 to 8 mEq/L (1.5 to 4 mmol/L). Disappearance of deep tendon reflexes, respiratory depression, weakness and coma were reported at magnesium levels of 2.5 to 7.5 mmol/L and cardiac arrest was reported at serum magnesium levels of > 7.5 mmol/L. Clinical signs of neuromuscular depression with floppiness, lethargy, and respiratory depression were shown to be frequent manifestations of severe neonatal hypermagnesemia.

The kidney is the main regulatory organ of magnesium homeostasis and impaired renal function is the most common cause of hypermagnesemia in children (*Ali et al*, 2003). Neonatal hypermagnesemia can also be caused by increased magnesium load such as with maternal magnesium sulphate administration for preeclampsia, newborn magnesium therapy, or decreased renal magnesium excretion due to prematurity and asphyxia (*Hyun et al*, 2011).

Clinical studies

One study was submitted in support of the marketing authorisation of Numeta G13%E and Numeta G16%E. It was a prospective, multicentre, non-comparative phase III study (*Ped3CB/P01/06/MuB)* sponsored by Baxter, conducted in the 115 preterm infants and 28 term infants/toddlers up to two years of age. In the study, the preterm infants received PN up to 80% of needs, and the

infants/toddlers received PN up to 50% of needs. The patients were treated for five consecutive days (with optional treatment period of additional five days).

The occurrence of all adverse events (AEs) was recorded from the start of the first infusion of study product through two days after the last infusion. Vital signs and adverse events were recorded daily for the 5 days of the study in all patients and during the optional treatment period (an additional 5 days) in preterm newborn infants. In the preterm newborn infants group, plasma ionogram (sodium, potassium, calcium, phosphorus), urea, triglycerides, glucose and bicarbonates were evaluated at baseline, Day 5, and Day 10/end of treatment. Measurement of serum magnesium levels was not part of the study protocol. Nutritional intakes were recorded daily.

The most frequently reported events in preterm infants were hyperglycaemia (13 events), anaemia (12 events), sepsis (10 events), hyponatraemia (9 events), constipation (8 events), staphylococcal sepsis (8 events), hypertriglyceridaemia (8 events) and patent ductus arteriosus (7 events): all other events in this group were reported ≤ 5 times.

In term infants and toddlers, the most frequently reported events were pyrexia (2 events) and hyperglycaemia (2 events): all other events in this group were unique events that occurred only once.

None of the AEs reported in preterm infants or term infants/toddlers were of the type generally associated with hypermagnesaemia.

Post-marketing reporting

The Baxter Pharmacovigilance safety database was searched for case reports of all formulations of Numeta received from the marketing of the products to 17 June 2013. This search identified 36 case reports in total. Of the 36 reports, 14 were identified with the adverse event of hypermagnesaemia or elevated magnesium. All of the case reports of hypermagnesaemia or elevated magnesium received were in patients receiving Numeta G13%E.

Normal serum magnesium levels in the literature are generally reported as ranging from 0.7-1 mmol/L in preterm infants. The levels of magnesium reported in these case reports mainly ranged from 1.025 mmol/L to > 1.5 mmol/L with levels greater than 1.2 mmol/L reported in 9 out of 14 cases while one case was reported as > 1.5 mmol/L (exact level not reported). None of the patients had additional adverse events reported beyond the abnormal laboratory value of hypermagnesaemia. There were no reports of possible clinical manifestations of hypermagnesaemia such as generalised weakness, hypo-reflexia, nausea, vomiting, hypocalcaemia, respiratory failure, hypotension and arrhythmias.

Only one report of hypermagnesaemia (magnesium level 1.14mmol/L) associated with Numeta G16%E has been reported, on 18 June 2013. Preliminary information on this report indicated that additional magnesium (other than Numeta) was administered to the patient. When it was withdrawn, the magnesium levels returned to an acceptable level.

