Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil and concerned by the PASS final report , the scientific conclusions are as follows:

The descriptive study final report submitted by the MAH complies with their obligation to 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 in routine clinical practice as imposed during the Article 107i procedure EMEA/H/A-107i/1373 for alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil containing products.

A total of 104 subjects were enrolled. Hypermagnesaemia was reported in 4 cases, 3 of which were mild and one moderate in severity. The levels of magnesium in these cases are not considered to represent clinically relevant hypermagnesemia. No potential risk factors for notable increase in serum magnesium were identified. No pattern of accumulation or continued increase in serum magnesium levels that would raise any safety concern was observed.

Overall, data suggest that neonates can tolerate during a short time a relatively wide range of serum magnesium concentrations without increased risk of adverse outcomes.

Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the conditions of the marketing authorisation were warranted.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for the results of the study for the medicinal product(s) containing the active substance Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil and concerned by the PASS final report , the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report should be varied.

Annex II

Conditions to the Marketing Authorisation(s)>

Changes to be made to the conditions of the marketing authorisation(s) of medicinal product(s) containing the active substance Alanine, arginine, aspartic acid, cysteine, glucose, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, calcium chloride, magnesium acetate, potassium acetate, sodium chloride, sodium glycerophosphate, refined soybean oil, refined olive oil concerned by the non-interventional imposed PASS final report

The marketing authorisation holder(s) shall remove the following condition(s) (new text **underlined and in bold**, deleted text ~~strike through~~)

~~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. The MAH should submit the protocol for the above-mentioned study. (Annex V of the CMDh position).~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	October 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 December 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 January 2019