LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Numeta G13E

(olive oil, refined, cysteine, glutamic acid, histidine, ornithine hydrochloride, phenylalanine, taurine, aspartic acid, threonine, glycine, magnesium acetate tetrahydrate, isoleucine, tyrosine, arginine, potassium acetate, leucine, serine, valine, soya-bean oil, refined, calcium chloride dihydrate, lysine monohydrate, proline, glucose monohydrate, sodium glycerophosphate, hydrated, alanine, methionine, tryptophan)

## Assessment Report on signal of hypermagnesemia reported in premature neonates

### Procedure number: SE/H/918

### MAH: Baxter Healthcare



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| **Reference Member State (RMS)** | Sweden |
| **Date of this report:** | 13 June 2013 |

**ADMINISTRATIVE INFORMATION**

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| **Product name:** | Numeta G13E |
| **Active substance(s) (INN or common name):** | olive oil, refined, cysteine, glutamic acid, histidine, ornithine hydrochloride, phenylalanine, taurine, aspartic acid, threonine, glycine, magnesium acetate tetrahydrate, isoleucine, tyrosine, arginine, potassium acetate, leucine, serine, valine, soya-bean oil, refined, calcium chloride dihydrate, lysine monohydrate, proline, glucose monohydrate, sodium glycerophosphate, hydrated, alanine, methionine, tryptophan |
| **Currently approved indications:** | Numeta is indicated for parenteral nutrition in preterm newborn infants when oral or enteral nutrition is not possible, insufficient or contraindicated. |
| **Pharmaceutical form and strengths:** | Emulsion for infusion |

# 1 Introduction

Parenteral nutrition is the use of intravenous macronutrients, micronutrients and fluids to provide nutritional support in patients who cannot be fed by oral or enteral nutrition. Nutritional support in the preterm neonate is important to prevent morbidity, growth retardation, promote positive nitrogen balance, reduce the incidence of respiratory distress syndrome and to promote neurocognitive development.

Numeta G13E (glucose, lipids, amino-acids and electrolytes) is an industrially manufactured, heat sterilized parenteral nutrition solution (300 ml container) which was specifically designed for preterm neonates, for whom oral or enteral nutrition is not possible, insufficient or contraindicated. It has a fixed content (per cc) of macronutrients and micronutrients including electrolytes.

Numeta G13E is licensed through EU Decentralized Procedure in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, United Kingdom, with Sweden being the Reference Member State. It is also registered nationally in Malta. It was first authorised in 2011.

**On 10 June 2013, Sweden, Reference Member State for Numeta G13E, was informed by the Marketing Authorisation Holder (MAH) that, on the basis of safety concerns, Numeta G13E batches have been put on hold at the warehouse level. Further, the MAH also outlined a decision to enact a recall of the product from the market to prevent any potential harm to preterm neonates.**

# 2 Safety concern

### Summary of the MAH's submission

In late March 2013, Baxter became aware of three (3) spontaneous case reports of hypermagnesemia in preterm infants from Italy. No other associated adverse events were reported in conjunction with hypermagnesemia in these patients. Based on those cases, a decision was made that while no clear signal was present, Baxter would continue to monitor Numeta case reports for hypermagnesemia going forward.

In May 2013, Baxter Global Pharmacovigilance was informed about eight (8) additional case reports of hypermagnesemia among 11 preterm infants from an investigator-initiated study running in Belgium (Study title: *Organization and surveillance of parenteral nutrition in premature newborn infants weighing less than 1500g using Numeta G13% from first day of life. A prospective mono-center, non-interventional, non-comparative, open-labeled study with data collection on intakes and nutritional markers as available*).

On 04 June 2013, the Baxter Pharmacovigilance database was searched for all case reports for Numeta to identify any specific case reports potentially associated with signs and/or symptoms suggestive of hypermagnesemia. The search identified thirteen (13) case reports (3 from Italy, 8 from the investigator-initiated study and 2 from Finland that had just been received). All of these case reports involve Numeta G13%E administered to preterm newborn infants with the only reported event being hypermagnesemia.

On 05 June 2013, after full analysis of the data and investigation, this was determined to be a confirmed safety signal.

The symptoms of hypermagnesemia include generalized weakness, respiratory failure, hypotension, arrhythmias. Many of these symptoms are present in preterm infants because of their early birth status and immature organ function. Therefore, it would be difficult to differentiate the clinical symptoms of hypermagnesemia from the clinical symptoms normally present in preterm infants Adverse events of hypermagnesemia in this patient population may not be identified and subsequently reported. In addition, the monitoring of daily serum magnesium levels in preterm neonates is not a standard of practice by many neonatologists. This may also have resulted in less episodes of hypermagnesemia being recognized and reported during the current use of Numeta G13. There is no published data detailing at what serum level of magnesium (hypermagnesemia) clinical symptoms develop in preterm neonates.

MAH's Investigation of the signal

Numeta G13%E (glucose, lipids, amino-acids and electrolytes) was developed with support from external expert neonatologists in the period 2003 - early 2005.