Available guidelines with recommendations for magnesium intake

In view of the uncertainties regarding the appropriateness of the levels of magnesium in Numeta, the MAH, at the request of the PRAC, performed a comprehensive review of the recommendations in the literature for magnesium intake in preterm infants and neonates and children up to two years, including independent studies and clinical guidelines.

This review showed that the recommendations for parenteral magnesium intake for preterm neonates are quite varied and range from 0.15-0.5 mmol/kg/d. However, the American Society of Parenteral and Enteral Nutrition (ASPEN) and the joint ESPEN/ESPGHAN guidelines have been considered gold standard for paediatric nutrition since they were published in 2005.

ASPEN specify the daily magnesium requirements for preterm neonates as 0.15 to 0.25mmol/kg/d (*Canada et al*, 2005; *Mirtallo et al*, 2004). The ESPGHAN/ESPEN guidelines do not specify the needs of preterm infants for parenteral magnesium intake but the enteral guidelines specify a requirement of 0.33-0.62 mmol/kg/d and assuming 40% retention of daily dietary intake this equates to a magnesium requirement of 0.13-0.25 mmol/kg/d (*Agostini et al*, 2010). However this needs to be interpreted with caution as retention can vary depending on magnesium status and dietary intake.

Similarly guidelines for parenteral magnesium intake for term infants and children up to two years also display a wide range with recommendations for neonates varying from 0.125-0.5 mmol/kg/d and for children up to 2 years of age varying from 0.125-0.25 mmol/kg/d. However, ESPGHAN/ESPEN have recommended parenteral magnesium intakes of 0.2 mmol/kg/d for infants of 0-12 months of age and 0.1 mmol/kg/d for children between 1 to 13 years of age. It is noted that these guidelines are based on limited evidence (grading of recommendation D). The ASPEN guidelines are the same as for preterm neonates and range between 0.15-0.25 mmol/kg/d.

The recommendations of the ASPEN and joint ESPEN/ESPGHAN guidelines are summarised and compared to the level of Magnesium in Numeta G13%E and Numeta G16%E at maximal dose in the tables below:

Table 1. Magnesium Intake Recommendations in Premature Neonates

ESPEN/ESPGHAN Recommendation	**ASPEN Recommendation**	**Magnesium in Numeta G13%E at maximal dose**
No recommendation for parenteral magnesium intake in preterm infants	0.15-0.25 mmol/kg/d	0.55 mmol/kg/d

Table 2. Magnesium Intake Recommendations in neonates and children up to 2 years of age

Age group	**ESPEN/ESPGHAN Recommendation**	**ASPEN Recommendation**	**Magnesium in Numeta G16%E at maximal dose**
0-12 months	0.2 mmol/kg/d	0.15-0.25 mmol/kg/d	0.3 mmol/kg/d
1-2 years	0.1 mmol/kg/d	0.15-0.25 mmol/kg/d	0.3 mmol/kg/d

Request for Paediatric Committee (PDCO) advice

Pursuant to Article 6(1)(d) of Regulation (EC) No 1901/2006 as amended, the PDCO's opinion on Numeta was sought. The PCDO discussed the issue at their August 9th meeting, and a summary of its advice is presented hereinafter.

The PDCO noted that while the levels of hypermagnesaemia observed with Numeta G13%E were not considered to be of undue clinical concern, the MAH decision to reformulate was welcomed due to the potential for development of adverse events in patients with additional risk factors for hypermagnesaemia or its consequences. It was also recommended that the MAH should take the

opportunity to review the levels of other constituents, including the calcium level, present in the product.

Regarding Numeta G16%E, PDCO noted that recent data suggest that normal magnesium levels in infants are believed to be higher than previously thought (Canadian Laboratory Initiative on PEdiatric Reference Intervals [CALIPER][1]).

