Annex II

Scientific conclusions and grounds for the conclusions

Scientific conclusions and grounds for the conclusions

The CMDh, having considered the PRAC recommendation dated 5 September 2013 with regards to Numeta G13%E and Numeta G16%E agrees with the overall PRAC scientific conclusions and grounds for the conclusions therein as stated below:

Overall summary of the scientific evaluation of Numeta G13%E and Numeta G16%E by PRAC

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.

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.

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 products outlined in the initial application and risk management plan include drug administration errors, 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 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).

A new safety concern with Numeta G13%E was identified based on a signal raised by the marketing authorisation holder (MAH) following receipt of case reports of hypermagnesaemia in preterm neonates. In order to prevent any potential harm to premature infants, the MAH decided to recall the product from the market.

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, 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.

Pursuant to Article 6(1)(d) of Regulation (EC) No 1901/2006 as amended, the PDCO's opinion on Numeta was sought in the context of this review.

Clinical safety

The MAH 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 ranged mainly 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.

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.

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). 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.

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.

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.

Early recognition and treatment of hypermagnesemia may prevent or minimise life-threatening events, however the vast majority of mild hypermagnesaemia patients may be missed as measurement of magnesium levels is not routine in clinical practice.

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).

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.

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. This magnesium intake with Numeta G13%E appears higher than the recommendation of the American Society of Parenteral and Enteral Nutrition (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 recommendations for magnesium intake in guidelines and literature, the MAH identified the need for reformulation the product.

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 with a level of magnesium which is justified based on the most recent knowledge in the area.

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 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][1]). 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

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

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 direct healthcare professional communication (DHPC), changes to the product information) should be reflected in a revised risk management plan (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.

Overall conclusion and conditions to the Marketing Authorisations

Numeta G13%E

Having considered the overall submitted data provided by the MAH 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 therefore 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.

Numeta G16%E

Having considered the overall submitted data provided by the MAH 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 to relevant healthcare professionals.

The PRAC also recommended that the MAH should submit a revised RMP within 3 months after finalisation of the procedure including proposals for evaluating the effectiveness of the risk minimisation activities. 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 should be conducted. The MAH should submit the protocol for the above mentioned study within the revised RMP submission.

The PRAC concluded that the benefit-risk 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.

Grounds for PRAC 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).

CMDh agreement

The CMDh, having considered the PRAC recommendation dated 5 September 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached an agreement on the suspension of the marketing authorisations for Numeta G13%E. The condition for lifting the suspension of the Marketing Authorisations for Numeta G13%E are set out in Annex III. In order to facilitate its implementation at national level, the CMDh considered that clarification on the supervision of the appropriate procedure for the fulfilment of the condition to lift the suspension of Numeta G13%E should be provided and therefore the following was added to Annex III:

“The MAH should liaise with the Reference Member State to agree on the appropriate procedure to be used for the fulfilment of this condition for lifting the suspension.”

The CMDh also reached an agreement on the variation to the terms of the Marketing Authorisations for Numeta G16%E for which the relevant sections of Summary of Product Characteristics and package leaflet are set out in Annex IV, subject to the conditions set out in Annex V.

The timetable for the implementation of the agreement is set out in Annex VI.