13 June 2013
Patient Health Protection
EMA/PRAC/365946/2012

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for Numeta G13%E and Numeta G16%E emulsions for infusion, and associated names

Article 107i of Directive 2001/83/EC

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

On 10 June 2013, the marketing authorisation holder (MAH) for Numeta G13%E informed the European national competent authorities that following reports of hypermagnesaemia in preterm neonates, Numeta G13%E batches had been put on hold at warehouse level. Furthermore, the MAH also outlined a decision to enact a recall of the product from the market to prevent any potential harm to preterm neonates.

On 13 June 2013, considering uncertainties regarding the availability of adequate alternatives across the European Union Member States, the Swedish Competent Authority (MPA – Medical Products Agency) notified the European Medicines Agency, in accordance with Article 107i of Directive 2001/83/EC, of the urgency to undertake a review and agree whether the benefit/risk balance of Numeta G13E% remains positive, and if there is need for additional risk minimisation measures.

Although no reports were received for Numeta G16%E, the Pharmacovigilance Risk Assessment Committee (PRAC) has decided at its June 2013 meeting that this product would also be included in the EMA review because of its magnesium content and of its use in neonates and infants/toddlers up to the age of 2 years, who may also be at risk of developing hypermagnesaemia.

In view of the above, the marketing authorisation holder for Numeta G13%E and Numeta G16%E is requested to:

1. Provide an overview of the EU Member States (MS) where the products Numeta G13%E and Numeta G16%E are authorised and marketed and an analysis of exposure since initial marketing authorisations. An analysis by age groups (premature neonates, neonates and infants/toddlers up to the age of 2 years) should also be included.

2. Provide a discussion on the place of Numeta G13%E and Numeta G16%E in current clinical practice, including a summary of the availability of alternatives in all EU Member States.

3. Provide a thorough and evidence-based discussion on recommendations for daily levels of intravenous magnesium which should be administered to premature neonates, neonate and infants/toddlers up to the age of 2 years as part of parenteral nutritional therapy regimes.

4. In relation to the risk of hypermagnesaemia in premature neonates, neonates and infants/toddlers up to the age of 2 years, please provide a critical appraisal of its epidemiology including frequency, potential mechanisms, seriousness, potential severity, preventability, treatment and impact on individual paediatric patients.

5. Provide a thorough review of the available information from all relevant data sources in order to identify potential cases of hypermagnesemia in premature neonates, neonates and infants/toddlers up to the age of 2 years (including potential reports of the consequences of hypermagnesaemia) with possible causal association with Numeta G13%E and Numeta G16%E. Please submit a summary and critical assessment of these reviews as well as all relevant case narratives.
   The discussion should include a discussion of possible explanations for the occurrence of the hypermagnesaemia/ clinical symptoms of hypermagnesaemia including whether it could in some cases be related to increased administration of magnesium from other sources including administration of magnesium to the mother during labour.

6. Given the MAH's suspicion that the levels of magnesium in Numeta G13%E can result in hypermagnesemia in the preterm neonate, please provide an assessment of the appropriateness of the levels of magnesium in the fixed combination products Numeta G13%E and Numeta G16%E indicated for premature neonates, neonates and infants (up to 2 years of age). This assessment should be supported by relevant scientific evidence and reference to relevant guidelines as appropriate.

7. Provide a benefit/risk balance assessment for Numeta G13%E and Numeta G16%E as currently formulated for use in 1)preterm neonates, 2) neonates (3 infants/toddlers under 2 years.

8. Please provide proposals and justification with supportive evidence for any risk minimisation measures to address the risk of hypermagnesaemia due to administration of Numeta G13%E which could be taken in order to improve the benefit/risk of Numeta G16%E in preterm and term neonates and infants/toddlers< 2years. Please also comment on how the impact of such measures should be monitored and assessed.