The PDCO considered Numeta G16%E could remain on the market as long as warnings and advice on magnesium intake and monitoring are provided to healthcare professionals (HCPs) within the product information. It was also highlighted that evidence of adverse events was absent. It was recommended that a study of magnesium intake and serum levels is in the intended age range be conducted to inform any decisions on reformulation. The PDCO was of the view that the product information should highlight the need for appropriate patient selection and baseline monitoring with follow-up monitoring in accordance with routine clinical practice and the clinical needs of the individual patient. The potential for accumulation in patients with renal impairment and/or other risk factors in addition to clarification relating to the hourly/ daily infusion rates were also recommended for the product information.

Safety overview and discussion

The MAH has identified 14 case reports of hypermagnesaemia or increased magnesium associated with Numeta G13%E in their global safety database and 1 case associated with Numeta G16%.

The levels of magnesium reported in these case reports mainly ranged from 1.025mmol/L to > 1.5mmol/L with levels greater than 1.2mmol/L reported in 9 out of 14 cases while one case was reported as > 1.5mmol/L.

No clinical symptoms relative to hypermagnesaemia have been reported with the use of Numeta G13%E or Numeta G16%E. However, the symptoms of hypermagnesaemia include generalised weakness, respiratory failure, hypotension, arrhythmias and altered mental status and many of these symptoms are present in preterm infants because of their early birth status and immature organ function. It was acknowledged that it would be difficult to differentiate the clinical symptoms of hypermagnesaemia from the clinical symptoms normally present in preterm infants. In this regards, adverse events of hypermagnesaemia in pre-term neonatal patient population may not be identified and may be underreported, which raises concerns. In addition, the regular monitoring of serum magnesium levels in preterm neonates is not standard clinical practice for most neonatologists and may not always be appropriate for the patient. This could also result in fewer episodes of hypermagnesaemia noted and reported with Numeta G13%E.

The magnesium content of Numeta G13%E is 0.43mmol/100mL. In order to receive on the third day 4g amino acids/kg/d, the preterm infant would receive 127.7 ml/kg/d or 0.55 mmol/kg/d of magnesium (Numeta G13%E maximal content of amino acid is 3.9g/100ml). This magnesium intake with Numeta G13%E appears higher than the recommendation of the ASPEN and ESPGHAN/ESPEN guidelines for preterm neonates (0.15 to 0.25mmol/kg/d and 0.13-0.25mmol/kg/d respectively).

Considering the number of cases of hypermagnesemia reported with Numeta G13%, the vulnerability of the patient population, difficulties in recognising clinical symptoms of hypermagnesaemia in this patient population and the content of Magnesium in Numeta G13%E in the context of relevant

[1] Canadian Laboratory Initiative on PEdiatric Reference Intervals, http://www.caliperdatabase.com/caliperdatabase/controller?op=menu_reference_intervals&sm=0, accessed 29/08/2013

recommendations for Magnesium intake in guidelines and literature, the MAH identified the need for reformulation the product.

With regards to Numeta G16%E, the maximum total licensed amount of magnesium that can be delivered to term neonates with Numeta G16%E is 0.30 mmol/kg/d. Although this is within the recommendations reported in the literature as a whole, it is above the recommendations of the ASPEN guideline of 0.15-0.25 mmol/kg/d and above the ESPEN/ESPGHAN guideline of 0.2mmol/kg/d. In the case of children up to two years of age, the maximum total licensed amount of magnesium that can be delivered is 0.30mmol/kg/day. This is above the magnesium dosing recommendations from the literature and above the ASPEN guideline of 0.15-0.25 mmol/kg/g and the ESPEN/ESPGHAN guideline of 0.1mmol/kg/d for children from one year and older.

However the PRAC noted that there was only one case of hypermagnesaemia reported (magnesium level 1.14mmol/L) and the report was confounded by the fact that additional magnesium may have been administered. The corresponding serum levels of magnesium following administration of a maximum daily dose of Numeta G16%E is unknown. In addition there is no evidence that the amount administered will result in abnormal serum magnesium levels, and this will likely depend of various factors, including the renal function of the subjects. In order to minimise the potential risks of hypermagnesemia, the PRAC, in line with the PDCO advice, considered that adequate advice could be included in the product information of Numeta G16%E, including a recommendation to monitor the magnesium level in patients at increased risk of developing hypermagnesaemia, e.g. patients with impaired renal function, patients receiving other medicinal products which place them at risk of developing hypermagnesaemia or patients receiving magnesium from other sources, including neonates whose mother's recently received magnesium in the antepartum period.

