ANNEX

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

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The Member States shall agree with the Marketing Authorisation Holder the final text of a card suitable for display in neonatal intensive care units. The Member States shall ensure that the card contains the following key elements and is provided by the Marketing Authorisation Holder to all neonatal intensive care units where the product is likely to be used at launch of the product:

- That Peyona is for the treatment of primary apnoea
- That treatment with Peyona must be provided in a neonatal intensive care unit and initiated and supervised by a physician experienced in neonatal intensive care
- Details of the loading and maintenance dosages and that caffeine may accumulate in premature neonates because of its long half-life.
- That the dose of caffeine expressed as caffeine base is one half the dose of caffeine expressed as caffeine citrate (20mg caffeine citrate is equivalent to 10mg caffeine base) and that prescriptions should clearly indicate that caffeine citrate is to be administered.
- That the product should be used immediately after opening the ampoule and unused portions left in the ampoule should be discarded
- That baseline plasma levels may need measuring because of an increased risk of toxicity if
    - The neonate has been previously treated with theophylline
    - The mother has been consuming large amounts of caffeine prior to delivery or breast feeding
- That caffeine and theophylline should not be used concurrently
- That if caffeine and doxapram are used concurrently, the patient should be closely monitored
- That additional plasma caffeine monitoring and dosage adjustment may be necessary in at risk situations such as preterm infants:
    - With cholestatic hepatitis
    - With significant renal impairment
    - With seizure disorders
    - With cardiac disease
    - less than 28 weeks gestational age and/or body weight <1000g particularly when receiving parenteral nutrition
    - with co-administration of medicinal products known to interfere with caffeine metabolism
- That cardiac disorders (including arrhythmias) may arise in neonates with pre-existing cardiac disease
- That all suspected adverse reactions should be reported in accordance with national reporting requirements
- In particular, if convulsions, seizures, necrotising enterocolitis, symptoms and signs of caffeine withdrawal, medically abnormal decrease in infant weight gain or interactions with other medicines are suspected as being associated with the use of caffeine citrate, these should be reported to <insert local name and address of Chiesi Farmaceutici S.p.A.