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Numeta G13%E to be suspended and new risk minimisation measures to be introduced for Numeta G16%E

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), a medicines regulatory body representing the European Union (EU) Member States, has endorsed by consensus the recommendation to suspend the marketing authorisation of Numeta G13%E because of a risk of hypermagnesaemia (high blood levels of magnesium). Numeta G13%E, which is given into a vein to premature babies to provide nutritional support (intravenous nutrition or parenteral nutrition), will remain suspended until a re-formulated preparation is made available.

For another nutrition preparation given into a vein, Numeta G16%E, used in full-term newborns and children up to 2 years, the CMDh agreed that the benefit-risk balance remains positive, provided that healthcare professionals monitor their patients' blood magnesium levels before giving the preparation and at appropriate intervals thereafter in accordance with routine clinical practice and the clinical needs of the individual patient. In patients whose blood magnesium levels are elevated or signs of hypermagnesaemia are identified Numeta G16%E should be stopped or the infusion rate reduced.

Numeta preparations are given to provide nutritional support in children who cannot be fed by mouth or with a feeding tube. They contain nutrients such as glucose (sugar), lipids (fats), aminoacids and other important substances including magnesium.

Hypermagnesaemia is a serious condition and symptoms may include weakness, nausea and vomiting, breathing difficulties, hypotension (low blood pressure) and arrhythmias (irregular heart beat).

The review of Numeta G13%E and Numeta G16%E was carried out by the the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) following several reports of hypermagnesaemia (without clinical symptoms) in preterm infants. As a precautionary measure, the manufacturer decided to voluntarily recall Numeta G13%E in the EU. The PRAC assessed the available data on the risk of hypermagnesaemia with Numeta G13%E and Numeta G16%E preparations from clinical studies, post-marketing reports and the published literature and considered available treatment guidelines. Stakeholders were also invited to submit any relevant information to support the assessment, and the Agency's Paediatric Committee (PDCO) was consulted for advice.

Having considered available guidelines and relevant literature and considering the magnesium content of Numeta, the PRAC concluded that the administration of Numeta G13%E could lead to a higher risk

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of hypermagnesaemia. In addition, the PRAC noted that this risk is further increased in premature newborns because their kidneys are immature and less able to clear the body of magnesium. The PRAC also noted the difficulty in identifying symptoms of hypermagnesaemia in premature newborns, which means that hypermagnesaemia may not be detected until it causes serious complications.

For Numeta G16%E, the PRAC concluded that although the magnesium content may result in a magnesium intake that is slightly higher than suggested in some guidelines, the proposed measures, including updating the product information and a further study, are sufficient to ensure the safe use of this product. The product information should be revised accordingly and healthcare professionals should be informed in writing of the potential risk of hypermagnesaemia, which is increased in patients with impaired kidney function and those whose mothers were receiving supplemental magnesium before delivery, and of the measures to be taken to minimise this risk. In addition, the PRAC recommended a study be carried out to further evaluate blood magnesium levels observed in term newborn infants and children up to two years of age following use of Numeta G16%E.

As the PRAC recommendations were endorsed by consensus by the CMDh, they will now be implemented directly in all Member States, according to an agreed timetable.

Information to parents and carers

- Because of the risk of hypermagnesaemia (high blood levels of magnesium), the nutrition preparation Numeta G13%E has been suspended until a re-formulated preparation is made available. Numeta G13%E is given into a vein to provide nutritional support in premature babies who cannot be fed by mouth or with a feeding tube.
- The nutrition preparation Numeta G16%E can continue to be used in full-term newborns and children up to 2 years, however the doctor will monitor the levels of magnesium in the child's blood before giving the preparation and at appropriate intervals thereafter. The doctor will stop giving Numeta G16%E if magnesium levels are high, or will give Numeta at a slower rate.
- Severe hypermagnesaemia is rare but can have adverse clinical consequences. Doctors will monitor newborns and children who are receiving Numeta G16%E for symptoms of hypermagnesaemia such as weakness, nausea and vomiting, breathing difficulties, hypotension (low blood pressure) and arrhythmias (irregular heart beat).
- Parents who have any questions or concerns should speak to the treating doctor or other healthcare professional.