2.2. Risk minimisation activities

Risk management plan

The PRAC recommended that an updated risk management plan (RMP) reflecting the following risk minimisation measures should be submitted, through the relevant regulatory procedure, to the national competent authorities for assessment within 3 months after finalisation of the current procedure.

Proposals for evaluating the effectiveness of the risk minimisation measures should also be provided as part of the updated RMP.

Changes to the Product Information

Based on above assessment, the PRAC recommended amendments to the product information (PI) for Numeta G16%E. Section 4.4 of the Summary of Product Characteristics (SmPC) was amended to reflect the potential risk of hypermagnesemia and associated symptoms, and the recommendation to monitor the serum magnesium level at baseline and at appropriate intervals thereafter, in accordance with routine clinical practice and the clinical needs of the individual patient, particularly in patients at increased risk of developing hypermagnesaemia, including patients with impaired renal function, patients receiving other medicinal products which place them at risk of developing hypermagnesaemia or patients receiving magnesium from other sources, including neonates whose mother's recently received magnesium in the antepartum period.

The recommendation to reduce the infusion rate or to stop the infusion of Numeta (as deemed clinically appropriate and safe) should the serum magnesium levels be elevated was also included in this section.

The section 2 of the package leaflet (PL) was amended accordingly.

In addition, the SmPC and PL should include information on the way of reporting of adverse reactions should also be added, in accordance with the latest template.

DHPC and Communication action plan

A direct healthcare professional communication (DHPC) was agreed to inform the healthcare professionals on the conclusions of the review and highlight the new recommendations in relation to the risk of hypermagnesaemia.

Future Monitoring

i. Active surveillance scheme

The PRAC recommended that routine pharmacovigilance measures are strengthened and that active surveillance schemes for hypermagnesaemia and follow-up questionnaires for case reports of hypermagnesaemia/suspected hypermagnesaemia are put in place.

ii. Post-authorisation safety study (PASS)

As a condition of the marketing authorisation, the PRAC requested the MAH to conduct a prospective non-interventional post-authorisation safety study to further evaluate magnesium levels observed in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice. The protocol of this study should be submitted with the risk management plan for agreement with the national competent authorities of the Member States.

In accordance also with the Article 23 of Regulation (EC) No 726/2004 the products will be included in the additional monitoring list. The corresponding inverted triangle and explanatory statement will therefore be added in the product information.

3. Benefit-risk assessment

Magnesium is an important electrolyte, particularly for a preterm infant. Magnesium serves several important functions in the human body; it is a co-factor for DNA and protein synthesis, oxidative phosphorylation, enzyme activity and regulation of parathyroid hormone secretion (*Volpe*, 2013; *Ayuk & Gittoes*, 2011; *Shils et al*, 1999). Magnesium also plays a critical role in maintaining normal nerve and muscle function, cardiac excitability, neuromuscular conduction, muscular contraction, vasomotor tone and for a balanced immune response (*Brandao et al*, 2013).

Magnesium has been shown to improve neurological outcome for premature babies when given antenatally to the mother (*Doyle et al*, 2010) and is thought to have neuroprotective effects also in other circumstances. The vasodilating effect of magnesium has been used to treat pulmonary hypertension in newborns (*Tolsa et al*, 1995). In this study on ventilated newborns serum magnesium levels of 3.5-5.5 mmol/l did not give any adverse events. Even though no studies fulfil criteria to show evidence of effectiveness and new effective treatments have replaced magnesium in therapy of pulmonary hypertension.

Low serum magnesium generally indicates total body magnesium depletion but can be normal in the presence of total body magnesium deficiency.

