Summary of risk management plan for Numeta

This is a summary of the risk management plan (RMP) for Numeta. The RMP provides details on the important risks of Numeta, how these risks can be minimized, and how more information will be obtained about the risks and uncertainties (missing information) for Numeta. The summary of product characteristics (SmPC) and package leaflet (PL) for Numeta provide essential information to healthcare professionals and patients on how Numeta should be used.

I. The medicine and what it is used for

Numeta is authorized for parenteral nutrition in pediatric patients when oral or enteral nutrition is not possible, insufficient or contraindicated; refer to the SmPC for complete indication wording. It contains glucose, amino acids with electrolytes, and lipids as the active substances, and it is given by intravenous infusion.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

The important risks of Numeta, together with measures to minimize such risks and the proposed studies for learning more about Numeta's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size – the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine’s legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

The important risks of Numeta are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of medicinal products. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine). The important risks and missing information for Numeta are listed in the table below.

Important identified risks	Drug administration error – peripheral infusion with insufficient or no dilution
	Metabolic/electrolyte abnormalities
Important potential risks	Hypersensitivity reactions
	Refeeding syndrome
	Drug administration error – failure to mix compartments of 3-chamber bag
	Pulmonary vascular precipitates
	Ceftriaxone-calcium salt precipitation
Missing information	Lack of data on use of Numeta G19%E in pregnant or lactating females
	Lack of data in patients with certain organ impairments (specifically heart failure, liver insufficiency, renal insufficiency, and/or blood coagulation disorders)

II.B Summary of important risks and missing information

Drug administration error – peripheral infusion with insufficient or no dilution	
Evidence for linking the risk to the medicine	Post-market reports and medical literature. Extravasation, skin necrosis, and/or tissue damage have been reported in the post-marketing setting with Numeta when peripherally administered with insufficient dilution. Administration of Numeta via a peripheral vein with insufficient or no dilution may, in its severe form, result in skin necrosis and/or tissue damage which may require medical or surgical intervention.

Risk factors and risk groups	Pediatric patients who do not have an established central venous catheter and who will be receiving Numeta via peripheral intravenous infusion may be at increased risk.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC sections 4.2 and 4.4. Included in section 4.8 of the SmPC as an adverse reaction. Discussed in PL section 2. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Metabolic/electrolyte abnormalities	
Evidence for linking the risk to the medicine	Ped3CB/P01/06/Mu.B clinical study report (CSR) and post-market reports. Metabolic/electrolyte abnormalities are a well-known side effect of parenteral nutrition therapies, including Numeta. The severity of metabolic/electrolyte abnormalities may range from mild to severe. Hypophosphatemia, hyperglycemia, hypercalcemia, hypertriglyceridemia, hyperlipidemia, and hyponatremia were reported in study Ped3CB/P01/06/Mu.B in patients receiving Numeta.
Risk factors and risk groups	Patients with a congenital abnormality of amino acid metabolism, pathologically elevated plasma concentrations of sodium, potassium, magnesium, calcium, and/or phosphorus, severe hyperglycemia, severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia are at increased risk for metabolic/electrolyte abnormalities. Numeta is contraindicated in such patients.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC sections 4.3 and 4.4. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Medical literature. Hypersensitivity is a known reaction to parenteral nutrition therapy. Documented cases of allergic responses to the lipid and multivitamin components of PN are available in literature (Nagata 1993, Bartels 2012, Singhi 2003, Scolapio 2005). Hypersensitivity reactions may range in severity from mild to severe.
Risk factors and risk groups	Atopic patients and/or patients with known history of hypersensitivity to egg, soy or peanut proteins, or to any of the active substances, excipients, or components of the container.

Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC sections 4.3 and 4.4. Discussed in PL sections 2 and 4. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Refeeding syndrome	
Evidence for linking the risk to the medicine	Medical literature. Case reports of refeeding syndrome have been discussed in medical literature in patients receiving artificial nutrition (Fan 2004, Mehanna 2008, Lin 2006, Huang 2001). No reports of refeeding syndrome have been received in the post-marketing experience with Numeta.
Risk factors and risk groups	Patients who are severely undernourished or with electrolyte imbalances of potassium, phosphorus, and magnesium.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC section 4.4. Discussed in PL section 2. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Drug administration error – failure to mix compartments of 3-chamber bag	
Evidence for linking the risk to the medicine	Medical literature. Medication errors with the administration of parenteral nutrition therapy have been reported in literature (Sacks 2009). Omission of lipids which were intended for administration would result in a lack of calories, but this is not a safety issue over a single day. Not activating the bag can lead to only the amino acids/electrolytes portion being infused, resulting in hypoglycemia. Severity of the risk is mild.
Risk factors and risk groups	Pediatric patients receiving parenteral nutrition via a Numeta 3-chamber bag.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC section 6.6. Discussed in PL section 2 and 3. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Pulmonary vascular precipitates	
Evidence for linking the risk to the medicine	Medical literature. Published case reports on the formation of pulmonary vascular precipitates in PN admixtures are documented

	in literature (Strickland 2015, Felton 2006, Hammar 2003, McNearney 2003, Shay 1997, Reedy 1999, Hill 1996, Turrentine 1994, Knowles 1989). Pulmonary vascular precipitates (pulmonary vascular emboli and pulmonary distress) are a known class reaction reported with other parenteral nutrition admixtures. Pulmonary vascular precipitates have not been reported with post-marketing use of Numeta.
Risk factors and risk groups	Pediatric patients receiving parenteral nutrition.
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC section 4.4. Discussed in SmPC section 4.8 as an adverse reaction reported with other parenteral nutrition admixtures. Discussed in PL sections 2 and 4. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Ceftriaxone-calcium salt precipitation	
Evidence for linking the risk to the medicine	Medical literature. Cases of fatal reactions with calcium-ceftriaxone precipitates have been described in medical literature (Bradley 2009, Steadman 2010). Ceftriaxone-calcium salt precipitation has not been reported with post-marketing use of Numeta.
Risk factors and risk groups	Newborns up to 28 days of age may be at greater risk of ceftriaxone-calcium precipitation than older patients, particularly if they are premature or have impaired bilirubin binding.
Risk minimization measures	**Routine risk minimization measures:** Discussed in section 4.3 of the Numeta G13%E and Numeta G16%E SmPCs. Discussed in sections 4.5 and 6.2 of the Numeta G13%E, Numeta G16%E, and Numeta G19%E SmPCs. Discussed in PL section 2. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Lack of data on use of Numeta G19%E in pregnant or lactating females	
Risk minimization measures	**Routine risk minimization measures:** Discussed in section 4.6 of the Numeta G19%E SmPC. Discussed in section 2 of the Numeta G19%E PL. **Additional risk minimization measures:** None proposed.

Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.
Lack of data in patients with certain organ impairments (specifically heart failure, liver insufficiency, renal insufficiency, and/or blood coagulation disorders)	
Risk minimization measures	**Routine risk minimization measures:** Discussed in SmPC section 4.4. Discussed in PL section 2. **Additional risk minimization measures:** None proposed.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None proposed.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligations of Numeta.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Numeta.