Guidelines or publications since 1988 have recommended daily intravenous magnesium intakes of 0.2-0.44 mmol/kg/day for preterm and term neonates.

Subsequent to the formulation of Numeta, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPHAGEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) have published the first European guidelines on paediatric parenteral nutrition end of 2005. This board recommended based on lowest level of evidence (GORD) for full term neonates a parenteral magnesium intake of 0.2 mmol/kg/day. There were no recommendations made for preterm neonates related to parenteral magnesium intake.

Numeta G13%E comes in a 300ml bag, which contains 0.43 mmol Magnesium per 100ml. The prescribed daily volume of Numeta G13%E depends on the body weight of the preterm neonate and its parenteral nutrient requirements.

In cases when the whole nutrient requirements need to be covered parenterally usually more than 100 ml/kg/day of Numeta G13%E would be infused resulting in an average daily magnesium intake of 0.52 mmol/kg/day.

Consequently, in these cases Numeta G13%E provides higher levels of magnesium than given in available guidelines for preterm infants.

MAH's Conclusion and proposed further actions

In the submission from the MAH received on 10 June 2013, the following plan for further actions was outlined:

1. **Recall** product from the market and **reformulate** Numeta G13%E.
2. Send a **Direct Healthcare Professional Communication** to our customers (which was attached).

However, the MAH realized that there might be situations where healthcare facilities are currently dependent on Numeta G13%E for the feeding of premature neonates. This dependency and the risk of malnutrition and its resultant co-morbidities in preterm neonates not receiving parenteral nutrition must be weighed against the risk of hypermagnesemia that may develop with the use of Numeta G13%E. Baxter is therefore proposing the following actions in those cases:

- Determining whether alternative parenteral nutrition products for preterm newborn infants are available on the markets in the different countries (see algorithm in the medical assessment in Attachment 1);
- Performing a step wise recall based on the alternative product availability;
- Distributing Numeta G13%E only in emergency case when no alternative product is available while still looking for an alternative;
- When Numeta G13%E is to be used, providing appropriate HCP education with the following instruction:
    a. Daily monitoring of serum magnesium levels in the premature neonates receiving Numeta G13%E,
    b. If serum magnesium levels are determined to be elevated (above reference range normal values), the HCP will be instructed to stop or reduce the infusion rate of Numeta G13%E as deemed clinically appropriate and safe.

RMS comment: see Section 3 Discussion and Conclusions below

# 3 RMS's Discussion and conclusions

As outlined above, the MAH has submitted information about their decision to put on hold / recall Numeta G13E, and a short summary about the reasons for taking this decision. The submitted information is very limited including that no description of, including no narratives, the cases reported have been provided. Thus, it is not possible to undertake an in depth assessment of this issue based in the available information.

The occurrence of hypermagnesemia in a preterm neonate can lead to clinical symptoms which can be serious, including generalized weakness, respiratory failure, hypotension, arrhythmias.

The MAH suspects that the levels of magnesium in Numeta G13E can result in hypermagnsesemia in the preterm neonate, and this is the basis for their decision to recall and reformulate Numeta G13E to reduce the levels of magnesium in the product.

Based on the arguments provided by the MAH, too high levels of magnesium in Numeta G13E cannot be excluded, and this issue warrants further in depth assessment.

As proposed by the MAH, and based on the currently available information, it is agreed that the use of Numeta G13E should be avoided unless there is no other treatment alternative available. Availability of alternatives can differ in different Member States, and at present this is not a full picture about the situation across all EU MSs where Numeta G13E is on the market. Therefore, there could be situations where it can be justified to use Numeta G13E, if such use is carefully monitored. Such monitoring can include:

- to be vigilant of symptoms of hypermagnesmia such as generalized weakness, respiratory failure, hypotension, arrhythmias
- to monitor serum magnesium levels closely
- and if serum magnesium levels are elevated (above reference range normal values) the infusion rate of Numeta G13%E should be stopped or reduced as deemed clinically appropriate and safe.

**To conclude:** Case reports of hypermagnesemia have been received by the MAH. The MAH suspects that the levels of magnsesium in Numeta G13E can be too high, and thus have a potential to cause hypermagnesemia which also can lead to clinical consequences, including serious events. Therefore, they have decided to recall the product, although they can in situations where there is no alternative available make the product available.

Based on the submitted information, an in depth assessment cannot be undertaken. Nevertheless, from the information provided by the MAH, it is suggested that the levels of magnesium in Numeta G13E may in certain cases result in hypermagnesemia in preterm neonates. Given the uncertainty regarding the appropriateness of the levels of magnesium in Numeta G13E, and the clinical consequences of this, there is a need to undertake an in depth assessment of the benefit/risk balance for Numeta as currently formulated.

There is currently also a concern about the availability of adequate alternatives across the European Union Member States. Thus, there is urgency to undertake this review, to agree whether the benefit/risk balance remains positive, and if there is need for additional risk minimisation measures.

In view of the above, the RMS will request the PRAC to give a recommendation under the urgent union procedure, Article 107i of Directive 2001/83/EC, for Numeta G13E (300 ml).