Most patients with hypomagnesemia show no acute symptoms but it can still lead to osteoporosis and is correlated to increased inflammation and metabolic syndrome. Severe hypomagnesemia is

uncommon but can cause seizures, drowsiness, cardiac ventricular defibrillation, hypokalemia and hypocalcemia (*Whang et al*, 1994).

Thus, it is warranted that a nutrition solution for preterm newborn infants contains magnesium as one electrolyte, although the amount should be balanced to result in appropriate levels.

Numeta G13%E

Numeta G13%E is indicated for PN in preterm newborn infants when oral or enteral nutrition is not possible, insufficient or contraindicated. PN is a well-established medical support modality that has been routinely used for many years and can improve survival in infants and children whose nutritional requirements cannot be met through oral or enteral nutrition.

The initial application for Numeta G13%E and Numeta G16%E was supported by a prospective, multicentre, non-comparative, open-label phase 3 study (Ped3CB/P01/06/MuB). This study found Numeta to be acceptable to paediatric clinical staff in terms of handling, ease of use and time from prescription to infusion. In terms of efficacy measurements, the different Numeta formulations were able to maintain or increase body weight.

A new safety concern with Numeta G13%E has been identified based on a signal raised by the MAH following receipt of case reports of hypermagnesaemia in preterm neonates.

Hypermagnesaemia is a serious clinical condition which can lead to generalised weakness, respiratory failure, hypotension, arrhythmias (especially if not otherwise explained by the clinical condition of the infant/child). Hypermagnesaemia may also cause non-specific symptoms such as nausea, vomiting and flushing. It should be noted that clinical signs may not be identifiable unless hypermagnesaemia is severe.

The PRAC, considering all evidence available, including the PDCO advice, concluded that the risk of hypermagnesaemia is enhanced by both the clinical complexity of identifying the symptoms in this patient population and the fact that renal clearance of magnesium is decreased in neonates leading to the potential for persistence of increased magnesium levels (Mittendorf et al, 2001).

Therefore, the benefit-risk balance for Numeta G13%E as currently formulated is considered as not favourable. It is therefore recommended that the marketing authorisation is suspended, and the product reformulated to reflect acceptable magnesium levels.

Numeta G16%E

Numeta G16%E is indicated for PN in term newborn infants and children up to 2 years when oral or enteral nutritional is not possible, insufficient or contraindicated. The marketing authorisation of Numeta G16%E was based on the same study (Ped3CB/P01/06/MuB) which showed that Numeta shares the same benefits of a standardised PN solution as outlined for the lower strength product for premature neonates above.

The ESPEN/ESPGHAN guideline recommends a lower magnesium intake of 0.2mmol/kg/d for infants of 0-12 months of age and 0.1mmol/kg/d for children between 1 to 13 years of age.

At a maximal dose of 96.2 ml/kg/d Numeta G16%E delivers 0.3 mmol/kg/d of magnesium which is above the recommended levels. Consequently there is a potential risk for hypermagnesemia particularly in patients with reduced renal function.

To date there has been only one report of hypermagnesaemia received for Numeta G16%E (magnesium level 1.14 mmol/L) but this report was confounded because Numeta G16% E was

supplemented with additional magnesium administration and no associated adverse events were reported. In addition, recent data highlighted by the PDCO suggest paediatric reference ranges for magnesium may be higher than previously thought (Canadian Laboratory Initiative on PEdiatric Reference Intervals [CALIPER][2]). Therefore, in summary, there is no unconfounded report of hypermagnesemia with Numeta G16%E, no evidence of harm and there are uncertainties in relation to paediatric reference ranges for magnesium which may be higher than previously thought.