Information to healthcare professionals

For Numeta G13%E:

- Following several reports of hypermagnesaemia in preterm infants, the nutrition preparation Numeta G13%E has been suspended until a re-formulated preparation is made available. While Numeta G13%E is suspended, healthcare professionals should use alternative nutrition solutions which may include authorised standardised or individually prepared solutions.

For Numeta G16%E:

- The benefit-risk balance of the nutrition preparation Numeta G16%E, used in full-term newborns and children up to 2 years, remains positive. However, healthcare professionals should be aware of the potential risk for hypermagnesaemia. This risk is increased in patients with reduced renal function, and in newborn infants of mothers who were receiving supplemental magnesium prior to delivery.

- When giving Numeta G16%E, doctors should monitor serum magnesium levels, along with other electrolyte levels at baseline and at appropriate intervals thereafter. This should be done in accordance with routine clinical practice and the clinical needs of the individual patient.
- Doctors should also monitor patients for signs and symptoms of hypermagnesaemia such as nausea, vomiting and flushing, generalized weakness, respiratory failure, hypotension and arrhythmias. Clinical signs may not be identifiable unless hypermagnesaemia is severe.
- In case of hypermagnesaemia, the infusion of Numeta G16%E should be stopped or infusion rate reduced and alternative fluids, nutrition and electrolytes prescribed as deemed clinically appropriate.

Further information about the EU-wide safety review:

- The company marketing Numeta identified 14 case reports of hypermagnesaemia with Numeta G13%E. Magnesium levels mainly ranged from 1.025 mmol/L to > 1.5 mmol/L and no clinical signs or symptoms were reported for any of the cases.
- The appropriate parenteral magnesium intake in preterm infants is uncertain. However, widely-recognised guidelines [1,2] recommend a parenteral magnesium intake of 0.15 – 0.25 mmol/kg/day. The maximum total licensed amount of magnesium that can be delivered to preterm infants using Numeta G13%E is 0.55 mmol/kg/day which is above this recommended intake.
- The company identified one case of hypermagnesaemia associated with Numeta G16%E. This report was confounded by the fact that additional magnesium may have been given.
- The maximum total amount of magnesium that can be delivered to term infants using Numeta G16%E according to its product information is 0.3 mmol/kg/day. Although this is within the recommendations reported in the literature as a whole, it is slightly more than suggested by some recognised guidelines[1,2,3] (0.15-0.25 mmol/kg/day and 0.2 mmol/kg/day for term infant to one year of age, 0.15-0.25 mmol/kg/day and 0.1 mmol/kg/day for children from one year to two years of age).

References:

1. Canada T, Crill C, Guenter P. A.S.P.E.N. Parenteral Nutrition Handbook. Silver Spring,Maryland: American Society for Parenteral and Enteral Nutrition. 2009; 167
2. Mirtallo et al. Safe Practices for Parenteral Nutrition JPEN 2004; 28: S 39 – S 70
3. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatric Gastroenterology Nutrition 2005; 41:S1-S87.

More about the medicine

Numeta G13%E and Numeta G16%E (glucose, lipids, aminoacids and electrolytes) are parenteral nutrition solutions. Parenteral nutrition is the providing of nutrients and fluids through a vein in patients who cannot be fed by mouth or by enteral nutrition (the use of a feeding tube passed directly into the gut). Parenteral nutrition is necessary in premature neonates and in some full-term babies in order to prevent complications such as growth retardation and breathing complications and to promote the normal development of the brain.

Numeta G13%E and Numeta G16%E have been authorised since 2011 via national procedures in the following Member States: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Sweden, United Kingdom.

More about the procedure

The review of Numeta G13%E and Numeta G16%E was initiated on 13 June 2013 at the request of Sweden, under Article 107i of Directive 2001/83/EC, also known as the urgent Union procedure.

The review was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As the review only covers nationally authorised medicines, the PRAC recommendation was forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh is a medicines regulatory body representing the EU Member States.

Because the CMDh position was agreed by consensus, the agreement will be directly implemented by the Member States where the medicines are authorised.

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