Additionally, the PRAC took account of differences in the indicated population for Numeta G16%E versus Numeta G13%E and that full term neonates and children up to two years have further progressed in terms of nephrogenic development. Although glomerular immaturity does persist during the first few months after birth and the immature kidney has limited adaptability in case of excess administrations of electrolytes, monitoring of serum magnesium levels should mitigate the potential risk, with initial monitoring at baseline and frequency of follow-up monitoring determined by the clinical circumstances and routine clinical practice. The product information should be updated to inform health care professionals of the potential risk of hypermagnesemia and to provide monitoring advice particularly for more vulnerable subgroups.

The risk of hypermagnesemia and all measures considered necessary to mitigate this risk (i.e. agreed additional pharmacovigilance activities, as listed above and risk minimisation activities such as DHPC, changes to the product information) should be reflected in a revised RMP, which should also include proposals for evaluating the effectiveness of the risk minimisation activities.

In addition to these measures, it is also considered that the MAH should conduct a prospective non-interventional post-authorisation safety study to further evaluate magnesium levels observed in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice.

Based on the currently available information, the benefit-risk balance of Numeta G16%E is considered to remain favourable subject to the warnings, additional pharmacovigilance activities and additional risk minimisation measures agreed.

4. Overall conclusion

Numeta G13%E

Having considered the overall submitted data provided by the MAHs in writing, the stakeholder's submission and the PDCO advice, the PRAC concluded that the benefit-risk balance of Numeta G13%E for parenteral nutrition in preterm newborn infants when oral or enteral nutrition is not possible, insufficient or contraindicated is no longer favourable.

The PRAC, having considered the matter, recommended the suspension of the marketing authorisation for Numeta G13%E.

For the suspension of the marketing authorisation to be lifted, the MAH should reformulate the product, to include a level of magnesium which is justified based on the most recent knowledge in the area.

[2] Canadian Laboratory Initiative on PEdiatric Reference Intervals, http://www.caliperdatabase.com/caliperdatabase/controller?op=menu_reference_intervals&sm=0, accessed 29/08/2013

Numeta G16%E

Having considered the overall submitted data provided by the MAHs in writing, the stakeholder's submission and the PDCO advice, the PRAC concluded that:

a. the marketing authorisation holders should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;

b. the marketing authorisation holders should implement risk minimisation measures;

c. the marketing authorisations should be varied.

The PRAC considered that a DHPC was needed to communicate the outcome of the present review.

The PRAC also recommended that the MAH should submit a revised RMP within 3 months following the decision of this procedure. The MAH is also requested to conduct a non-interventional prospective observational post-authorisation study to further investigate serum magnesium levels in term newborn infants and children up to two years following use of Numeta G16%E as well as proposals for evaluating the effectiveness of the risk minimisation activities.

The protocol should be submitted within the revised risk management plan submission.

The PRAC concluded that the risk-benefit balance of Numeta G16%E for parenteral nutrition in term newborn infants and children up to two years when oral or enteral nutrition is not possible, insufficient or contraindicated remains favourable subject to the warnings, additional pharmacovigilance activities and additional risk minimisation measures agreed.

5. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate the outcome of the assessment and the measures taken for the safe use of Numeta G16%E.

Relevant European healthcare professional organisations were consulted and provided input on the draft DHPC. The final version of this DHPC agreed by the PRAC is provided together with the communication plan (see attachments to this report).

The MAH should agree the translations and local specificities of the DHPC with national competent authorities.

6. Conclusion and grounds for the recommendation

Numeta G13%E

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC for Numeta G13%E;
- The PRAC reviewed all available data from clinical studies, published literature, post-marketing experience on the safety and efficacy of Numeta G13%E in particular with regards to the risk of hypermagnesemia, as well as the stakeholder's submission and the PDCO advice;

- The PRAC considered the role of magnesium in the development of pre-term newborn infants and reviewed all available data on the risk of hypermagnesemia in this population, the available clinical guidelines on parenteral magnesium intake in preterm newborn infants and the content of magnesium in the current formulation of Numeta G13%E;
- The PRAC concluded that there is a risk for hypermagnesaemia when Numeta G13%E is administered to preterm newborn infants.

In view of the safety concerns in relation to hypermagnesemia in the vulnerable indicated patient population (preterm neonates) arising from the magnesium content in the current formulation of Numeta G13%E and taking account of the reported cases and the available evidence from literature and guidelines, the PRAC concluded that pursuant to Article 116 of Directive 2001/83/EC the benefit-risk balance of Numeta G13%E as parenteral nutrition for preterm newborn infants for whom oral or enteral nutrition is not possible, insufficient or contraindicated is no longer favourable.

Therefore, following the provisions under Article 107j(3) of Directive 2001/83/EC, the PRAC recommends the suspension of the marketing authorisations for Numeta G13%E.

For the suspension to be lifted, the National competent authorities of Member States shall verify that the following conditions are fulfilled by the MAH:

The MAH should reformulate the product, to include a level of magnesium which is justified based on the most recent knowledge in the area (see Annex III – Conditions for lifting the suspension of the marketing authorisations).

Numeta G16%

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC for Numeta G16%E;
- The PRAC reviewed all available data from clinical studies, published literature, post-marketing experience on the safety and efficacy of Numeta G16%E in particular with regards to the risk of hypermagnesemia, as well as the stakeholder's submission and the PDCO advice;
- The PRAC reviewed all available data on the risk of hypermagnesemia in term newborn infants and children up to two years;
- The PRAC considered the role of magnesium in the development of term newborn infants and children up to two years, all available guidance providing recommendation for parenteral magnesium intake in newborn infants and in children up to two years, and the content of magnesium in the current formulation of Numeta G16%E;
- The PRAC is of the opinion that there is a potential risk for hypermagnesaemia when Numeta G16%E is administered to term newborn infants and children up to two years, particularly in patients with reduced renal function, and newborn infants of mothers who were receiving supplemental magnesium prior to delivery;
- The PRAC concluded that in view of the currently available safety data in order to maintain a favourable benefit-risk as parenteral nutrition in term newborn infants and children up to 2 years when oral or enteral nutrition is not possible, insufficient or contraindicated, additional warnings on the risk of hypermagnesemia should be introduced in the Product Information;

- In addition, the magnesium level should be monitored at baseline and at appropriate intervals thereafter, in accordance with routine clinical practice and the needs of the individual patient. This is especially important in those patients at increased risk of developing hypermagnesaemia including patients with impaired renal function, patients receiving other medicinal products which place them at risk of developing hypermagnesaemia or patients receiving magnesium from other sources, including neonates whose mother's recently received magnesium in the antepartum period. If serum magnesium levels are elevated the infusion of Numeta G16%E should be stopped or infusion rate reduced as deemed clinically appropriate and safe.
- The PRAC also concluded that there was need for further risk minimisation measures such as information to healthcare professionals. A DHPC was agreed, together with the timelines for distribution;
- The PRAC also concluded that a prospective non-interventional post-authorisation safety study should be conducted to further evaluate magnesium levels observed in term newborn infants and children up to two years of age treated with Numeta G16%E in routine clinical practice.

The PRAC, as a consequence, concluded that the benefit-risk balance for Numeta G16%E as parenteral nutrition in term newborn infants and children up to two years when oral or enteral nutrition is not possible, insufficient or contraindicated remains favourable subject to the warnings, additional pharmacovigilance activities and additional risk minimisation measures agreed.

The PRAC in accordance with Article 107j(3) of Directive 2001/83/EC, recommends by consensus that

a. the marketing authorisation holders should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study (see Annex V – Conditions of marketing Authorisations);

b. the marketing authorisation holders should implement risk minimisation measures;

c. the marketing authorisations of Numeta G16%E should be varied (in accordance with changes to the product information as set out in Annex IV).

Appendix 1

Listing of submissions of all data received by the Agency (i.e. from MAHs and other stakeholders) for Numeta G13%E and Numeta G16%E emulsions for infusion, and associated names

Submission
MAHs
Baxter
Stakeholders
Healthcare professional - Pharmacist